SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF OXIME ESTERS FROM DIHYDROCUMIC ACID

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Dihydrocumic acid was prepared from β-pinene through oxidation and dehydration. Then, ten oxime esters from dihydrocumic acid were synthesized. Reaction conditions of the oxime esters were adjusted and their structures were characterized by IR, ^{1}H-NMR, MS, and elemental analysis. The antibacterial activity of these newly synthesized oxime esters against Gram-negative bacteria and Gram-positive bacteria was also investigated using the inhibition zone method. The preliminary results indicated that seven compounds displayed better antibacterial activity against Gram-negative bacteria compared with bromogeramine, a commercially available antibacterial agent.

Keywords: β-pinene; Dihydrocumic acid; Oxime esters; Antibacterial activity

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INTRODUCTION

As an important natural bioresource in China, turpentine has attracted great interest because of its special chemical structure (Song *et al.* 1993). Turpentine and its derivatives have been used as a starting material for synthesizing various pharmaceutical intermediates, and their broad-spectrum biological activity has been reported for such products as bactericides (Mies and Blanc 1997; Grodnitzky and Coats 2002; Martinuzzi and Arago 1963; Uhing *et al.* 1988), antifeedants (Paruch *et al.* 2001; Josep and Yudelsy 2005; Satdive *et al.* 2007; Zhang *et al.* 1993; Neoliya *et al.* 2007; Dhingra *et al.* 2006; Kumar and Singh 2005; Wang *et al.* 2008), repellents of insects in agriculture (Mullen 2005; Wang *et al.* 2008; Wang *et al.* 2004), and antifungals (Pitarokili *et al.* 2002). β-pinene is an important component in turpentine, and dihydrocumic acid is a derivative of β-pinene through an easy synthetic path. However, there have been very few reports on antibacterial activity of dihydrocumic acid and its derivatives.

Recently oxime ester and its derivatives have been shown to have favorable bioactivities, attracting attention from researchers in many areas, especially in the agrochemical and medicinal areas. It has been found that oxime esters have a lot of bioactivity, such as fungicidal (Liu *et al.* 2008), insecticidal (Ma *et al.* 2002; Jin *et al.* 1997), antitumor (Stefan *et al.* 1999; Song *et al.* 2005), herbicidal (Li *et al.* 2009; William *et al.* 2001), and antiphytoviral (Bromidge *et al.* 1997; Bekhit *et al.* 2006) activities. The first oxime ester, Tranid, was developed in 1963 (Song *et al.* 2005). Since

these nearly fifty years, the synthesis and biological activities of oxime esters have been noticeable, and a large number of investigations have been reported.

In this study, ten oxime esters from dihydrocumic acid were synthesized, and their structures were characterized by IR, ^{1}H-NMR, MS, and elemental analysis. Antimicrobial activity against Gram-negative and Gram-positive bacteria was also investigated. This preliminary exploration would promote the application of β-pinene and its derivatives in an antibacterial activity aspect.

EXPERIMENTAL

Materials and Instruments

β-pinene was obtained from a commercial source (Hong Da Spice Ltd., Jiangxi, China). All other chemicals were of reagent grade. IR spectra were taken on a Nicolet IS10 FT-IR (Nicolet, Madison, USA) spectrophotometer. The ^{1}H-NMR spectra were recorded on a Bruker AV-300 (Bruker, Karlsruhe, Germany) nuclear magnetic resonance spectrometer with $CDCl_3$ as solvent and TMS as internal standard. The MS spectra were taken on an Agilent-5973 (Agilent, Santa Clara, USA) spectrophotometer. The melting point was determined using XT-5 (Saiao, Beijing, China) melting point apparatus. The elemental analysis (C, H, and N) was actualized using a Vario EL-III (Elementar, Hauau, Germany) elemental analyzer. The crystal structure was tested by ENRAF-NONIONS CAD4 (ENRAF NOMUS, Holland). Bacteria strains originated in the clinical isolates.

The target compounds were synthesized through oxidation of β-pinene, dehydration and isomerization of nopinic acid (1), and the activation of dihydrocumic acid (2) with $SOCl_2$. Oximes (4) were obtained through the reaction of aldehyde or ketone and $NH_2OH{\cdot}HCl$, which used ethanol as a solvent and sodium carbonate as a base in this preparation. The synthetic route is shown in Fig. 1.

General Synthetic Procedure for Nopinic Acid (2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid)(1)

By the process discussed in previous work (Gao *et al.* 2009), nopinic acid was obtained with a 50% yield.

General Synthetic Procedure for Dihydrocumic Acid (4-isopropylcyclohexa-1, 3-dienecarboxylic acid) (2)

By the process discussed in previous work (Gao *et al.* 2011a, b, c), dihydrocumic acid can be obtained.

General Synthetic Procedure for Dihydrocumyl chloride (3)

In a 250 mL flask with a water-cooled condenser, thermometer, drying tube, and dropping funnel, 27 mmol of dihydrocumic acid and 50 mL of CH_2Cl_2 were stirred until the solid was dissolved. Thionyl chloride (82 mmol) was then added dropwise through a dropping funnel within 1 h and refluxed for 4 h at 65°C. Dihydrocumyl chloride was then obtained after removing the dichloromethane and the excess thionyl chloride under reduced pressure.

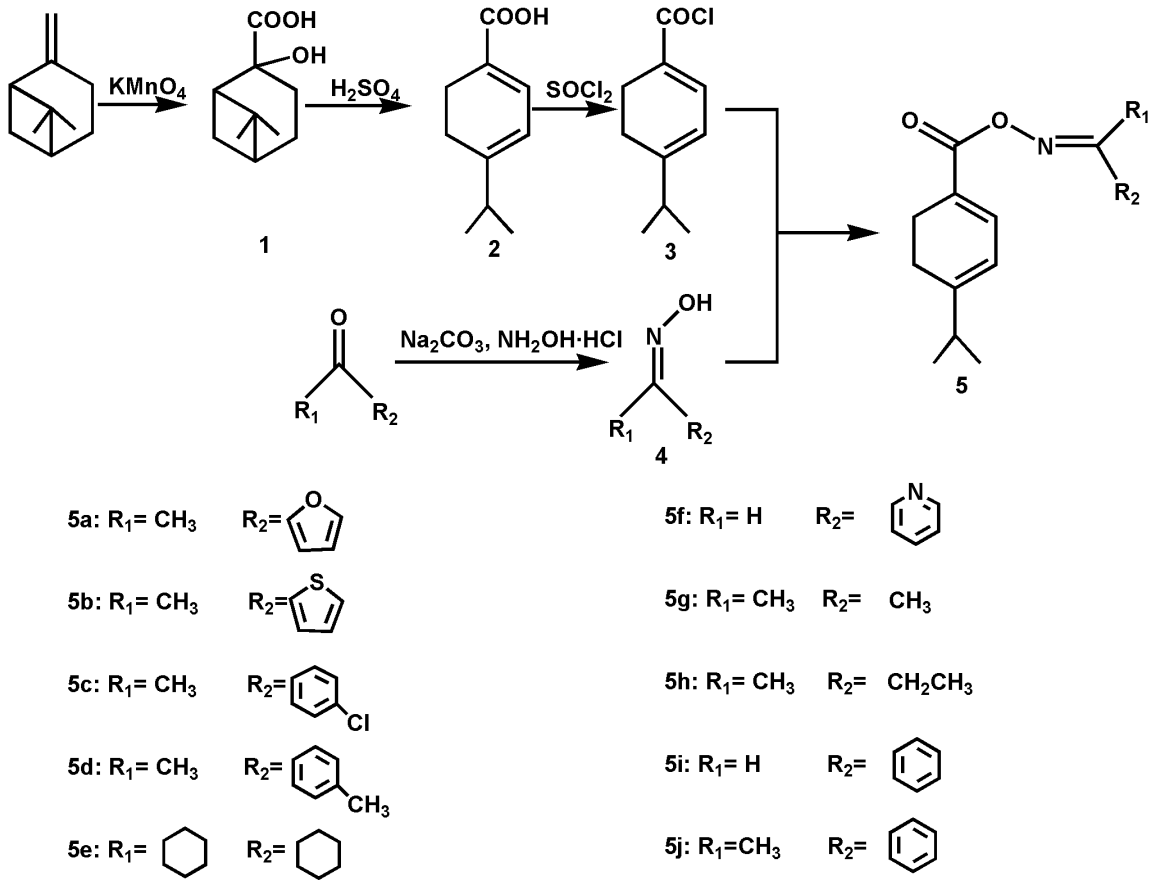

Fig. 1. General synthetic route for target compounds

General Synthetic Procedure for Oximes (4)

To a solution of 0.1 mol of aldehyde or ketone and 0.15 mol of hydroxylammonium in 150 mL of ethanol, 0.5 mol of sodium carbonate was added in batch within 30 min at room temperature. Reacting time depends on the monitoring results of TLC. After that, the mixture was poured into ice water; the separated solid was washed with water, dried, and recrystallized from ethanol to get title compounds (4) with the yield over 85%.

General Synthetic Procedure for Oximyl Dihydrocumic Carboxylate (5a-5j)

A solution of the above dihydrocumyl chloride in 50 mL of CH_2Cl_2 was added dropwise to a solution of 30 mmol of oxime and 40 mmol of triethylamine in 40 mL of CH_2Cl_2 within 30 min at the temperature range of 0 to 5 °C. After that, the reaction mixture was kept at room temperature over 2 h and washed with water. It was then dried with anhydrous $MgSO_4$. Purification of the residue by silica gel chromatography [v (ethyl acetate)/ v (petroleum ether) =10:1] gave the compounds 5a-5j.

Antibacterial Activity

The antibacterial activity of these derivatives was estimated by a disc paper method. Compounds were dissolved in ethanol and sterile water to get a solution concentration of 256 μg/mL. As test species, *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria) were cultivated in beef extract-peptone for 1 week. A small amount (1 to 2 scratch) of fresh bacteria from the culture medium were then added into the culture solution, and in turn, the solution was diluted 10-fold to a concentration of 5.0 to 10.0 × 10^6 (CFU) mL^{-1}. 1 mL of the bacterial solution was then evenly coated on a 90 mm plate of the beef extract peptone medium. A 6 mm diameter sterile filter paper was dipped in the solution of chemicals for 10 minutes and then placed on the plate. The inhibition zones were measured by calipers (in units of mm) at the end of an incubation period of 24 h. All of the experiments were conducted in triplicate to be positive at a given concentration,

$$\text{Diameter of inhibition zone (mm)} = A_1 - A_0 \quad (1)$$

where A_0 is the diameter of the control (blank, ethanol, and sterile water without chemical), and A_1 is the diameter in the presence of the test chemical.

RESULTS AND DISCUSSION

Nopinic acid can be synthesized through the oxidation of β-pinene using potassium permanganate as the oxidant. β-pinene is oil-soluble, but potassium permanganate is water-soluble. A homogeneous phase is required for a good yield. In this work, a mixture of water/t-butanol (v/v = 1:2) was chosen for the reaction solvent. The yield of nopinic acid was more than 50%.

The preparation of compounds (4) plays an important role in the synthesis of compounds (5). In a previous study, the yield may be affected by a solvent or base (Liu *et al.* 2008; Song *et al.* 2005; Li *et al.* 2012). In our previous work, the compatibility of base and solvent was discussed by Li *et al.* (2012). In this paper, hypnone was selected as a model to optimize the reaction conditions. When sodium carbonate was used for base, ethanol, THF, and acetone as solvent, the yield was 85%, 80%, and 83%, respectively; this was much higher than DMF and methanol, which were 65% and 60%, respectively (entries 1-5 in Table 1). In the same method, when ethanol was used as solvent, sodium hydroxide (50%), triethylamine (46%), and sodium carbonate (85%) were also demonstrated as the preferable base conditions (entries 5, 7, and 9 in Table 1). Therefore, ethanol and sodium carbonate were selected as the solvent and base in preparing compounds (5).

The compounds were identified by FT-IR spectroscopy, ^{1}H-NMR, MS, and elemental analysis. The crystal of 2-hydroxy-6,6-dimethylbicyclo [3.1.1] heptane-2-carboxylic acid(1) belongs to a monoclinic system; parameters of the unit cell are: a = 26.796 (5) Å, b = 6.6560 (13) Å, c = 12.250 (3) Å, β = 112.23 (3) °, Z = 8, composition $C_{10}H_{16}O_3$, The configuration of 2-hydroxy-6, 6-dimethylbicyclo [3.1.1] heptane-2-carboxylic acid is shown in Fig. 2 (Gao *et al.* 2009).

Table 1. Synthesis of Hypnone Oxime under Various Reaction Conditions

Entry *	Solvent	Temperature (°C)	Base	Yield/%
1	THF	25	Sodium carbonate	80
2	Acetone	25	Sodium carbonate	83
3	DMF	25	Sodium carbonate	65
4	Methanol	25	Sodium carbonate	60
5	Ethanol	25	Sodium carbonate	85
6	Ethanol	reflux	Sodium hydroxide	50
7	Ethanol	25	Triethylamine	46
8	Ethanol	reflux	Triethylamine	46
9	Ethanol	25	Sodium hydroxide	50
10	Ethanol	reflux	Sodium carbonate	85

*Reaction conditions: hypnone (10mmol), hydroxylammonium (15mol), solvent (150 mL), base (50 mmol)

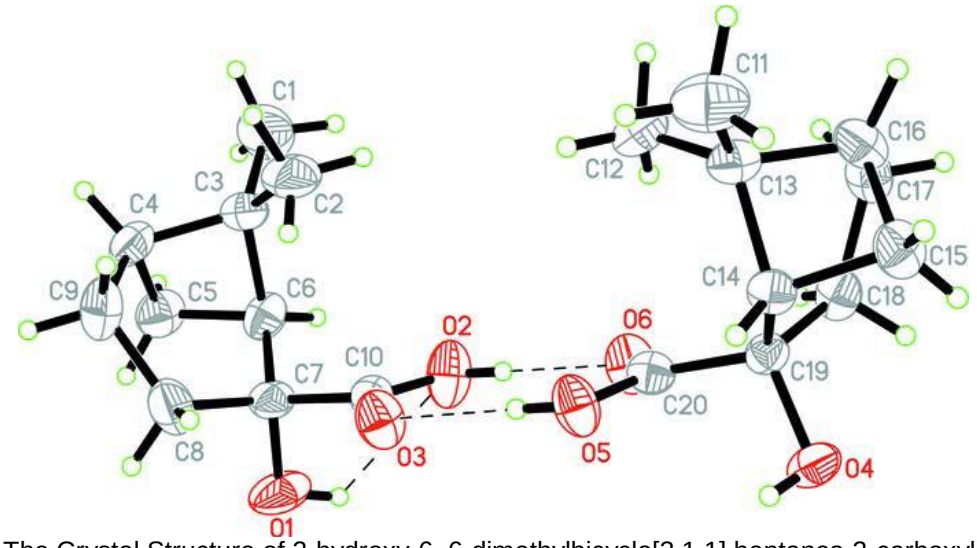

Fig. 2. The Crystal Structure of 2-hydroxy-6, 6-dimethylbicyclo[3.1.1] heptanes-2-carboxylic acid

Oxime esters

1-(furan-2-yl)ethanone oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate (5a, $C_{16}H_{19}NO_3$)

Yellow powder, yield: 60.3%, m.p. 63.1-64.8°C. IR (cm^{-1}): 1729 (-O-C=O); 1606 (C=N). ^{1}H-NMR ($CDCl_3$. 300 MHz. δ/ ppm): 8.06,8.03 (d, 1H, furan-α-C-H); 7.57, 7.54 (d, 2H, furan-β-C-H); 6.93-6.94 (d, 1H, OC-C =CH-); 5.89, 5.90 (d, 1H, -CH=C-$(Me)_2$); 2.89-2.91 (m, 1H,-CH- $(Me)_2$); 2.52-2.58 (t, 2H, -CH_2-C-CO); 2.35 (s, 3H, -N=C-CH_3); 2.22-2.29 (t, 2H, -CH_2-C-C=C); 1.07-1.10 (d, 6H, CH_3). ESI-MS m/z= 295 $[M+Na]^+$. Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.21; H, 7.03; N, 5.18.

1-(thiophen-2-yl)ethanone oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate (5b, $C_{16}H_{19}NO_2S$)

Yellow powder, yield: 55.3%, m.p. 45.7-46.3°C. IR (cm^{-1}): 1738 (-O-C=O); 1584 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 8.05, 8.03 (d, 1H, thiophene-α-C-H); 7.49, 7.50 (d, 2H, thiophene - β-C-H); 7.09, 7.11 (d, 1H, OC-C=CH-); 5.87, 5.89 (d, 1H, -CH=C-$(Me)_2$); 2.50-2.59 (m, 1H, -CH-$(Me)_2$); 2.40-2.43 (t, 2H, -CH_2-C-CO); 2.31 (s, 3H, -N=C-CH_3); 2.23-2.24 (t, 2H, -CH_2-C-C=C); 1.06-1.10 (d, 6H, CH_3). ESI-MS m/z= 289 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.44; H, 6.57; N, 9.69. Found: C, 66.88; H, 6.34; N, 9.48.

1-(4-chlorophenyl)ethanone oximyl4-isopropylcyclohexa-1,3-dienecarboxylate(5c, $C_{18}H_{20}ClNO_2$)

Yellow powder, yield: 65.3%, m.p. 45.8-46.7°C. IR (cm^{-1}): 1734 (-O-C=O); 1592 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 7.70, 7.72 (d, 2H, o-C-H); 7.33, 7.36 (d, 2H, m-C-H); 7.13,7.14 (d, 1H, OC-C=CH-); 5.91, 5.92 (d, 1H, -CH=C-$(Me)_2$); 2.53-2.55 (m, 1H, -CH-$(Me)_2$); 2.40-2.41 (t, 2H, -CH_2-C-CO); 2.30 (s, 3H, -N=C-CH_3); 2.20-2.23 (t, 2H, -CH_2-C-C=C); 1.04-1.08 (d, 6H, CH_3). ESI-MS m/z= 317 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{20}ClNO_2$: C, 68.03; H, 6.30; N, 4.41. Found: C, 67.86; H, 6.37; N, 4.51.

1-p-tolylethanone oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5d, $C_{19}H_{23}NO_2$)

Yellow powder, yield: 65.3%, m.p. 32.3-34.2°C. IR (cm^{-1}): 1734 (-O-C=O);1592 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 7.64, 7.79 (d, 2H, o-C-H); 7.51, 7.54 (d, 2H, m-C-H); 7.12,7.17 (d, 1H, OC-C=CH-); 5.87, 5.88 (d, 1H, -CH=C-$(Me)_2$); 2.50-2.58 (m, 1H, -CH-$(Me)_2$); 2.40-2.41 (t, 2H, -CH_2-C-CO); 2.21-2.23 (t, 2H, -CH_2-C-C=C); 2.27 (s, 3H, Ar-H); 1.80 (s, 3H, -N=C-CH_3); 1.04-1.08 (d, 6H, CH_3). ESI-MS m/z=297 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.77; H, 7.74; N, 4.71. Found: C, 75.86; H, 8.15; N, 5.21.

Dicyclohexylmethanone oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5e, $C_{23}H_{35}NO_2$)

Yellow powder, yield: 55.3%, m.p. 30.3-31.2°C. IR (cm^{-1}): 1735 (-O-C=O); 1608 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 7.04, 7.05 (d, 1H, OC-C=CH-); 5.83, 5.85 (d, 1H,-CH=C-$(Me)_2$); 2.51-2.57 (m, 1H, -CH-$(Me)_2$); 2.35-2.40(t, 2H, -CH_2-C-CO); 2.20-2.26 (t, 2H, -CH_2-C-C=C); 1.66-1.78 (m, 10H, hexo-C-H); 1.02-1.06 (d, 6H, CH_3). ESI-MS m/z=261 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{35}NO_2$: C, 77.31; H, 9.80; N, 3.92. Found: C, 77.65; H, 9.63; N, 3.35.

Picolinaldehyde oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5f, $C_{16}H_{18}N_2O_2$)

White powder, yield: 55.3%, m.p. 67.3-69.1°C. IR (cm^{-1}): 1728 (-O-C=O); 1646 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 8.66, 8.68 (d, 1H, pyridine-α-C-H); 7.75-7.80 (t, 1H, pyridine- γ-C-H); 7.35-7.37 (t, 2H, pyridine-β-C-H); 7.18, 7.20 (d, 1H, OC-C=CH-); 5.83, 5.85 (d, 1H, -CH=C-$(Me)_2$); 2.89 (s, 1H, -N=C-H); 2.40-2.45 (m, 1H, -CH-$(Me)_2$); 2.40-2.41 (t, 2H, -CH_2-C-CO); 2.20-2.23 (t, 2H, -CH_2-C-C=C); 1.04-1.08 (d,

6H, CH_3). ESI-MS m/z= 270 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.67; N, 10.37. Found: C, 71.22; H, 6.87; N, 10.58.

Propan-2-one oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5g, $C_{13}H_{19}NO_2$)

White powder, yield: 55.3%, m.p. 37.3-39.1°C. IR (cm^{-1}): 1735(-O-C=O);1643(C=N).^{1}H-NMR($CDCl_3$. 300MHz. δ/ppm):7.04, 7.06(d, 1H, OC-C=CH-); 5.83, 5.85 (d, 1H, -CH=C-$(Me)_2$); 2.42-2.54 (m, 1H, -CH-$(Me)_2$); 2.39-2.41 (t, 2H, -CH_2-C-CO); 2.20-2.26 (t, 2H, -CH_2-C-C=C); 2.00 (s, 6H, -N=C-$(Me)_2$); 1.02-1.06 (d, 6H, CH_3). ESI-MS m/z= 221 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60; N, 6.33. Found: C, 71.11; H, 8.68; N, 5.73.

Butan-2-one oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5h, $C_{14}H_{21}NO_2$)

Yellow powder, yield: 60.3%, m.p. 37.0-38.1°C. IR (cm^{-1}): 1729 (-O-C=O); 1643 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 7.04, 7.07 (d, 1H, OC-C=CH-); 5.84, 5.86 (d, 1H, -CH=C-$(Me)_2$); 2.57-2.60 (m, 1H, -CH-$(Me)_2$); 2.39-2.41 (t, 2H, -CH_2-C-CO); 2.15-2.17 (t, 2H, -CH_2-C-C=C); 2.00 (s, 3H, -N=C-CH_3); 1.37-1.41 (m, H, -N=C-CH_2-); 1.03-1.05 (d, 6H, CH_3); 0.90-1.00 (t, 3H, -CH_2-CH_3). ESI-MS m/z=236 $[M+H]^+$; 278 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.49; H, 8.94; N, 5.96. Found: C, 70.79; H, 9.00; N, 6.60.

E)-benzaldehyde oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5i, $C_{17}H_{19}NO_2$)

Yellowpowder, yield: 40.3%, m.p. 66.6-67.8°C. IR (cm^{-1}): 3395 (H-C=N); 1725 (-O-C=O); 1646 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 8.43 (s, 1H, -N=CH); 7.76, 7.78 (d, 2H, o-C-H); 7.33, 7.43 (m, 3H, p-C-H); 7.15, 7.16 (d, 1H, OC-C=CH-); 5.84, 5.85 (d, 1H, -CH=C-$(Me)_2$); 2.52-2.58 (m, 1H, -CH-$(Me)_2$); 2.40-2.41 (t, 2H, -CH_2-C-CO); 2.21-2.29 (t, 2H, -CH_2-C-C=C); 1.04-1.10 (d, 6H, CH_3). ESI-MS m/z= 269 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 76.12; H, 7.06; N, 5.20. Found: C, 75.92; H, 7.16; N, 5.30.

Acetophenone oximyl 4-isopropylcyclohexa-1,3-dienecarboxylate(5j, $C_{18}H_{21}NO_2$)

Yellow powder, yield: 59.6%, m.p. 60.8-61.8°C. IR (cm^{-1}): 1727 (-O-C=O); 1641 (C=N). ^{1}H-NMR ($CDCl_3$. 300MHz. δ/ ppm): 7.77, 7.79 (d, 2H, o-C-H); 7.37-7.42 (m, 3H, p-C-H); 7.14, 7.17 (d, 1H, OC-C=CH-); 5.83, 5.85 (d, 1H, -CH=C-$(Me)_2$); 2.52-2.57 (m, 1H, -CH-$(Me)_2$); 2.40-2.42 (t, 2H, -CH_2-C-CO); 2.21-2.23 (t, 2H, -CH_2-C-C=C); 2.30 (s, 3H, -N=C-CH_3); 1.04-1.10 (d, 6H, CH_3). ESI-MS m/z =283 $[M+H]^+$. Anal. Cacld. for $C_{18}H_{21}NO_2$: C, 76.33; H, 7.42; N, 4.95. Found: C, 76.35; H, 7.57; N, 4.78.

As shown in Table 2, through the inhibition zones (mean diameter of inhibition) as a criterion of antibacterial activity of the target compounds against *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive), we can see that except for compounds 5d, 5g, and 5i, the inhibition zones of the compounds were all bigger than the 9.67 mm of the reference compound bromogeramine. The inhibition of all target compounds against *Escherichia coli* was generally higher than *Staphylococcus aureus*. These preliminary findings can provide an introduction for future work, and additional work would be needed in order to determine the full implications of the current findings.

Table 2. Inhibition Zones of Title Compounds

Compounds	*Escherichia coli*[*b] (mm)	*Staphylococcus aureus*[*b] (mm)
CK	8.00	12.33
Bromogeramine[a]	9.67	24.67
5a	10.00	7.67
5b	12.00	10.00
5c	12.00	7.00
5d	8.00	7.67
5e	9.70	6.03
5f	10.00	9.00
5g	8.30	8.33
5h	10.30	8.67
5i	7.30	9.67
5j	11.70	9.67

[*a] Reference compound
[*b] Values are mean of three independent trials

CONCLUSIONS

1. Ten new oxime esters from β-pinene were synthesized, and the structures were characterized by IR, ^{1}H-NMR, MS, and elemental analysis. This work has the potential to promote the valuable and effective utilization of β-pinene.
2. The antibacterial activity of oxime esters against *Staphylococcus aureus* and *Escherichia coli* were investigated. Results from biological assay indicated that seven compounds displayed better antibacterial activity than bromogeramine against *Escherichia coli*. In particular, compounds 5b, 5c, and 5j showed much higher antibacterial activity than others against *Escherichia coli*. Structure-activity relationship analysis revealed that the halogen-substituted and sulphur-heterocyclic compounds showed visible antibacterial activity compared with other compounds.
3. The satisfying results illustrated that these new derivatives have potential value in use. It is presumable that the work can promote the valuable and meaningful application of turpentine in the aspect of antimicrobial activity.

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