European Journal of Medicinal Chemistry 60 (2013) 451–455

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and evaluation of antibacterial activity of 7-alkyloxy-4,5-dihydro-imidazo[1,2-*a*]quinoline derivatives

Xian-Yu Sun [a,*], Rui Wu [a], Xiang Wen [b], Li Guo [a], Chang-Ping Zhou [a], Jian Li [a], Zhe-Shan Quan [b], Jun Bao [a,**]

[a] College of Animal Science and Technique, Bayi Agriculture University, Daqing 163319, Heilongjiang, PR China
[b] College of Pharmacy, Yanbian University, No. 1829, JuZi Street, Yanji 133000, Jilin, PR China

ARTICLE INFO

Article history:
Received 22 October 2012
Received in revised form
11 December 2012
Accepted 17 December 2012
Available online 26 December 2012

Keywords:
Synthesis
Imidazo[1,2-*a*]quinoline
Antibacterial activity

ABSTRACT

In this study, a series of 7-alkyloxy-4,5-dihydro-imidazo[1,2-*a*]quinoline derivatives was synthesized and tested for their antibacterial activity against various bacterial strains. Most of the compounds exhibited potential antibacterial activity against gram-negative and gram-positive bacteria. Compound **7p** (7-heptyloxy-4,5-dihydro-imidazo[1,2-*a*]quinoline) was found to be the most potent inhibitor. The minimum inhibitory concentration (MIC) of compound **7p** against *Escherichia coli* was 0.5 μg/mL, better than that of reference agent ciprofloxacin and amoxicillin. Furthermore, compound **7p** exhibited a modest activity against several gram-negative bacterial strains at a dose range of 2–64 μg/mL.

1. Introduction

Several antibiotics are widely prescribed for the treatment of respiratory tract infections; however, novel antimicrobial drugs remain in demand because of the increasing global prevalence of drug-resistant pathogens. Therefore, development of antibacterial compounds with novel structural features and activity against resistant pathogens is necessary.

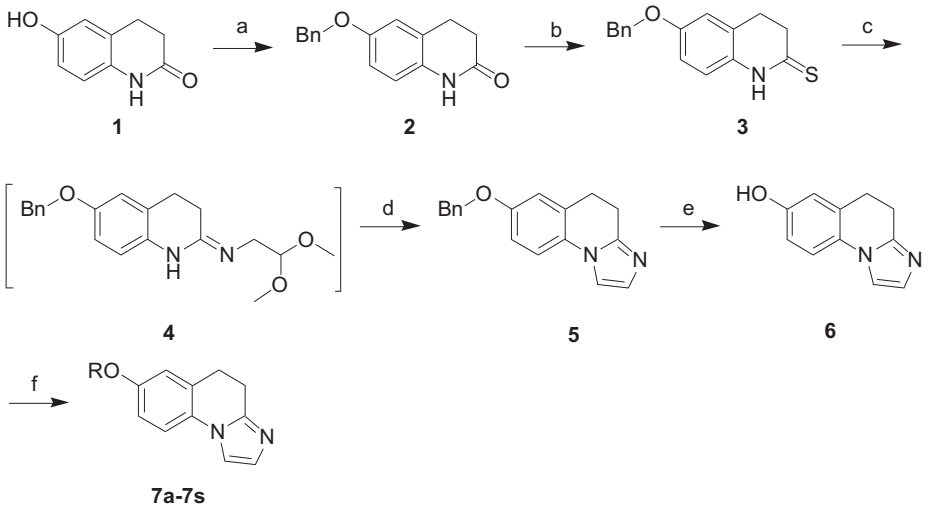
Quinoline derivatives have attracted considerable interest because of their diverse biological activities, such as antimicrobial [1], anti-depressant [2], anti-convulsant [3], antimalarial [4], and anti-inflammatory [5] activities. In our laboratory, we had prepared several quinoline-derived heterocyclic compounds [6–8], but none of them were found to possess antimicrobial active. Previous biological data have revealed that small heterocycles, e.g. imidazole [9], pyrazole [10], thiophene, and furane, can be beneficial substituents, resulting in increased biological activity [11,12]. These results encouraged us to investigate small heterocycles like imidazole, which would ultimately allow the introduction of a diverse set of substituted heterocycles to gain further knowledge of the structure–activity relationships. Therefore, to further investigate the activity of quinoline derivatives, we introduced an imidazole ring at the first and second positions of the quinoline ring and designed a novel series of imidazo[1,2-*a*]quinoline derivatives. Herein, we report the synthesis of 7-alkyloxy-4,5-dihydro-imidazo[1,2-*a*]quinoline derivatives and evaluation of their experimental antimicrobial activity in vitro.

2. Chemistry

We designed a series of 7-alkyloxy-4,5-dihydro-imidazo[1,2-*a*]quinoline derivatives (**7a**–**7s**) and synthesized them according to Scheme 1. Compound **3** was synthesized according to a method described previously [**2**]. The starting material 6-hydroxy-3,4-dihydro-2(1*H*)-quinolone (**1**) was treated with benzyl chloride in a solution of sodium hydroxide in ethanol to yield 6-alkoxy-3,4-dihydroquinolin-2(1*H*)-one (**2**). 6-Alkoxy-3,4-dihydroquinolin-2(1*H*)-thione (**3**) was prepared by the reaction of compound **2** with phosphorous pentasulphide in the presence of triethylamine in acetonitrile. Subsequently, thione **3** was treated with amino-acetaldehyde dimethyl acetal to yield intermediate **4**. Compound **4** was isolated and subsequently heated in acetic acid without any treating it with other reagents to yield compound **5**. Catalytic hydrogenation (Pd/C, H_2) of compound **5** provided the scaffold **6**. Finally, test derivatives were prepared by the reaction of scaffold **6** with an appropriate alkyl halide. All the synthesized compounds were confirmed by ^{1}H NMR, mass spectrometry, and elemental analyses.

* Corresponding author. Tel.: +86 459 6819198.
** Corresponding author. Tel./fax: +86 459 6819002.
E-mail addresses: sxianyu@163.com (X.-Y. Sun), jbao@neau.edu.cn (J. Bao).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2012.12.034



Scheme 1. Synthesis of target compounds **7a**–**7s**. (a) BnCl, NaOH, ethanol, reflux; (b) P_2S_5, TEA, CH_3CN, reflux; (c) aminoacetaldehyde dimethyl acetal, TEA, ethanol, reflux; (d) AcOH, 100 °C (e) H_2, Pd/C, ethanol, 60 °C; (f) RX, NaOH, DMF, 80 °C.

3. Results and discussions

All the synthesized compounds were screened for their in vitro antibacterial activity against gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli*. Minimum inhibitory concentrations (MIC) were determined using the serial dilution technique. We used ciprofloxacin and amoxicillin as reference compounds in the evaluation of antibacterial activity and measured the MIC in μmol/mL units.

As shown in Table 1, most of the synthesized compounds showed modest antibacterial activity in vitro against both gram-positive and gram-negative strains. Further, the results showed that the synthesized compounds exhibited a little stronger inhibitory activity against *E. coli* than against *S. aureus*.

A study of the data shown in Table 1 shows that all 20 test compounds exhibited antibacterial activity against *S. aureus* (MIC: 50–200 μg/mL). Among the benzyl-substituted derivatives, compound **5** with no substitution on the phenyl ring had a weaker activity against *S. aureus* than that of compounds **7a**–**7k** with different substitutions on the phenyl ring. This showed that the introduction of substitutions benefited the antibacterial activity against *S. aureus*. We found that the Br atom contributed more to the inhibitory activity against *S. aureus* than the F and Cl atoms. Compounds **7c**, **7f**, and **7i** inhibited *S. aureus* at 50 μg/mL. This indicated that the position of the halogen atom on the phenyl ring greatly influenced the antibacterial activity, with the *para*-substituted compounds being more active than the *ortho*- and *meta*-substituted compounds. Derivatives **7j** and **7k**, containing electron-donating groups (*p*-CH_3 and *p*-CH_3O), had MIC values against *S. aureus* of 50 μg/mL and 100 μg/mL, respectively. Thus, there was no significant difference between the activity of compounds containing electron-donating groups and those containing electron-withdrawing groups. Among compounds **7l**–**7s**, compounds **7p**, **7q**, and **7r** were moderately active against *S. aureus* at 50 μg/mL.

Table 1
Inhibitory activity[a] of compounds **5**, **7a**–**7s**, and controls against bacteria.

Compound	R	MIC[b] (μg/mL) vs. *S. aureus*	MIC[b] (μg/mL) vs. *E. coli*
5	$C_6H_5CH_2$	200	50
7a	(*o*-F)$C_6H_4CH_2$	150	50
7b	(*m*-F)$C_6H_4CH_2$	150	50
7c	(*p*-F)$C_6H_4CH_2$	50	50
7d	(*o*-Cl)$C_6H_4CH_2$	150	100
7e	(*m*-Cl)$C_6H_4CH_2$	150	50
7f	(*p*-Cl)$C_6H_4CH_2$	50	50
7g	(*o*-Br)$C_6H_4CH_2$	100	50
7h	(*m*-Br)$C_6H_4CH_2$	100	50
7i	(*p*-Br)$C_6H_4CH_2$	50	25
7j	(*p*-CH_3)$C_6H_4CH_2$	50	25
7k	(*p*-CH_3O)$C_6H_4CH_2$	100	50
7l	*n*-C_3H_7	150	50
7m	*n*-C_4H_9	150	50
7n	*n*-C_5H_{11}	100	50
7o	*n*-C_6H_{13}	75	16
7p	*n*-C_7H_{15}	50	0.5
7q	*n*-C_8H_{17}	50	25
7r	*n*-C_9H_{19}	50	50
7s	*n*-$C_{10}H_{21}$	100	50
Ciprofloxacin	–	16	1
Amoxicillin	–	25	150

[a] Anti-bacterial testing was carried out in triplicate.
[b] MIC values represent the average of 3 readings.

The synthesized compounds exhibited antibacterial activity against *E. coli* in the dose range of 0.5–100 μg/mL. Most of the compounds containing a substituted benzyl ring (**7a**–**7k**) exhibited antibacterial activity against *E. coli* at 50 μg/mL with compound **7i** (with *p*-Br substitution) and compound **7j** (with *p*-CH_3 substitution) active at 25 μg/mL. Furthermore, analysis of the inhibitory activity of compounds **7l**–**7s** against *E. coli* showed that the length of the alkyl chain appeared to have a direct impact on the antibacterial activity of the 7-alkyloxy-4,5-dihydro-imidazo[1,2-*a*] quinoline derivatives. As the alkyl chain length increased in the compounds starting from **7l** onwards, the MIC gradually decreased, with the compound **7p** (with an *n*-heptyl substituent) being the most active. However, this trend reversed when the alkyl chain consisted of more than 7 carbon atoms. Compound **7p** with an MIC value of 0.5 μg/mL against *E. coli* was the most potent inhibitor and showed better activity than that shown by the reference agents ciprofloxacin and amoxicillin.

In view of its promising antibacterial activity, compound **7p** was further evaluated against a range of gram-negative bacteria, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Salmonella*, and *Pasteurella*. These bacteria easily cause severe infection illness or food poisoning, and at the same time, they are widely applied to the antimicrobial activity screening experiments [13–16]. A study of the data in Table 2 showed that compound **7p** exhibited inhibitory activity against *P. aeruginosa*, *P.*

Table 2
Inhibitory activity[a] of compound **7p** and controls against gram-negative bacterial strains.

Gram-negative strains	**7p** (MIC,[b] μg/mL)	Amoxicillin (MIC,[b] μg/mL)	Ciprofloxacin (MIC,[b] μg/mL)
Pseudomonas aeruginosa	16	16	4
K. pneumoniae	>128	>128	4
Proteus vulgaris	16	>128	128
Salmonella	64	>128	>128
Pasteurella	2	16	128

[a] Anti-bacterial testing was carried out in triplicate.
[b] MIC values represent the average of 3 readings.

vulgaris, *Salmonella*, and *Pasteurella* at a dose of 64 μg/mL or less. The MIC of **7p** against *P. aeruginosa* was 16 μg/mL, which was similar to that of the control amoxicillin and weaker than that of ciprofloxacin (4 μg/mL). Both compound **7p** and amoxicillin did not exhibit antibacterial activity against *K. pneumoniae* at 128 μg/mL. Compound **7p** with an MIC value of 16 μg/mL was 8-fold more potent than the controls amoxicillin and ciprofloxacin against *P. vulgaris*. Furthermore, **7p** exhibited antibacterial activity against *Salmonella* at 64 μg/mL, whereas the two controls were inactive at 128 μg/mL. Notably, compound **7p** exhibited stronger inhibitory activity (MIC: 2 μg/mL) against *Pasteurella* than that of the controls amoxicillin (MIC: 16 μg/mL) and ciprofloxacin (MIC: 128 μg/mL).

The present study revealed that these bacterial effects were mainly influenced by lipid-hydro partition coefficient of the test compounds. Interestingly, all the reported compounds show better antibacterial activity against G^- bacteria than G^+ bacteria. For these effects may be somewhat specific, we hypothesized that the changes in cell wall permeability lead to dissipation of the potential. It is well-known that the cell wall of G^+ bacteria is mainly composed of a network structure formed by the peptidoglycan. While the cell wall of G^- bacteria consists of a lower content of the peptidoglycan, teichoic acid and a higher content of lipids. Moreover, affinity trapping of antibacterial molecules by the cell wall and clogging of the outer layers of peptidoglycan by bound antibacterial molecules were considered to be the mechanism of antibacterial resistance [17]. Yet the exact explanations on these antibacterial activities require an understanding of membrane packing, permeability, and partition behavior on a molecular basis.

4. Conclusions

We have synthesized a series of novel imidazo[1,2-*a*]quinoline derivatives and evaluated their antibacterial activity against gram-positive and gram-negative bacteria. Most of the compounds exhibited modest antibacterial activity against gram-negative bacteria except for compound **7p**. Compound **7p** with an MIC value of 0.5 μg/mL against *E. coli* was the most potent inhibitor and showed better activity than that shown by the reference agents ciprofloxacin and amoxicillin. This suggests that hybrid compounds containing quinoline and imidazole moieties may possess better antibacterial properties. The results of this evaluation suggest that further development of such compounds may be of therapeutic interest.

5. Experimental procedures

5.1. Chemistry

The reactions were monitored by thin layer chromatography (TLC) on silica gel plates precoated with F254. The developed plates were examined under a UV lamp (254 nm). Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded using AV-300 FT-NMR spectrometer (Bruker BioSpin AG, Fallanden, Switzerland). Chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were recorded on an HP1100LC/MSD electrospray ionization mass spectrometer (ESI-MS) (Agilent Technologies, Santa Clara, CA, USA). Elemental analyses were performed using a 204Q CHN Rapid Analyzer instrument (PerkinElmer, Fremont, CA). All chemicals were purchased from Sigma–Aldrich Chemical Corporation (Shanghai, China). All other chemicals were of analytical grade.

Intermediates **2** and **3** were synthesized according to the methods previously described in literature [2]. The detailed procedures for preparing compounds **4**–**7** are described below.

5.2. 7-Benzyloxy-4,5-dihydro-imidazo[1,2-a]quinoline (*5*)

A mixture of compound **3** (10 g, 37.2 mmol), 2,2-dimethoxyethylamine (3.9 g, 37.2 mmol), and DIPEA (15 mL) in ethanol (100 mL) was stirred and heated to reflux. After confirming the end of the reaction by TLC after 6 h, the reaction mixture was dried under reduced pressure to yield compound **4** as crude yellow oil.

A solution of compound **4** in acetic acid (50 mL) was stirred for 2 h at 100 °C. The reaction was cooled and evaporated to dryness under reduced pressure to give a dark solid that was dissolved in ethyl acetate (200 mL) and water (200 mL). The organic layer was separated and washed with water (200 mL) followed by brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by TLC on silica gel (ethyl acetate) to give **5** as a yellow solid (3.5 g; overall yield of 2 steps, 34.1%). M.p. 189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89–3.10 (m, 4H, H-4, H-5), 5.08 (s, 2H, $-OCH_2-$), 6.92–7.43 (m, 10H, H–Ar). MS (*m*/*z*): 277 (M + 1). Analyses Calcd. for $C_{18}H_{16}N_2O$: C, 78.24%; H, 5.84%; N, 10.14%. Found: C, 78.30%; H, 5.81%; N, 10.09%.

5.3. 7-Hydroxy-4,5-dihydro-imidazo[1,2-a]quinoline (*6*)

A mixture of compound **5** (3.5 g, 12.7 mmol) and Pd/C (1 g, 60% H_2O) in ethanol (50 mL) was stirred under an atmosphere of hydrogen for 6 h at 60 °C. After the solution was cooled, the reaction mixture was filtered and evaporated to give a moderate yield of compound **6**. The compound was used directly in the next step without further purification.

5.4. General synthetic procedure for target compounds *7a*–*7s*

To a solution of compound **6** (0.1 g, 0.54 mmol) and sodium hydroxide (0.032 g, 0.8 mmol) in DMF (10 mL) was added the relevant alkyl halide of equivalent molarity, and the mixture was stirred at 80 °C until the completion of the reaction, which was as confirmed by TLC. The reaction was cooled and evaporated to dryness in vacuum. Target compounds **7a**–**7s** were obtained after purification of the crude residues on a silica gel column (ethyl acetate). The yields, melting points, and spectral data for each compound are provided below.

5.4.1. 7-(2-Fluoro-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (*7a*)

Yield 85%; m.p. 189–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.95–3.09 (m, 4H, H-4, H-5), 5.05 (s, 2H, $-OCH_2-$), 6.92–7.57 (m, 9H, H–Ar). MS *m*/*z* 295 (M + 1). Anal. Calcd. for $C_{18}H_{15}FN_2O$: C, 73.45; H, 5.14; N, 9.52. Found: 73.51; H, 5.11; N, 9.49.

5.4.2. 7-(3-Fluoro-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (*7b*)

Yield 80%; m.p. 175–177 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.96–3.10 (m, 4H, H-4, H-5), 5.02 (s, 2H, $-OCH_2-$), 6.88–7.45 (m, 9H, H–

Ar). MS *m/z* 295 (M + 1). Anal. Calcd. for $C_{18}H_{15}FN_2O$: C, 73.45; H, 5.14; N, 9.52. Found: 73.51; H, 5.12; N, 9.48.

*5.4.3. 7-(4-Fluoro-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7c**)*

Yield 86%; m.p. 167–169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.96–3.12 (m, 4H, H-4, H-5), 5.04 (s, 2H, $-OCH_2-$), 6.91–7.41 (m, 9H, H–Ar). MS *m/z* 295 (M + 1). Anal. Calcd. for $C_{18}H_{15}FN_2O$: C, 73.45; H, 5.14; N, 9.52. Found: 73.50; H, 5.12; N, 9.49.

*5.4.4. 7-(2-Chloro-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7d**)*

Yield 79%; m.p. 178–180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.97–3.09 (m, 4H, H-4, H-5), 5.14 (s, 2H, $-OCH_2-$), 6.95–7.50 (m, 9H, H–Ar). MS *m/z* 311 (M + 1), 313 (M+3). Anal. Calcd. for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.62; H, 4.83; N, 8.98.

*5.4.5. 7-(3-Chloro-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7e**)*

Yield 88%; m.p. 166–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.95–3.08 (m, 4H, H-4, H-5), 5.09 (s, 2H, $-OCH_2-$), 6.88–7.52 (m, 9H, H–Ar). MS *m/z* 311 (M + 1), 313 (M + 3). Anal. Calcd. for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.61; H, 4.84; N, 8.97.

*5.4.6. 7-(4-Chloro-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7f**)*

Yield 79%; m.p. 161–163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.93–3.11 (m, 4H, H-4, H-5), 5.11 (s, 2H, $-OCH_2-$), 6.94–7.48 (m, 9H, H–Ar). MS *m/z* 311 (M + 1), 313 (M + 3). Anal. Calcd. for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.63; H, 4.84; N, 8.99.

*5.4.7. 7-(2-Bromo-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7g**)*

Yield 85%; m.p. 192–194 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.99–3.10 (m, 4H, H-4, H-5), 5.15 (s, 2H, $-OCH_2-$), 6.93–7.62 (m, 9H, H–Ar). MS *m/z* 355 (M + 1), 357 (M + 3). Anal. Calcd. for $C_{18}H_{15}BrN_2O$: C, 60.86; H, 4.26; N, 7.89. Found: C, 60.90; H, 4.24; N, 7.86.

*5.4.8. 7-(3-Bromo-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7h**)*

Yield 73%; m.p. 181–183 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.92–3.07 (m, 4H, H-4, H-5), 5.19 (s, 2H, $-OCH_2-$), 6.91–7.58 (m, 9H, H–Ar). MS *m/z* 355 (M + 1), 357 (M + 3). Anal. Calcd. for $C_{18}H_{15}BrN_2O$: C, 60.86; H, 4.26; N, 7.89. Found: C, 60.91; H, 4.23; N, 7.84.

*5.4.9. 7-(4-Bromo-benzyloxy)-4,5-dihydro-imidazo[1,2-a]quinoline (**7i**)*

Yield 78%; m.p. 172–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.96–3.10 (m, 4H, H-4, H-5), 5.02 (s, 2H, $-OCH_2-$), 6.85–7.54 (m, 9H, H–Ar). MS *m/z* 355 (M + 1), 357 (M + 3). Anal. Calcd. for $C_{18}H_{15}BrN_2O$: C, 60.86; H, 4.26; N, 7.89. Found: C, 60.92; H, 4.22; N, 7.83.

*5.4.10. 7-(4-Methyl-benzyloxy)-4,5-dihydro-imidazo[1,2-a] quinoline (**7j**)*

Yield 89%; m.p. 161–163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45 (s, 3H, $-CH_3$), 2.96–3.10 (m, 4H, H-4, H-5), 5.07 (s, 2H, $-OCH_2-$), 6.88–7.47 (m, 9H, H–Ar). MS *m/z* 291 (M + 1). Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.65; H, 6.21; N, 9.60.

*5.4.11. 7-(4-Methyloxy-benzyloxy)-4,5-dihydro-imidazo[1,2-a] quinoline (**7k**)*

Yield 87%; m.p. 177–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.95–3.09 (m, 4H, H-4, H-5), 3.83 (s, 3H, $-OCH_3$), 5.03 (s, 2H, $-OCH_2-$), 6.88–7.38 (m, 9H, H–Ar). MS *m/z* 307 (M + 1). Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.55; H, 5.89; N, 9.07.

*5.4.12. 7-Propoxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7l**)*

Yield 74%; m.p. 108–110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98–1.03 (t, 3H, $-CH_3$), 1.82–1.85 (m, 2H, $-CH_2-$), 2.96–3.09 (m, 4H, H-4, H-5), 3.94–3.97 (t, 2H, $-OCH_2-$), 6.85–7.37 (m, 5H, H–Ar). MS *m/z* 229 (M + 1). Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.72; H, 7.01; N, 12.23.

*5.4.13. 7-Butoxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7m**)*

Yield 83%; m.p. 117–119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.97–1.02 (t, 3H, $-CH_3$), 1.48–1.55 (m, 2H, $-CH_2-$), 1.80–1.83 (m, 2H, $-CH_2-$), 2.98–3.10 (m, 4H, H-4, H-5), 3.96–4.00 (t, 2H, $-OCH_2-$), 6.81–7.32 (m, 5H, H–Ar). MS *m/z* 243 (M + 1). Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.41; H, 7.46; N, 11.51.

*5.4.14. 7-Pentoxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7n**)*

Yield 89%; m.p. 135–137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92–0.97 (t, 3H, $-CH_3$), 1.34–1.83 (m, 6H, $-(CH_2)_3-$), 2.96–3.13 (m, 4H, H-4, H-5), 3.91–3.96 (t, 2H, $-OCH_2-$), 6.81–7.47 (m, 5H, H–Ar). MS *m/z* 257 (M + 1). Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.04; H, 7.82; N, 10.88.

*5.4.15. 7-Hexyloxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7o**)*

Yield 80%; m.p. 126–128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92–0.99 (t, 3H, $-CH_3$), 1.32–1.79 (m, 8H, $-(CH_2)_4-$), 2.98–3.15 (m, 2H, H-4, H-5), 3.93–3.99 (t, 2H, $-OCH_2-$), 6.90–7.44 (m, 5H, H–Ar). MS *m/z* 271 (M + 1). Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.59; H, 8.15; N, 10.30.

*5.4.16. 7-Heptyloxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7p**)*

Yield 90%; m.p. 119–121 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87–0.94 (t, 3H, $-CH_3$), 1.35–1.88 (m, 10H, $-(CH_2)_5-$), 2.96–3.14 (m, 2H, H-4, H-5), 3.93–3.98 (t, 2H, $-OCH_2-$), 6.92–7.50 (m, 5H, H–Ar). MS *m/z* 285 (M + 1). Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.09; H, 8.47; N, 9.82.

*5.4.17. 7-Octyloxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7q**)*

Yield 76%; m.p. 109–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88–0.90 (s, 3H, $-CH_3$), 1.27–1.56 (m, 10H, $-(CH_2)_5-$), 1.76–1.84 (m, 2H, $-CH_2-$), 2.96–3.10 (m, 4H, H-4, H-5), 3.95–4.00 (t, 2H, $-OCH_2$), 6.81–7.37 (m, 4H, H–Ar). MS *m/z* 299 (M + 1). Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.55; H, 8.73; N, 9.35.

*5.4.18. 7-Nonoxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7r**)*

Yield 83%; m.p. 88–100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.89 (s, 3H, $-CH_3$), 1.22–1.57 (m, 12H, $-(CH_2)_6-$), 1.74–1.87 (m, 2H, $-CH_2-$), 2.97–3.12 (m, 4H, H-4, H-5), 3.97–4.02 (t, 2H, $-OCH_2$), 6.88–7.42 (m, 4H, H–Ar). MS *m/z* 313 (M + 1). Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.95; H, 8.99; N, 8.91.

*5.4.19. 7-Decoxy-4,5-dihydro-imidazo[1,2-a]quinoline (**7s**)*

Yield 89%; m.p. 84–86 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.87 (s, 3H, $-CH_3$), 1.22–1.85 (m, 16H, $-(CH_2)_8-$), 2.93–3.09 (m, 4H, H-4, H-5), 3.98–4.07 (t, 2H, $-OCH_2$), 6.82–7.36 (m, 4H, H–Ar). MS *m/z* 327 (M + 1). Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.26; H, 9.26; N, 8.58. Found: C, 77.32; H, 9.226; N, 8.53.

5.5. Evaluation of antibacterial activity in vitro

MIC values of compounds **5** and **7a**–**7s** against several bacterial strains were measured using the broth microdilution method in 96-

well plates [18]. The microorganisms used in the present study were as follows: *S. aureus* (ATCC 29213), *E. coli* (ATCC 8739), *P. aeruginosa* (ATCC 27853), *K. pneumoniae* (ATCC 10031), *P. vulgaris* (ATCC 35659), *Salmonella* (ATCC 14028), and *Pasteurella* (ATCC 6529). Test compounds dissolved in DMSO were added to the culture medium Mueller–Hinton broth (MHB; G-S Biotech. Shanghai, China) to obtain final concentrations of 0.5–64 mg/mL. The final bacterial concentration was approximately 105 CFU/mL. MIC values were measured after incubation for 20 h at 37 °C. MIC was defined as the lowest concentration of test sequences that completely inhibited the growth. Ciprofloxacin and amoxicillin were used as controls and assayed under identical conditions. All experiments were performed in triplicates.

Acknowledgment

We are grateful for the financial support from the Heilongjiang Young College Academic Backbone Project (1252G041), Animal Good Farming Innovation Team Project (2010TD05), and the Doctoral Research Start Foundation (B2011-10) of Heilongjiang Bayi Agriculture University.

References

[1] E. Rajanarendar, M. Nagi Reddy, S. Rama Krishna, K. Rama Murthy, Y.N. Reddy, M.V. Rajam, Eur. J. Med. Chem. 55 (2012) 273–283.
[2] X.-Y. Sun, X.-J. He, C.-Y. Pan, Y.-P. Liu, Y.-P. Zou, Med. Chem. Res. 21 (2012) 3692–3698.
[3] L.-P. Guan, Q.-H. Jin, S.-F. Wang, F.-N. Li, Z.-S. Quan, Arch. Pharm. (Weinheim) 341 (2008) 774–779.
[4] D.D. N'Da, J.C. Breytenbach, P.J. Smith, C. Lategan, Arzneimittelforschung 60 (2010) 627–635.
[5] A.B. El-Gazzar, M.M. Youssef, A.M. Youssef, A.A. Abu-Hashem, F.A. Badria, Eur. J. Med. Chem. 44 (2009) 609–624.
[6] C.-X. Wei, X.-Q. Deng, K.-Y. Chai, Z.-G. Sun, Z.-S. Quan, Arch. Pharm. Res. 33 (2010) 655–662.
[7] H.-J. Wang, C.-X. Wei, X.-Q. Deng, F.-L. Li, Z.-S. Quan, Arch. Pharm. (Weinheim) 342 (2009) 671–675.
[8] X.-Y. Sun, L. Zhang, C.-X. Wei, H.-R. Piao, Z.-S. Quan, Eur. J. Med. Chem. 44 (2009) 1265–1270.
[9] M.T. Chhabria, M.H. Jani, Eur. J. Med. Chem. 44 (2009) 3837–3844.
[10] P.K. Sahu, P.K. Sahu, S.K. Gupta, D. Thavaselvam, D.D. Agarwal, Eur. J. Med. Chem. 54 (2012) 366–378.
[11] E. Chorell, J.S. Pinkner, G. Phan, S. Edvinsson, F. Buelens, H. Remaut, G. Waksman, S.J. Hultgren, F. Almqvist, J. Med. Chem. 53 (2010) 5690–5695.
[12] E. Chorell, J.S. Pinkner, C. Bengtsson, T. Sainte-Luce Banchelin, S. Edvinsson, A. Linusson, S.J. Hultgren, F. Almqvist, Bioorg. Med. Chem. 20 (2012) 3128–3142.
[13] S.L. Iconaru, A.M. Prodan, M. Motelica-Heino, S. Sizaret, D. Predoi, Nanoscale Res. Lett. 7 (2012) 576–583.
[14] K. Poole, K. Krebes, C. McNally, S. Neshat, J. Bacteriol. 175 (1993) 7363–7372.
[15] V.K. Tandon, S. Kumar, N.N. Mishra, P.K. Shukla, Eur. J. Med. Chem. 56 (2012) 375–386.
[16] T.N. Akhaja, J.P. Raval, Eur. J. Med. Chem. 46 (2011) 5573–5579.
[17] L.-Z. Cui, H. Murakami, K. Kuwahara-Arai, H. Hanaki, H. Keiichi, Antimicrob. Agents Chemother. 44 (2000) 2276–2285.
[18] National Committee for Clinical Laboratory Standards (NCCLs), Standard Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, Which Grows Aerobically, National Commitee of Laboratory Standards, Villanova, 1982, p. 242.