High Performance Liquid Chromatography Enantioseparation of the Novel Designed Mexiletine Derivatives and Its Analogs

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ABSTRACT A series of novel designed mexiletine derivatives and its analogs were prepared, the structures were confirmed by Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR), and Electrospray Ionization-Mass Spectrometry (ESI-MS), and the enantioseparations were performed on polysaccharide-based chiral stationary phase (CSP), Chiralcel OD-H, and Chiralcel OJ-H, under normal-phase mode. The effects of the concentration of isopropanol in the mobile phase were studied, seven of the eight enantiomers got baseline separation on Chiralcel OD-H, and five of the eight enantiomers got successfully separation on Chiralcel OJ-H. The effects of structural features were also discussed. *Chirality 23:99–104, 2011.*

KEY WORDS: synthesis; enantioseparation; HPLC; mexiletine; derivatives

INTRODUCTION

As the enantiomers of a chiral drug candidate often have differences in their pharmacokinetic, physiological, toxicological, and metabolic activities, the enantiomeric purity of a chiral drug became an important issue for both pharmaceutical industry and regulatory agencies.[1] Therefore, chiral separations are becoming increasingly important.

Mexiletine, [1-(2,6-dimethylphenoxy)-2-amino-propane], which is classified as a Class Ib antiarrhythmic drug widely used in the treatment of ventricular tachyarrhythmias, is clinically used in its racemic form.[2] At the same time, a narrow therapeutic ratio[3] and many adverse effects of mexiletine may occur at cardiac and central nervous system levels upon chronic treatments.[4,5] However, mexiletine derivatives or analogs can solve some of these problems, such as present a wider therapeutic ratio, being more selectively active on hyperexcited tissues,[6] etc. In recent years, some mexiletine derivatives or analogs have been reported. Desaphy et al. reported that two myotonia causing mutants of the human skeletal muscle Na^+ channel showed different sensitivity to mexiletine and its derivatives.[7] Li et al. reported that a pyrroline derivative of mexiletine offered marked protection against ischemia-/reperfusion-induced myocardial contractile dysfunction.[8] Clark reported that mexiletine derivatives could be used a medicaments for pain.[9]

The derivatives of drugs can give therapeutic advantages in improving drug delivery, solubility, and bioavailability.[10,11] In this article, a series of (*R,S*)-*N*-mexiletine derivatives with different length of the alkyl chain (Figs. 1a–1h) were synthesized. The enantioseparations were investigated on Chiralcel OD-H and Chiralcel OJ-H column. The influences of isopropanol concentration and structure on the chromatographic resolution were studied.

EXPERIMENTAL

Chemicals and Reagents

(*R,S*)-Mexiletine hydrochloride was purchased from Jiangsu Jintan Yabang Pharmaceutical Co. Ltd (Changzhou, China), (*R,S*)-1-methyl-3-phenylpropylamine, and (*R,S*)-1-phenylethylamine were purchased from Sigma (USA). Divinyl adipate, divinyl azelate, and divinyl sebacate were produced and purified as described in the literature.[12] Vinyl acetate and all solvents were of analytical grade or chromatographic grade.

Apparatus

The ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane as internal standard using a Bruker AMX 400 MHz spectrometer at 400 and 100 MHz, respectively. Infrared spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. Mass spectrometric data were obtained on Bruker ESI-MS measurements.

Sample Preparation

Preparation of Sample a, b, c, g, and h. The reaction mixture, including (*R,S*)-mexiletine hydrochloride (1 mmol), divinyl dicarboxylates (4 mmol), toluene (5 ml) and sodium methoxide (0.1 mmol), was stirred at refluxed temperature for 12 h. Formation of (*R,S*)-*N*-mexiletine vinyl ester derivatives was monitored by Thin-Layer Chromatography (TLC). The products were purified by silica gel chromatography with an eluent consisting of petroleum ether/ethyl acetate 7:3 (v/v) and characterized by Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR), and Electrospray Ionization-Mass Spectrometry (ESI-MS). The reaction and separation method of Sample **g** and **h** was the same with the preparation of Sample **a**, **b** and **c**.

Additional Supporting Information may be found in the online version of this article.

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The reaction time of Sample **a** was 12 h and the yield was 67%. IR (KBr): 3297 (—NH—), 1756 (O—C=O), and 1646 (HN—C=O and C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (m, 1H, =CH—), 7.00–6.89 (m, 3H, Ar-H), 5.95 (d, 1H, NH), 4.85 (m, 1H, $=CH_2$), 4.55 (m, 1H, $=CH_2$), 4.33 (m, 1H, —CH—), 3.80–3.68 (dd, 2H, O—CH_2—), 2.40 (t, 2H, —CH_2—), 2.22 (d, 8H, Ar—CH_3 and —CH_2—), 1.69 (m, 4H, —CH_2—), 1.38 (d, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 171.7(HN—C=O), 170.4 (O—C=O), 154.8 (Ar—O), 141.0 (O—C=), 130.6, 128.9, 124.0 (Ar—C), 97.6 (=CH_2), 73.8 (O—CH_2—), 45.3 (HN—CH—), 36.3, 33.5, 24.9, 24.1 (—CH_2—), 17.7 (—CH_3), 16.1 (Ar—CH_3). ESI-MS *m/z*: 356.0 $[M + Na]^+$.

The reaction time of Sample **b** was 12 h and the yield was 65%. IR (KBr): 3295 (—NH—), 1756 (O—C=O), and 1646 (HN—C=O and C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 1H, =CH—), 7.01–6.91 (m, 3H, Ar—H), 5.89 (d, 1H, —NH—), 4.85 (m, 1H, $=CH_2$), 4.55 (m, 1H, $=CH_2$), 4.34 (m, 1H, —CH—), 3.81–3.70 (dd, 2H, O—CH_2—), 2.36 (t, 2H, —CH_2—), 2.26 (s, 6H, Ar—CH_3), 2.19 (t, 2H, —CH_2—), 1.64 (t, 4H, —CH_2—), 1.39 (t, 3H, —CH_3), 1.35 (s, 6H, —CH_2—). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 172.3 (HN—C=O), 170.7 (—C=O), 154.8 (Ar—O), 141.1 (O—C=), 130.6, 128.9, 124.0 (Ar—C), 97.4 (=CH_2), 73.9 (O—CH_2—), 45.1 (HN—CH—), 36.8, 33.8, 29.0, 28.9, 28.7, 25.5, 24.4 (—CH_2—), 17.8 (—CH_3), 16.1 (Ar—CH_3). ESI-MS *m/z*: 398.1 $[M + Na]^+$.

The reaction time of Sample **c** was 12 h and the yield was 62%. IR (KBr): 3294 (—NH—), 1756 (O—C=O), and 1646 (HN—C=O and C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 1H, =CH—), 7.00–6.90 (m, 3H, Ar—H), 5.90 (d, 1H, —NH—), 4.85 (m, 1H, $=CH_2$), 4.54 (m, 1H, $=CH_2$), 4.36 (s, 1H, —CH—), 3.80–3.69 (dd, 2H, O—CH_2—), 2.35 (t, 2H, —CH_2—), 2.25 (s, 6H, Ar—CH_3), 2.18 (t, 2H, —CH_2—), 1.63 (t, 4H, —CH_2—), 1.39 (t, 3H, —CH_3), 1.32 (s, 8H, —CH_2—). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 172.3 (HN—C=O), 170.8 (O—C=O), 154.8 (Ar—O), 141.0 (O—C=), 130.6, 128.9, 124.0 (Ar—C), 97.4 (=CH_2), 73.9 (O—CH_2—), 45.1 (HN—CH—), 36.8, 33.8, 29.1, 29.0, 28.9, 28.9, 25.6, 24.5 (—CH_2—), 17.8 (—CH_3), 16.1 (Ar—CH_3). ESI-MS *m/z*: 412.1 $[M + Na]^+$.

The reaction time of Sample **g** was 12 h and the yield was 44%. IR (liquid film, cm^{-1}): 3290 (—NH—), 1755 (O—C=O), and 1645 (HN—C=O and C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.16 (m, 6H, =CH— and Ar-H), 5.40 (d, 1H, —NH—), 4.86 (d, 1H, $=CH_2$), 4.56 (d, 1H, $=CH_2$), 4.02 (m, 1H, —CH—), 2.62 (t, 2H, Ar—CH_2—), 2.40 (t, 2H, —CH_2—), 2.13 (t, 2H, —CH_2—), 1.79—1.63 (m, 6H, —CH_2—), 1.16 (d, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 171.6 (HN—C=O), 170.5 (O—C=O), 141.7 (O—C=), 141.0, 128.4, 128.3, 125.8 (Ar-C), 97.7 (=CH_2), 45.1 (HN—CH—), 38.5, 36.3, 33.5, 32.5, 25.0, 24.0 (—CH_2—), 15.2 (—CH_3). ESI-MS *m/z*: 326.1 $[M + Na]^+$.

The reaction time of Sample **h** was 12 h and the yield was 38%. IR (KBr): 3290 (—NH—), 1755 (O—C=O), and 1645 (HN—C=O and C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (m, 6H, =CH— and Ar-H), 5.88 (s, 1H, —NH—), 5.12 (m, 1H, Ar-CH—), 4.87 (m, 1H, $=CH_2$), 4.57 (m, 1H, $=CH_2$), 2.39 (t, 2H, —CH_2—), 2.17 (t, 2H, —CH_2—), 1.69 (s, 4H, —CH_2—), 1.48 (d, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 171.4 (HN—C=O), 170.5 (O—C=O), 143.3 (Ar-C), 141.1 (O—C=), 128.6, 127.3, 126.1 (Ar-C), 97.7 (=CH_2), 48.7 (HN—CH—), 36.2, 33.5, 24.9, 24.0 (—CH_2—), 21.7 (—CH_3). ESI-MS *m/z*: 298.1 $[M + Na]^+$.

Preparation of Sample d. The method of preparation of Sample **d** was according to the literature.[13] The reaction was controlled with TLC using petroleum ether/ethyl acetate 7:3 (v/v). The structure of product was confirmed by NMR, FTIR and ESI-MS.

The reaction time of Sample **d** was 5 h and the yield was ≥80%. IR (KBr): 3276 (—NH—) and 1649 (HN—C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00–6.90 (m, 3H, Ar-H), 5.97 (d, 1H, —NH—), 4.33 (m, 1H, —CH—), 3.81–3.68 (dd, 2H, O—CH_2—), 2.25 (s, 6H, Ar—CH_3), 2.02 (s, 3H, —$COCH_3$), 1.38 (d, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 169.5 (HN—C=O), 154.7 (Ar-O), 130.6, 128.9, 124.0 (Ar-C), 73.7 (O—CH_2—), 45.3 (HN—CH—), 23.4, 17.7 (—CH_3), 16.0 (Ar-CH_3). ESI-MS *m/z*: 243.9 $[M + Na]^+$.

Preparation of Sample e and f. The method of preparation of Samples **e** and **f** was according to the literature.[14] The reaction was controlled with TLC using petroleum ether/ethyl acetate 3:1 (v/v). Products were characterized by NMR, FTIR, and ESI-MS.

The reaction time of Sample **e** was 12 h and the yield was 83%. IR (KBr): 3304 (—NH—) and 1644 (HN—C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00–6.90 (m, 3H, Ar-H), 5.93 (d, 1H, —NH—), 4.35 (m, 1H, —CH—), 3.80–3.68 (dd, 2H, O—CH_2—), 2.25 (s, 6H, Ar-CH_3), 2.21–2.18 (t, 2H, —$COCH_2$), 1.66–1.61 (q, 2H, —CH_2—), 1.29–1.10 (dd, 8H, —CH_2—), 1.38 (d, 3H, —CH_3), 0.88–0.85 (t, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 172.4 (HN—C=O), 154.7 (Ar-O), 130.7, 128.9, 124.0 (Ar-C), 73.9 (O—CH_2—), 45.1 (HN—CH—), 36.9, 31.6, 29.2, 29.0, 25.7, 22.5(—CH_2—), 17.8, 16.0 (—CH_3), 14.0 (Ar-CH_3). ESI-MS *m/z*: 328.1 $[M + Na]^+$.

The reaction time of Sample **f** was 12 h and the yield was 81%. IR (KBr): 3305 (—NH—) and 1644 (HN—C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00–6.90 (m, 3H, Ar-H), 5.91 (d, 1H, —NH—), 4.35 (m, 1H, —CH—), 3.80–3.68 (dd, 2H, —O—CH_2—), 2.25 (s, 6H, Ar—CH_3), 2.21–2.18 (t, 3H, —$COCH_2$—), 1.24 (t, 22H, —CH_2—), 1.38 (s, 3H, —CH_3), 0.88–0.85 (t, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): ppm 172.4 (HN—C=O), 154.7 (Ar-O), 130.7, 128.9, 124.0 (Ar-C), 73.9 (O—CH_2—), 45.1 (HN—CH—), 36.9, 31.8, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 25.7, 22.6 (—CH_2—), 17.8, 16.1 (—CH_3), 14.1 (Ar-CH_3). ESI-MS *m/z*: 412.1 $[M + Na]^+$.

Chromatography

The chromatographic experiments were performed using an Agilent 1100 HPLC system (Agilent, USA) equipped with a quaternary pump and a diode-array detector at room temperature. The columns used were: Chiralcel OD-H (cellulose tris-3,5-dimethylphenylcarbamate) and Chiralcel OJ-H (cellulose tris-4-methyl-benzoate) from Daicel Chemical Industries (Tokyo, Japan). The mobile phase

compositions were 10%, 20% and 30% of isopropanol in *n*-hexane. The samples were dissolved in isopropanol. All solvents and mobile phase were filtered by 0.45 μm filter membrane. The flow rate was 1.0 ml/min. UV detection was performed at 220 nm. The results were summarized in Table 1.

RESULTS AND DISCUSSION

The Influence of Isopropanol Concentration on Enantioseparation

From Table 1, it was evident that the retention factors (k') and the resolutions (R_s) of all samples were increased with the decreasing isopropanol concentration in the mobile phase on both columns, whereas the separation factors (α) decreased on Chiralcel OD-H and increased on Chiralcel OJ-H. When the content of isopropanol was reduced, the polarity of the mobile phase decreased, the strength and number of hydrogen bonds between solutes and stationary phase increased, the eluting ability of mobile phase decreased, then the retention factors (k') and the resolutions (R_s) increased.

Notably, the enantioselectivity on Chiralcel OD-H column was essentially unchanged when the isopropanol concentration ranged from 10% to 30% (Table 1). It indicated that, within a certain range of isopropanol concentration and at a constant temperature, the conformation of Chiralcel OD-H and the selective adsorption sites were not affected by the isopropanol concentration. But when the concentration of isopropanol overstepped a certain range, the polarity alteration of mobile phase affected the nature of chiral stationary phase (CSP) discrimination. It was also possible that enantiomeric separation was a result of more than one type of interaction. For example, the enantioselectivity of the first group of samples on Chiralcel OJ-H was from baseline to partial resolved when the content of isopropanol increased from 10% to 20% (Table 1).

TABLE 1. Effects of the concentration of *n*-hexane and isopropanol on enantioseparation

Sample	Mobile phase Hex/IPA (v/v)	Chiralcel OD-H			Chiralcel OJ-H		
		k'_1	α	R_s	k'_1	α	R_s
a	70:30	0.67	2.75	6.13	0.40	1.28	0.69
	80:20	1.14	2.63	6.40	0.76	1.34	1.29
	90:10	3.12	2.26	6.83	2.09	1.45	2.44
b	70:30	0.58	3.60	7.31	0.30	1.31	0.47
	80:20	1.04	3.24	8.22	0.58	1.38	1.10
	90:10	2.72	2.78	8.28	1.60	1.48	2.15
c	70:30	0.53	3.61	6.97	0.26	1.34	0.35
	80:20	0.97	3.23	7.83	0.50	1.43	1.10
	90:10	2.51	2.73	7.64	1.38	1.55	2.17
d	70:30	0.45	2.47	3.64	0.20	1.00	–
	80:20	0.82	2.23	4.20	0.37	1.34	0.51
	90:10	1.97	2.03	4.87	1.00	1.41	1.34
e	70:30	0.27	4.29	4.54	0.06	1.00	–
	80:20	0.49	3.59	5.77	0.14	1.00	–
	90:10	1.05	3.07	6.72	0.37	1.25	0.10
f	70:30	0.21	4.72	4.09	0.03	1.00	–
	80:20	0.39	3.78	4.97	0.05	1.00	–
	90:10	0.90	3.23	6.36	0.17	1.00	–
g	70:30	0.70	1.61	2.65	0.79	1.00	–
	80:20	1.34	1.57	3.35	1.66	1.00	–
	90:10	4.01	1.49	3.71	5.27	1.08	0.63
h	70:30	0.81	1.00	–	0.69	1.10	0.21
	80:20	1.59	1.00	–	1.41	1.12	0.75
	90:10	4.63	1.04	0.22	4.48	1.14	1.22

k' is the retention factor; α is separation factor; R_s is resolution. Flow rate: 1.0 ml/min; absorbance wavelength: 220 nm.

The Influence of the Structure on Enantioseparation

As seen from Figure 1, the structures of the compounds examined were similar, all had a chiral center connected directly to a methyl ($-CH_3$) group, aminocarbonyl group, and 2,6-dimethylphenoxy or phenyl group. The samples were divided into three groups according to their structures. The first group included the Samples **a–c**, which contains a vinyl group at the terminal and different chain length. Group 2 comprised the Samples **d–f** without the terminal vinyl group compared with the first group of samples. The Samples **a**, **g** and **h**, containing the terminal vinyl group, the same chain length and different matrix, formed Group 3.

It was well known that the CSP of Chiralcel OD-H contains cellulose *tris*-3,5-dimethylphenylcarbamate as chiral selector offers additional hydrogen-bonding sites for selector-sample interactions compared with the 4-methylbenzoate substituents on Chiralcel OJ-H. Therefore, Chiralcel OD-H, in general, exhibited higher chiral resolving ability compared with Chiralcel OJ-H for numerous samples.[15,16] This trend was also confirmed in the present study (Table 1, Figs. 2, 3 and the Supporting Information). The enantiomers of seven samples were baseline resolved on Chiralcel OD-H and three got baseline separation on Chiralcel OJ-H. The enatiomeric recognition ability of Chiralcel OD-H toward the eight samples in descending order was **b** > **c** > **a** > **e** > **f** > **d** > **g** > **h** and on Chiralcel OJ-H was **a** > **c** > **b** > **d** > **h** > **g** > **e** > **f**. The retention behavior of the CSP toward the samples was not related with enantiomeric recognition ability. Among the samples, Sample **h** showed the strongest retention on Chiralcel OD-H and only gave little separation. In ascending order, the retention factor was **f** < **e** < **d** < **c** < **b** < **a** < **g** < **h** on Chiralcel OD-H and **f** < **e** < **d** < **c** < **b** < **a** < **h** < **g** on Chiralcel OJ-H.

For the first and second group of samples, the retention factors decreased with the increasing alkyl chain length on both Chiralcel OD-H and OJ-H column. It was probably due to the fact that chiral recognition involved a different stability in transient diastereomeric complexes between the enantiomers and the CSP, and a fit of the asymmetric sample into a chiral groove of the CSP.[17–22] Other potential interactions, including π–π interactions, dipole–dipole interactions and Van der Waals interactions, had significant impact on retention and enantioselectivity.

At the same time, Chiralcel OD-H had carbamate group whereas Chiralcel OJ-H had ester group. The carbonyl and amino groups of the carbamate function were considered to be a sort of Lewis acid and base, respectively. Introduction of an electron-withdrawing atom or group on the phenyl group can enhance the acidity of the hydrogen on the amino group, which can lead to a stronger hydro-

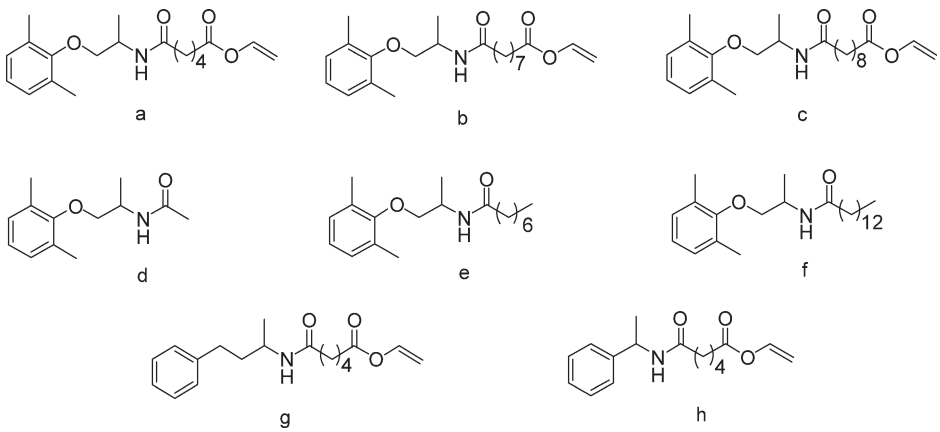

Fig. 1. Structures of the racemic samples. *N*-mexiletine vinyladipoyl ester (**a**), *N*-mexiletine vinylazeloyl ester (**b**), *N*-mexiletine vinylsebacoyl ester (**c**), *N*-mexiletine acetyl ester (**d**), *N*-mexiletine octanoyl ester (**e**), *N*-mexiletine myristoyl ester (**f**), *N*-1-methyl-3-phenylpropylamine vinyladipoyl ester (**g**) and *N*-1-phenylethylamine vinyladipoyl ester (**h**).

gen bonding interaction with Lewis basic parts of samples. The samples **a, b, c, g** and **h** had ester group, whereas the Samples **d, e** and **f** only had alkyl line connect with amide group. With the increase of CH_2 group in the molecular, the polarity decreased and the steric effects increased, leading to decreased interactions and retention factor. It was also suggested that flexibility and steric adaptability may play an important role in the enantiosepa-

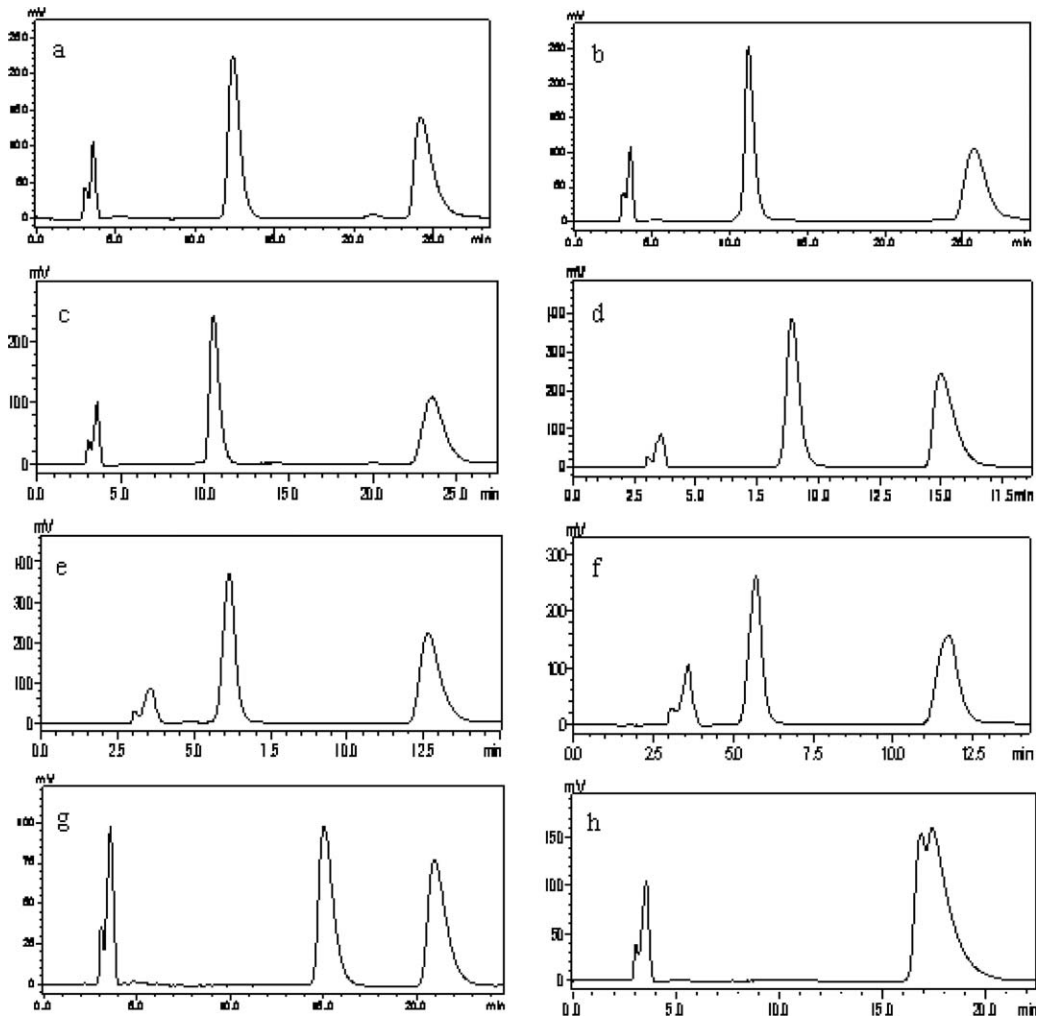

Fig. 2. Chromatograms of the chiral separation of Samples **a–h** on Chiralcel OD-H column using the mobile phase of *n*-hexane/isopropanol 90:10 (v/v); flow rate: 1.0 ml/min; absorbance wavelength: 220 nm.

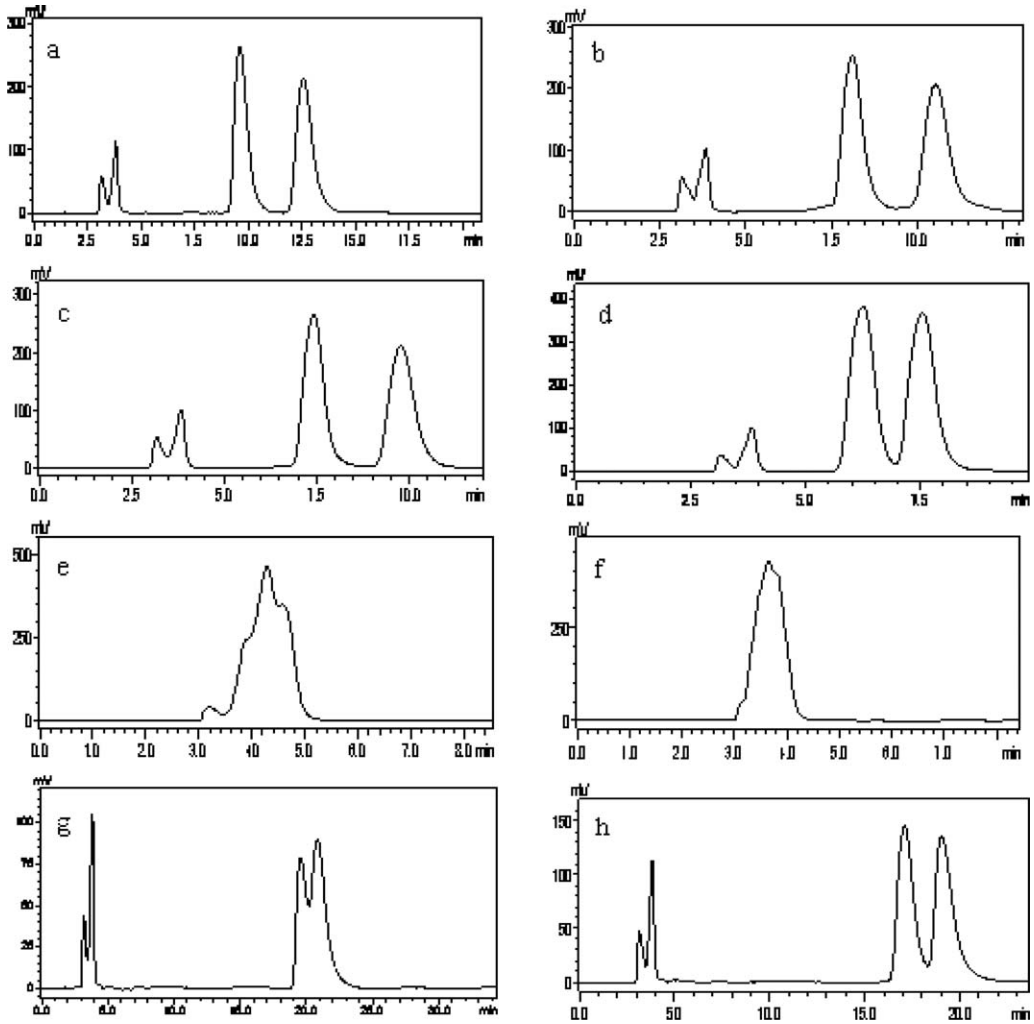

Fig. 3. Curves of the chiral separation of Samples **a–h** on Chiralcel OJ-H column using the mobile phase of *n*-hexane/isopropanol 90:10 (v/v); flow rate: 1.0 ml/min; absorbance wavelength: 220 nm.

ration. Thus, higher interaction did not mean better resolution. The retention between Samples **g** and **h** and CSPs were stronger than other samples. However, the resolutions were lower than others. Compared with Sample **d**, Sample **c** contained two ester groups, which provided an additional hydrogen bonding site, leading to stronger interaction between Sample **c** and CSPs. Thus, the retention factor was higher.

The retention times of the third group of samples in the descending order on Chiralcel OD-H was **a** > **g** > **h**, and on Chiralcel OJ-H was **a** > **h** > **g**. None but Sample **a** was resolved on both columns. Samples **g** and **h** were only resolved on Chiralcel OD-H and OJ-H, respectively. It suggested that the selectivity can be changed by varying cellulose derivatives CSP, as hydrogen bond was possible both for the samples and for protic (proton-donating) modifiers,[23] which was not only in competition between samples and solvent for the CSP but also altered the steric environment of the chiral grooves on the CSP by binding to or close to the achiral sites at the groove.[24] Although Chiralcel OD-H allowed the resolution of more samples, some of the samples which were effectively resolved on Chiralcel OJ-H were not resolved on Chiralcel OD-H. For example, Sample **h** eluted from Chiralcel OD-H as a partial resolved wide peak, whereas it was baseline resolved on Chiralcel OJ-H using the same mobile phase (Figs. 2h and 3h). This may indicate that the configuration of this compound was instable. Besides a methyl and a secondary amine group connecting with the chiral carbon of the Sample **h**, there was a phenyl group, instead of a CH_2 group existed in other samples, which suggest that the phenyl groups of the sample might play an important role in the enantioseparation of Sample **h** on CSP of cellulose *tris*-3,5-dimethylphenylcarbamate.

CONCLUSIONS

A series of novel derivatives of mexiletine and its analogs on enantioseparation by HPLC using Chiralcel OD-H and OJ-H column were studied. Based on the set of chromatographic data collected, the mechanism regarding of enantioseparation and the structure of the sam-

ples were discussed. The methods have potential applications in the determination of mexiletine and its analogs' derivatives. Furthermore, it is important to study the relation between the samples' structure and CSP for enantioseparation.

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