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The preparation of polymerizable, optically active non-steroidal anti-inflammatory drugs derivatives by irreversible enzymatic methods

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Abstract

A lipase-catalyzed irreversible resolution of 2-arylpropionic acids was developed using the corresponding racemic vinyl esters as activated substrates. The obtained products, (*S*)-ketoprofen vinyl ester, (*S*)-naproxen vinyl ester and (*S*)-ibuprofen vinyl ester would be useful as significant monomers for polymeric drug. The effect of enzyme sources, solvent, water amount and temperature on the hydrolysis resolution was investigated. Optically active, polymerizable ketoprofen prodrug can be obtained with excellent enantioselectivity (ee ~ 90%) after optimization of the reaction conditions. Lipased-catalyzed transesterification of (*R*,*S*)-ketoprofen vinyl esters with various alcohols was also studied. The use of vinyl ester effectively enhanced the enantioselectivity compared with other common ester, such as ethyl and butyl esters.

Keywords: NSAIDs; Irreversible resolution; Enantioselectivity; Lipases; Prodrug; Vinyl esters

1. Introduction

2-Arylpropionic acids (i.e. profens), such as ketoprofen, naproxen and ibuprofen, are an important class of non-steroidal anti-inflammatory drug (NSAIDs), which are widely used for alleviation of pain and inflammation associated with tissue injury [1]. Since the bioactivity of profens is mainly due to the (*S*)-enantiomer, the preparation of optically active 2-arylpropionic acids has become an important subject of increasing interest over the past decades [2].

Enzymes have been widely recognized as useful chiral catalysts for the production of optically active compounds [3,4]. In the last few years, considerable efforts have been made to prepare enantiopure profens by enzymatic resolutions, which are usually carried out by hydrolysis or transesterification of their simple ester (e.g., methyl or ethyl esters) [5,6]. However, these methods are hampered by an unfavored equilibrium causing long reaction times and low enantioselectivity [7]. Therefore, various strategies have been reported to circumvent these problems, such as optimization of reaction conditions [5,8], modification of substrate [9], purification of enzyme [10,11], stabilization of enzyme [12], introduction of additives [13] and seeking for microbial resolution [14].

Among these techniques, it is more practical and attractive to develop an irreversible method by modification of substrate. Vinyl acetate has been used as acylating agents in many successful resolution of alcohol [15,16], since the alcohols freed from the reaction rapidly tautomerize to volatile acetaldehyde, making the process irreversible and simple for product isolation [17]. To the best of our knowledge, its application to resolution of racemic carboxylic acid is still not well documented. Yang et al. and Miyazawa et al. have already reported irreversible resolution of racemic carboxylic acid, but the *E*-values obtained were moderate [7,18].

Previous pharmacological studies of profens have indicated the gastrointestinal (GI) side effects due to the acidic moiety of the profen. Therefore, extensive modifications have been made to prepare the ester prodrug of profens, which can temporarily mask their acidic moiety [19]. However, there are still no reports of enantiopure and polymerizable profen prodrugs that can be used for the preparation of optically active macromolec-

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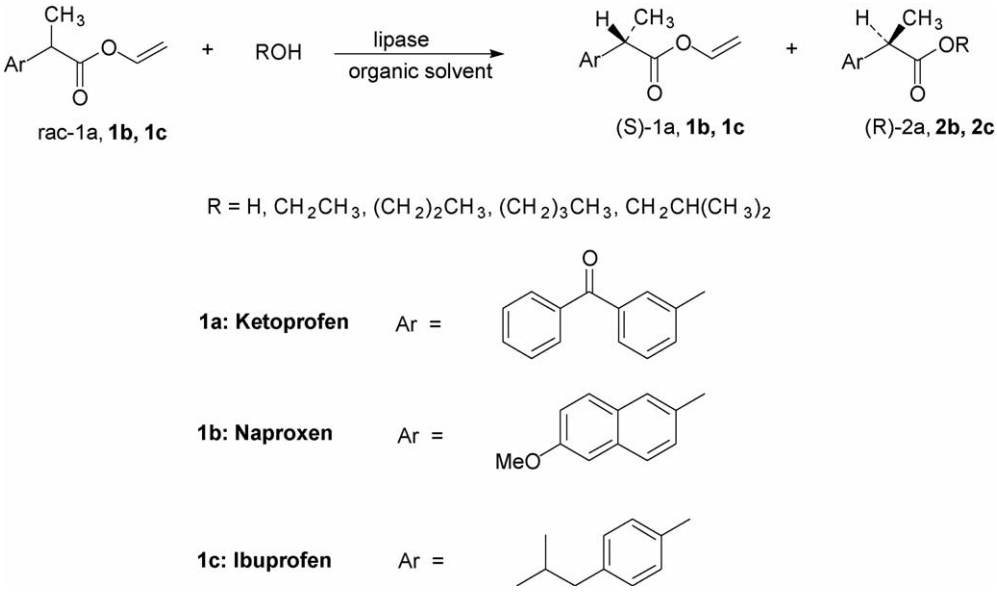

Fig. 1. Lipase-catalyzed resolution of 2-arylpropionic vinyl ester in organic solvents.

ular drugs, which can effectively control the rate of the drug release and administered at low doses, increase the therapeutic benefit [20].

In this paper, an irreversible enzymatic resolution of 2-arylpropionic acids using their vinyl esters as activated substrates by hydrolysis as well as transesterification was investigated (Fig. 1). The obtained enantiopure vinyl esters can be polymerized through free radical polymerization for biodegradable polymer drugs, which is anticipated to improve curative effects and control drug release.

2. Experimental

2.1. Materials

Lipozyme® immobilized from *Mucor miehei*, EC 3.1.1.1, 42 units/g (the unit of the enzyme was defined as the amount of enzyme which liberates 1 μmol oleic acid/min at pH 8.0 and 40 °C) was purchased from Fluka. Lipase Type VII from *Candida rugosa*, EC 3.1.1.3, 706 units/g (the unit of the enzyme was defined as the amount of enzyme which hydrolyzes 1.0 microequivalent of fatty acid from a triglyceride in 1 h at pH 7.7 at 37 °C) and Lipase immobilized on acrylic resin from *Candida antarctica*, EC 3.1.1.3, ≥10,000 units/g (recombinant, expressed in *Aspergillus oryzae*) were purchased from Sigma. Racemic and optically pure ketoprofen (2-(3-benzoylphenyl) propionic acid) were a generous gift from Zhejiang Jiuzhou Pharmaceutical Co. Ltd. (Taizhou, PR China). Racemic and optically pure naproxen (2-(6-methoxy-2-naphthyl) propionic acid) were purchased from Zhejiang Charioteer Pharmaceutical Co. Ltd. (Taizhou, PR China). Racemic and optically pure ibuprofen (2-(4-isobutylphenyl) propionic acid) were purchased from Juhua Corp. Pharmaceutical Factory (Quzhou, PR China). All other chemicals used in this work were of analytical grade and were first dried over 3 Å molecular sieves for 24 h prior to use.

2.2. Analysis methods

^{1}H spectra were obtained on a Bruker AMX-500 MHz spectrometer. Spectra were run in $CDCl_3$. Infrared spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. HRMS were obtained on a Bruker 7-T FT-ICR MS equipped with an electrospray source (Billelica, MA, USA). The enantiomers of ketoprofen, naproxen and ibuprofen were analyzed using an Agilent 1100 series with a chiral column ((*S*,*S*)-Whelk-O1, 250 × 4.6 mm, Regis, USA) and were detected at 250, 232 and 220 nm, respectively. The mobile phase was *n*-hexane/isopropanol/acetic acid (95/5/0.1, v/v/v) for ketoprofen, (85/15/0.1, v/v/v) for naproxen and (98/2/0.1, v/v/v) for ibuprofen with a flow rate of 1.5 ml/min. The retention times of ketoprofen vinyl ester, (*R*)-ketoprofen and (*S*)-ketoprofen were 11.2, 18.7 and 20.8 min, respectively. The retention times of (*R*)-naproxen vinyl ester, (*S*)-naproxen vinyl ester, (*R*)-naproxen and (*S*)-naproxen were 6.3, 7.0, 8.3 and 14.6 min, respectively. The retention times of ibuprofen vinyl ester, (*R*)-ibuprofen and (*S*)-ibuprofen were 3.0, 11.0 and 13.1 min, respectively. The reaction conversion (*c*), enantiomeric excesses of product (ee_p) and substrate (ee_s) and enantioselectivity (*E*) were calculated using the following equations. The ee_s is related to the *S*-vinyl ester. The product is referred to the carboxylic acid, i.e. ketoprofen, naproxen and ibuprofen, and the substrate is referred to the corresponding vinyl ester, i.e. ketoprofen vinyl ester, naproxen vinyl ester and ibuprofen vinyl ester.

$$c\,(\%) = \frac{[(S)\text{-acid}] + [(R)\text{-acid}]}{[\text{Initial vinyl ester}]} \times 100$$

$$ee_p\,(\%) = \frac{[(R)\text{-acid}] - [(S)\text{-acid}]}{[(R)\text{-acid}] + [(S)\text{-acid}]} \times 100$$

$$ee_s\,(\%) = \frac{c}{100 - c} \times ee_p$$

$$E = \frac{\ln[1 - c(1 + ee_p)]}{\ln[1 - c(1 - ee_p)]}$$

2.3. Synthesis of (R,S)-ketoprofen vinyl ester (*1a*)

Ketoprofen vinyl ester was synthesized and purified as described by Yang et al. [7]. Racemic ketoprofen (3.2 g) and mercuric acetate (0.3 g) were dissolved in 30 ml of vinyl acetate. After stirring the mixture for 30 min at room temperature, 0.2 ml of concentrated sulphuric acid was added and the solution was refluxed for 3 h. Then the mixture was allowed to cool to room temperature, and sodium acetate (1.0 g) was added to quench the catalyst. The solution was filtered and concentrated. The crude products were purified by silica gel column chromatography by eluting with petroleum ether/ethyl acetate (30:1, v/v), with a yield of 90%. The identity of the products was determined by IR, ^{1}H NMR and HRMS. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.81–7.46 (9H, m, ArH), 7.26 (1H, dd, $J = 6.3$ and 14.0 Hz, –CH=CH_2), 4.88 (1H, dd, $J = 1.6$ and 14.0 Hz, –CH=CH_2), 4.58 (1H, dd, $J = 1.6$ and 6.2 Hz, –CH=CH_2), 3.87 (1H, q, –C_6H_4CH), 1.58 (3H, d, $J = 7.2$ Hz, –CH_3). IR (KBr, cm^{-1}): 1751 (C=O), 1660 (C=C). HRMS (ESI) *m/z* calcd. for [M + Na] $C_{18}H_{16}O_3Na$ 303.0992, found 303.0983.

2.4. Synthesis of (R,S)-naproxen vinyl ester (*1b*)

Naproxen vinyl ester was synthesized by the same synthesis method as for **1a**; yield: 85%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.38–7.15 (6H, m, ArH), 7.29 (1H, dd, $J = 5.6$ and 14.7 Hz, –CH=CH_2), 4.88 (1H, dd, $J = 1.3$ and 13.9 Hz, –CH=CH_2), 4.58 (1H, dd, $J = 1.3$ and 6.2 Hz, –CH=CH_2), 3.94 (3H, t, $J = 10.6$ Hz, CH_3O–), 2.11 (1H, m, –C_6H_4CH), 1.64 (3H, d, $J = 7.2$ Hz, –CH_3). IR (KBr, cm^{-1}): 1750 (C=O), 1644 (C=C). HRMS (ESI) *m/z* calcd. for [M + Na] $C_{16}H_{16}O_3Na$ 279.0992, found 279.0987.

2.5. Synthesis of (R,S)-ibuprofen vinyl ester (*1c*)

Ibuprofen vinyl ester was synthesized by the same synthesis method as for **1a**; yield: 90%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.26 (1H, dd, $J = 6.3$ and 14.0 Hz, –CH=CH_2), 7.22–7.10 (4H, m, ArH), 4.85 (1H, dd, $J = 1.3$ and 14.0 Hz, –CH=CH_2), 4.50 (1H, dd, $J = 1.4$ and 6.3 Hz, –CH=CH_2), 3.75 (1H, q, –C_6H_4CH), 2.44 (2H, d, $J = 7.2$ Hz, –$C_6H_4CH_2$), 1.84 (1H, m, CH), 1.52 (3H, d, $J = 7.2$ Hz, –CH_3), 0.89 (6H, d, $J = 6.6$ Hz). IR (KBr, cm^{-1}): 1751 (C=O), 1647 (C=C). HRMS (ESI) *m/z* calcd. for [M + Na] $C_5H_{20}O_2Na$ 255.1356, found 255.1350.

2.6. Synthesis of (R,S)-ketoprofen alkyl esters

(*R*,*S*)-Ketoprofen alkyl ester was synthesized by a general method for esterification. (*R*,*S*)-Ketoprofen (1.5 g) was solubilized in 25 ml of alcohol in a round-bottom flask. Sulphuric acid was added as a catalyst for esterification. The mixture was refluxed for 4 h at about 70 °C for ketoprofen ethyl ester, and at 80 °C for ketoprofen butyl ester with stirring. Sodium acetate (0.5 g) was added to quench the catalyst and the residual alcohol was removed by vacuum evaporation. The crude products were purified by silica gel column chromatography by eluting with petroleum ether/ethyl acetate (9:1, v/v). The identities of the products were determined by IR and ^{1}H NMR spectra. Ketoprofen ethyl ester and ketoprofen butyl ester were obtained in the yield of 90 and 92%, respectively.

Ketoprofen ethyl ester: ^{1}H NMR ($CDCl_3$), δ (ppm): (9H, m, ArH), 4.12 (2H, q, –CH_2O), 3.78 (1H, q, –C_6H_4CH), 1.53 (3H, d, $J = 7.2$ Hz, –$CHCH_3$), 1.25 (3H, t, –CH_2CH_3); IR (KBr, cm^{-1}): 1732, 1660, 1597, 1448, 1283, 1180, 722.

Ketoprofen butyl ester: ^{1}H NMR ($CDCl_3$), δ (ppm): 7.81–7.27 (9H, m, ArH), 4.09 (2H, q, –CH_2O), 3.79 (1H, q, –C_6H_4CH), 1.56 (2H, m, –$CH_2CH_2CH_3$), 1.53 (3H, d, $J = 7.2$ Hz, –$CHCH_3$), 1.27 (2H, m, –CH_2CH_3), 0.88 (3H, t, $J = 7.4$ Hz, –CH_2CH_3); IR (KBr, cm^{-1}): 1732, 1661, 1598, 1448, 1318, 1283, 1178, 722.

2.7. General procedure for the enzymatic hydrolysis of vinyl or alkyl esters

Ten milligrams of racemic 2-arylpropionic ester was dissolved in 1 ml organic solvent and the reaction was initiated by adding 10 mg enzyme. The mixture was incubated at 25 °C under shaking at 200 rpm. The reaction was terminated by filtering off the enzyme and samples were removed for HPLC analysis.

2.8. General procedure for the enzymatic transesterification of (R,S)-ketoprofen vinyl esters

Fifteen milligrams of (*R*,*S*)-ketoprofen vinyl ester (0.05 mmol) was dissolved in 1 ml solvent containing 4 equivalents of alcohol. Then 10 mg of Lipozyme® was added in order to initiate the reaction. The mixture was incubated at 25 °C under shaking at 200 rpm. The reaction was terminated by filtering off the enzyme and samples were removed for HPLC analysis.

2.9. Enzymatic hydrolysis of (R,S)-ketoprofen vinyl esters on a preparative scale

The reaction was initiated by adding 150 mg Lipozyme® to 15 ml dioxane composed of 2.5% (v/v) of water containing 1.5 g (*R*,*S*)-ketoprofen vinyl ester. The suspension was kept at 25 °C and shaken at 200 rpm. The reaction was detected by HPLC and terminated by filtering off the enzyme. The reaction was concentrated under reduced pressure. The products were sep-

arated by silica gel chromatography by eluting with petroleum ether/ethyl acetate (30:1, v/v). The obtained (*S*)-ketoprofen vinyl ester was light yellow liquid with a yield of 90%, ee ~ 90% and $[\alpha]_D^{20} = +41.2$ ($c = 1$, MeOH).

3. Results and discussion

3.1. Enzyme screening

Three commercial enzymes, Lipozyme® from *M. miehei*, Lipase Type VII from *C. rugosa* and Lipase from *C. antarctica*, which are known for their good enantioselectivity in the resolution of racemic profens [5,21], were tested for their ability to catalyze the hydrolysis of profen vinyl ester in isopropyl ether (IPE). From Table 1, it clearly shows that no hydrolysis occurs without enzyme participation. For ketoprofen vinyl ester, only Lipozyme® showed both high catalytic activity and selectivity ($ee_p \sim 90\%$, $E = 37$ at 8 h). Though Lipase *C. antarctica* showed good catalytic activity with the conversion higher than 50% at 0.5 h, it did not have a good stereoselectivity ($E = 1$). Lipase Type VII from *C. rugosa* was relatively inactive in the resolution of ketoprofen vinyl ester since the reaction was much slower with a low enantioselectivity ($E = 7$ at 58 h). For naproxen vinyl ester, Lipase from *C. antarctica* showed moderately high catalytic activity and selectivity ($ee_p \sim 88\%$, $E = 23$ at 2 h). Both Lipozyme® and Lipase Type VII from *C. rugosa* showed medium enantioselectivity ($E < 6$). For ibuprofen vinyl ester, all the three lipases showed little catalytic activity and selectivity ($E < 2$).

We chose Lipase from *C. antarctica* for the further investigation of the resolution of naproxen, and Lipozyme® for ketoprofen vinyl ester and ibuprofen vinyl ester.

3.2. Solvent screening

Enzymatic catalysis in organic media is greatly influenced by the nature of solvents [22]. In order to improve the *E*-value, the hydrolysis reaction was performed in various solvents (Table 2). The effects of solvents on the reactions of ketoprofen vinyl ester and naproxen vinyl ester were similar and the solvents can be classified into three categories. The first category includes dioxane and tetrahydrofuran with $\log P < 0.5$, which showed high selectivity ($E > 200$) but lower conversion (~20%). In the second category of solvents with $\log P$ ranging from 1.0 to 2.0, the reaction was faster and the enantioselectivity was moderately high. In the last category, which includes more hydrophobic solvents ($\log P > 3.0$), the reaction was slow but more selective ($E > 200$). However, for ibuprfen vinyl ester, the hydrolysis reaction in all these seven organic solvents showed low enantioselectivity ($E < 10$).

3.3. Further optimization for the hydrolysis reaction of ketoprofen vinyl ester

Since dioxane showed a high selectivity for the resolution of ketoprofen vinyl ester catalyzed by Lipozyme®, it was selected as the reaction media for further optimization studies such as the influence of water amount and temperature to improve the *E*-value. As the results shown in Fig. 2, the highest conversion and *E*-value were obtained at 2.5% water (v/v), and decreased at higher water content. Temperature effect was studied from 15 to 45 °C. As shown in Table 3, higher temperature caused lower enantioselectivity but higher conversion, as is the case in the resolution of other carboxylic acids [24–26]. The optimal temperature in terms of enantioselectivity and conversion

Table 1
Lipase-catalyzed hydrolysis of (*R*,*S*)-ketoprofen vinyl esters (**1a**), (*R*,*S*)-naproxen vinyl ester (**1b**) or (*R*,*S*)-ibuprofen vinyl ester (**1c**) in IPE

Substrate		No enzyme	Lipozyme® from *Mucor miehei*	Lipase from *Candida antarctica*	Lipase Type VII from *Candida rugosa*
1a	Time (h)	58	8	0.5	58
	Conversion (%)	0	42	59	43
	[a]ee_p (%)	–	90	7	63
	[b]ee_s (%)	–	65	10	48
	Selectivity	–	R	R	R
	E	–	37	1	7
1b	Time (h)	24	24	2	48
	Conversion (%)	0	43	32	44
	[a]ee_p (%)	–	55	88	46
	[b]ee_s (%)	–	41	41	36
	Selectivity	–	R	R	S
	E	–	5	23	4
1c	Time (h)	24	24	2	24
	Conversion (%)	0	26	23	17
	[a]ee_p (%)	–	15	9	14
	[b]ee_s (%)	–	5	3	3
	Selectivity	–	R	R	R
	E	–	1	1	1

Reaction conditions: substrate 10 mg, lipase 10 mg, IPE 1 ml, 25 °C, 200 rpm.
[a] Enantiomeric excess for the carboxylic acid.
[b] Enantiomeric excess for the vinyl ester.

Table 2
Solvent screening for hydrolysis reaction of (*R*,*S*)-ketoprofen vinyl esters (**1a**), (*R*,*S*)-naproxen vinyl ester (**1b**) or (*R*,*S*)-ibuprofen vinyl ester (**1c**)

Solvent	log *P*[c]	Vinyl ester	Time (h)	Conversion (%)	ee_p (%)	ee_s (%)	*E*
Dioxane	−1.1	**1a**[a]	58	22	>99	27	260
		1b[b]	24	17	>99	20	243
		1c[a]	24	7	81	6	10
Tetrahydrofuran	0.49	**1a**[a]	58	22	>99	27	260
		1b[b]	24	14	>99	16	234
		1c[a]	24	20	77	19	9
1,2-Dichloroethane	1.2	**1a**[a]	58	34	83	43	16
		1b[b]	24	17	88	18	18
		1c[a]	24	38	44	27	3
4-Methyl-2-pentanone	1.8	**1a**[a]	58	44	88	69	33
		1b[b]	24	27	77	28	10
		1c[a]	24	53	60	68	8
Isopropyl ether	1.9	**1a**[a]	8	42	90	65	37
		1b[b]	2	32	88	41	23
		1c[a]	24	26	15	5	1
Hexane	3.5	**1a**[a]	58	17	>99	20	243
		1b[b]	24	3	>99	3	205
		1c[a]	24	44	52	41	6
Octane	4.5	**1a**[a]	58	14	>99	16	233
		1b[b]	24	8	>99	9	216
		1c[a]	24	49	40	38	3

Reaction conditions: substrate 10 mg, lipase 10 mg, solvent 1 ml, 25 °C, 200 rpm.
[a] The reactions were catalyzed by Lipozyme® from *Mucor miehei.*
[b] The reactions were catalyzed by Lipase from *Candida antarctica.*
[c] From [23].

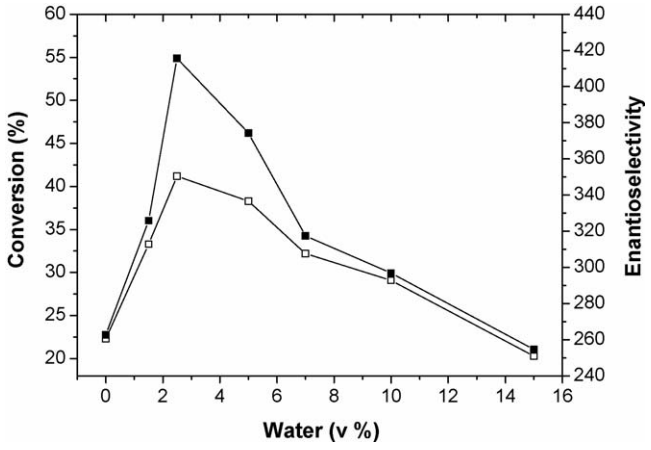

Fig. 2. Effect of the water amount in the reaction mixture on the conversion and enantioselectivity of the hydrolysis of ketoprofen vinyl esters. Conversion (□), enantioselectivity (■). Reaction conditions: substrate 10 mg, Lipozyme® 10 mg, solvent 1 ml, 200 rpm, 25 °C, 58 h.

Table 3
Effect of temperature on enantioselectivity and hydrolysis activity

Entry	T (°C)	Conversion (%)	ee_s (%)	ee_p (%)	*E*
1	15	8	8	>99	215
2	25	42	64	90	37
3	35	47	64	72	12
4	45	53	75	67	11

Reaction conditions: substrate 10 mg, Lipozyme® 10 mg, IPE 1 ml, 200 rpm, 8 h.

is 25 °C, which is close to ambient and thus environmentally benign. In short, the highest enantioselectivity ($E = 416$) was obtained with the use of Lipozyme® in a mixture of dioxane/water (97.5/2.5, v/v) at 25 °C. Further study indicated that (*S*)-ketoprofen vinyl ester could be obtained with higher ee_s by controlling the reaction time and conversion. The time course of the hydrolysis of ketoprofen vinyl ester under the optimal condition is shown in Table 4. As can be seen, after 72 h the conversion was about 53% and the ee_s reached about 90%. And (*S*)-ketoprofen vinyl ester could be obtained with higher optical purity ($ee_s \sim 97\%$) when the conversion reached 58% after 120 h.

Table 4
Time course of the hydrolysis of (*R*,*S*)-ketoprofen esters catalyzed by Lipozyme® in a mixture of dioxane/water (97.5/2.5, v/v) at 25 °C

Time (h)	Conversion (%)	ee_p (%)	ee_s (%)	*E*
3	4	>99	4	207
6	7	>99	8	214
12	19	>99	23	250
30	27	>99	37	285
48	34	>99	51	331
58	41	>99	69	416
60	49	85	82	31
72	53	79	89	25
120	58	70	97	22

Reaction conditions: substrate 10 mg, Lipozyme® 10 mg, solvent 1 ml, 200 rpm.

Table 5
Hydrolysis of different (*R*,*S*)-ketoprofen esters catalyzed by Lipozyme® in different organic solvents

	Dioxane (58 h)				IPE (24 h)			
	Conversion (%)	ee_p (%)	ee_s (%)	*E*	Conversion (%)	ee_p (%)	ee_s (%)	*E*
Ketoprofen ethyl ester	0	0	0	–	96	11	–	–
Ketoprofen butyl ester	1	61	1	4	7	67	5	5
Ketoprofen vinyl ester	22	>99	28	263	53	79	89	24

Reaction conditions: substrate 10 mg, Lipozyme® 10 mg, solvent 1 ml, 25 °C, 200 rpm.

Table 6
Resolution of (*R*,*S*)-ketoprofen vinyl ester by transesterification reaction catalyzed by Lipozyme® in different organic solvents

Alcohol	Dioxane (72 h)				IPE (24 h)			
	Conversion (%)	ee_p (%)	ee_s (%)	*E*	Conversion (%)	ee_p (%)	ee_s (%)	*E*
Ethanol	29	>99	40	295	50	80	80	16
Propanol	39	>99	63	382	52	81	88	26
Butanol	36	81	45	15	51	79	82	22
Isobutyl alcohol	32	>99	46	314	48	88	81	19

Reaction conditions: substrate 10 mg, Lipozyme® 10 mg, solvent 1 ml, 25 °C and 200 rpm.

3.4. Comparisons with simple alkyl esters

For comparison of enantioselectivities and reaction rates, the corresponding ethyl and butyl esters of ketoprofen were synthesized and subjected to enzymatic hydrolysis under the same reaction conditions. The results shown in Table 5 indicated that the hydrolysis of the activated ketoprofen vinyl esters proceeded with significantly higher reaction rates and enantioselectivity either in IPE or in dioxane.

3.5. Transesterification with simple alcohol

The resolution of ketoprofen vinyl ester was also examined by the transesterification with four simple alcohol, ethanol, propanol, butanol and isobutyl alcohol. Table 6 shows the results of the transesterifications performed in IPE and dioxane, respectively, all of which preferentially converted the (*R*)-enantiomer. It is obvious that the reaction carried out in dioxane proceeded with much higher enantioselectivity but lower reaction rate. Moreover, the nature of the alcohol in the lipase-catalyzed transesterification influenced the conversion and enantioselectivity. The optimal alcohol for the resolution of (*R*,*S*)-ketoprofen vinyl ester was propanol either in dioxane or IPE. Highest enantioselectivity ($E = 382$, $ee_p > 99\%$) was obtained with the use of propanol in dioxane. It can be concluded from the above studies that transesterification reaction was carried out with similar enantioselectivity but lower reaction rate compared with hydrolysis.

4. Conclusion

In conclusion, we have developed an efficient method to prepare polymerizable and optically active non-steroidal anti-inflammatory drugs derivatives by lipase-catalyzed irreversible resolution. Various reaction conditions were systematically examined. To summarize, hydrolysis resolution of ketoprofen vinyl ester catalyzed by Lipozyme® in the solvent of dioxane composed of 2.5% (v/v) of water at 25 °C gave the best results in term of conversion (∼53%) and *E*-values ($E = 25$, $ee_s \sim 90\%$). The vinyl ester starting materials can easily be prepared and the enzymatic resolution is easy to carry out. Furthermore, the obtained (*S*)-ketoprofen vinyl ester, (*S*)-naproxen vinyl ester and (*S*)-ibuprofen vinyl ester can produce corresponding (*S*)-profen by chemical hydrolysis, or can become useful building block for polymeric drug. Therefore, this methodology is of potential interest because it provides a facile and clean route to enantiopure prodrug, which is useful for a significant monomer for macromolecular drug. The polymerization of vinyl esters of non-steroidal anti-inflammatory drugs and preparation of copolymers with sugar branches are in progress.

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