Tetrahedron: *Asymmetry* 21 (2010) 1999–2004

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

CaL-B a highly selective biocatalyst for the kinetic resolution of furylbenzthiazole-2-yl-ethanols and acetates

László Csaba Bencze, Csaba Paizs, Monica Ioana Toşa, Maria Trif, Florin Dan Irimie *

Department of Biochemistry and Biochemical Engineering, Babeş-Bolyai University of Cluj-Napoca, RO-400028 Cluj-Napoca, Arany János 11, Romania

ARTICLE INFO

Article history:
Received 6 May 2010
Accepted 3 June 2010
Available online 3 July 2010

ABSTRACT

A highly stereoselective enzymatic kinetic resolution of novel various substituted racemic furylbenzthiazole-2-yl-ethanols and their acetates has been developed. Both processes, the enzymatic acylation of the racemic alcohols and the enzymatic methanolysis of racemic acetates yielded highly enantiomerically enriched (ee >98%) resolution product, when CaL-B was used as a biocatalyst in acetonitrile. The absolute configuration of the obtained (*R*)-(+)-1-(5-(4-chlorobenzo[d]thiazol-2-yl)furan-2-yl)ethanol was determined by a detailed ^{1}H NMR study of *rac*- and (+)-1-(5-(4-chlorobenzo[*d*]thiazol-2-yl)furan-2-yl)ethanol Mosher derivatives.

1. Introduction

Over the last decades, due to the high demand for fine materials and chemicals (agrochemicals and pharmaceuticals),[1] the synthesis of enantiomerically enriched compounds has become a research area of increasing interest. Synthetic routes to produce these compounds have emerged as one of the most important fields of organic chemistry. Due to their chiral nature, biocatalysts are predominantly suited for the production of enantiopure compounds.[1] Moreover, biocatalytic processes have proved to be greener, less hazardous and less polluting. Accordingly, biocatalysis has developed from a research technology to a widely used manufacturing method in the pharmaceutical and fine chemical industries.[2]

Benzthiazole and furan-based structures show a large spectrum of biological activities.[3] However, furylbenzthiazole derivatives have not been intensively studied, their fluorescence being the most known and employed property.[4] Recently, the biological activity of some furylbenzthiazoles was studied, and it was found that they exhibit strong antimicrobial effects.[5]

As part of our interest in the development of stereoselective methods for the preparation of optically active heteroaromatic compounds, with potential biological activity or with potential application as chiral intermediates, the enantioselective synthesis of furylbenzthiazole-based optically active secondary alcohols attracted our interest.

Based on the high activity and selectivity of lipases shown in the previously developed enantioselective synthesis of furylbenzthiazole-based cyanohydrin-acetates by dynamic kinetic resolution, and kinetic resolution,[6a] we opted for the development of a lipase-mediated kinetic resolution of 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)ethanols. Lipases (triacylglycerol hydrolases) are one of the most suitable enzymes for kinetic resolution processes. The major advantages of using lipases are that they are available in free and immobilized forms, can be produced in large quantities, do not require any cofactors and also that they can accept a wide range of unnatural substrates. The lipase-catalyzed kinetic resolution of racemic alcohols proved to be an efficient method for the synthesis of various enantiomerically pure secondary alcohols.[7] Besides its major drawback (maximal theoretic yield of 50%) it is still one of the most important methods for the preparation of enantiopure compounds. Exploiting the attribute of lipases that usually retain their enantiomeric preference in hydrolysis or alcoholysis correlating to the acylation, the development of the enzymatic acylation and alcoholysis or hydrolysis should result in opposite enantiomeric forms of the 1-heteroarylethanols and 1-heteroarylethyl acetates. This advantage has been successfully applied in various lipase-mediated kinetic resolution procedures, thus obtaining both enantiomers of the products.[8]

Herein, we describe the synthesis of both enantiomeric forms of various 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)ethanols and of their esters by enzymatic acylation of the racemic ethanols and by enzymatic alcoholysis of the corresponding racemic acetates.

2. Results and discussion

First the synthesis of racemic 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)ethanols *rac*-**2a**–**d** from the corresponding heteroaryl aldehydes **1a**–**d** by a Grignard reaction was performed. The corresponding acetates *rac*-**3a**–**d** were obtained by the chemical acylation of the heteroarylethanols *rac*-**2a**–**d**.

To investigate the stereoselectivity of the enzymatic kinetic resolution and the activity of the enzymes, the chromatographic

* Corresponding author. Tel.: +40 264 593833; fax: +40 264 590818.
E-mail address: irimie@chem.ubbcluj.ro (F.D. Irimie).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.06.010

enantiomeric separation of the racemates *rac*-**2**,**3a–d** was first established.

In order to obtain highly enantiomerically enriched resolution products, using racemic 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)ethanol *rac*-**2a** as a model compound, potentially useful lipases were screened in various organic solvents for enantiomer selective acylation of racemic alcohol *rac*-**2a** with vinyl acetate (5 equiv), and for alcoholysis with methanol, ethanol, propanol and butanol (8 equiv) of racemic acetate *rac*-**3a** (Scheme 1).

Due to the poor solubility of *rac*-**2a** in neat vinyl acetate screening with several lipases for the enzymatic acylation of the heteroaylethanol was performed in acetonitrile, in which the solubility of the substrates was highest. It was found that Novozyme 435 (lipase B from *Candida antarctica*, CaL-B) was the most active and selective enzyme for this purpose (Table 1, entry 5). Interestingly, lipase A from *C. antarctica*, (CaL-A) previously found to be the most efficient for the kinetic resolution and dynamic kinetic resolution of furylbenzthiazole-based cyanohydrins,[6a] showed lower activity (Table 1, entry 1) than lipase B from *C. antarctica* for the enzymatic acylation of *rac*-**2a**.

Further, using the most efficient enzyme, solvent effects on the enzymatic acylation was tested. Due to the low solubility of the substrate, only a small number of organic solvents proved to be useful for the CaL-B-mediated acylation. A strong solvent influence upon the reaction rate was observed, while the selectivities were high in most cases. In accordance with the values shown in Table 2, acetonitrile (Table 2, entry 1) proved to be the most appropriate solvent (high ee and highest reaction rate value) for the enzymatic acylation of *rac*-**2a**.

Performing the same screening procedure for the rest of the substrates *rac*-**2b–d**, the optimal method was the same as found for *rac*-**2a**.

To prepare the opposite enantiomers of the resolution products, the (*R*)-1-heteroarylethanols (*R*)-**2a–d** and the (*S*)-1-heteroarylethyl acetates (*S*)-**3a–d**, the analytical scale enzymatic alcoholysis of racemic 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)ethyl acetates *rac*-**3a–d** was investigated further. The screening process involved enzymatic alcoholysis with various amounts (2, 4, 6, 8, 10 equiv) of methanol, ethanol, propanol and butanol, in the same solvents used for the enzymatic acylation. Interestingly, only CaL-B was catalytically active. With all the other lipases showing activity for the enzymatic acylation (CaL-A, LPS, LAK, CCL and CRL), the alcoholysis failed. The nature and the concentration of the nucleophile strongly influenced the selectivity of the CaL-B-catalyzed alcoholysis. The best results were obtained when 8 equiv of methanol was used in acetonitrile. In Table 3 some selected results from the screening procedure for the enzymatic methanolysis of *rac*-**3a** are shown.

To verify the general validity of the optimal conditions for the enzymatic methanolysis of *rac*-**3a**, the same screening procedure was further extended to the other racemic acetates *rac*-**3b-d**. As was expected, the CaL-B-catalyzed methanolysis (8 equiv) in acetonitrile was found to be the most selective procedure.

The reaction times, conversions and ee values for both analytical scale enzymatic acylation of *rac*-**2a–d** and methanolysis of *rac*-**3a–d** are presented in Table 4. In all cases at 50% conversion, high ee values were obtained, for both product and unreacted

Table 1
The influence of the nature of the enzyme on the enzymatic acylation of *rac*-**2a** with vinyl acetate (8 equiv) in acetonitrile

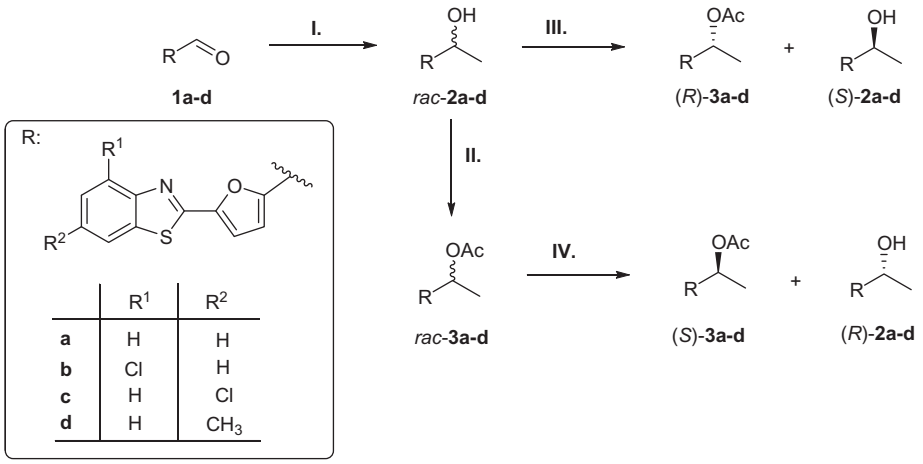
Entry	Enzyme	Time (h)	*c* (%)	ee_P (%)	ee_S (%)	*E*
1	CaL-A	14	34	>99.5	52.3	≫200
2	LPS	14	15	>99.5	18	>200
3	LF	14	0	—	—	—
4	LAK	3	26	98	34.4	138
5	CaL-B	3	50	>99.5	98	≫200
6	CCL	14	9	>99.5	10	>200
7	CRL	14	8	98	9	108
8	PPL	14	0	—	—	—

Table 2
The influence of the nature of the solvent on the CaL-B-mediated aceylation of *rac*-**2a** with vinyl acetate (8 equiv) in different solvents after 3 h

Entry	Solvent	*c* (%)	ee_P (%)	ee_S (%)	*E*
1	Acetonitrile	50	>99.5	98	≫200
2	MTBE	49	>99.5	95	≫200
3	Toluene	47	>99.5	90	≫200
4	1,4-Dioxane	16	>99.5	19.6	>200
5	Chloroform	38	>99.5	62.3	≫200

Table 3
The influence of the nature of solvent upon the selectivity and velocity of CaL-B catalyzed methanolysis (8 equiv) after 2 h

Entry	Solvent	*c* (%)	ee_P (%)	ee_S (%)	*E*
1	Acetonitrile	50	>99.5	99	≫200
2	MTBE	40	>99.5	66	≫200
3	Toluene	15	>99.5	17	>200
4	1,4-Dioxane	14	>99.5	16.6	>200
5	Chloroform	18	>99.5	22	>200



Scheme 1. Preparation and enzymatic kinetic resolution of racemic 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)ethanols *rac*-**2a–d** and their acetates *rac*-**3a–d**. Reagents and conditions: I (a) CH_3MgI/THF; (b) NH_4Cl/H_2O. II AcCl, DMAP/Py/CH_2Cl_2. III Lipase, vinyl-acetate/org.solv. IV Lipase, R′OH/org. solv.

Table 4
The optimal conditions for the analytical scale enzymatic kinetic resolution of racemic alcohols rac-**2a–d** and acetates *rac*-**3a–d** with CaL-B in acetonitrile

Entry	Substrate	Time (h)	*c* (%)	ee_p (%)	ee_s (%)
1	*rac*-**2a**	4	50	>99.5	>99.5
2	*rac*-**2b**	8	50	>99.5	98
3	*rac*-**2c**	14	50	>99.5	>99.5
4	*rac*-**2d**	12	50	>99.5	>99.5
5	*rac*-**3a**	2	50	>99.5	>99.5
6	*rac*-**3b**	12	50	>99.5	98
7	*rac*-**3c**	8	50	98	98
8	*rac*-**3d**	8	50	>99.5	>99.5

enantiomer of the substrate, showing high enantioselectivity and activity of CaL-B in acetonitrile towards all the investigated 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl)-based derivatives.

Based on the analytical scale optimal procedure, the preparative scale enzymatic resolutions were performed for both *rac*-1-heteroarylethanols *rac*-**2a–d** and the corresponding ethyl acetates *rac*-**3a–d**. All dilutions, substrate–biocatalyst ratio and reaction conditions were the same as in the case of the analytical scale reactions. The reactions were monitored by HPLC and TLC and were stopped at an approx. 50% conversion, removing the enzyme by filtration. Data on yield, enantiomeric excess and specific rotatory value of the obtained enantiomers are presented in Table 5.

2.1. The absolute configuration of the resolution products

According to Kazlauskas' empirical rule[9] for predicting which enantiomer reacts faster during the resolution of secondary chiral alcohols, the absolute configurations of the products obtained by the lipase-mediated kinetic resolution can be assigned.[10] However, a few exceptions to this rule have been reported so far.[11] Therefore, the absolute configurations of the novel enantiopure alcohols was determined by a detailed ^{1}H NMR study in the case of the Mosher's derivative[12] of **2b**. Thus, the racemic and enantiomerically pure **2b** was esterified with (*R*)-MTPA-Cl and the resulting diastereomers were differentiated by their ^{1}H NMR spectra. The esterification of racemic *rac*-**2b** with the (*R*)-MTPA-Cl occured selectively affording the expected mixture of the corresponding Mosher esters, but in a 1.7:1 ratio (Fig. 2a) in agreement with the previous observation of Heathcock.[13] We noted that, depending on the sterical hindrance involving the OH group, the above unequal distribution is not always observed.[14] Next, previous structural data[15] suggested that the most plausible conformation of the (*S*)-MTPA fragment is that presented in Figure 1. If so, in the case of (*S*)-MTPA-(*R*)-**2b**, there is a steric repulsion between the heteroaryl moiety of **2b** and the phenyl group of the MTPA counterpart. In contrast, in the case of (*S*)-MTPA-(*S*)-**2b**, the heteroaryl and phenyl groups are not proximal. Hence, based on the observed selectivity of the esterification, the ^{1}H NMR signals of the two diastereomers, (*S*)-MTPA-(*R*)-**2b** and (*S*)-MTPA-(*S*)-**2b**, could be assigned unambiguously as follows: the signals with major intensity (δ = 1.70 ppm and δ = 3.54 ppm) belonged to the $-CH_3$ and $-OCH_3$ groups, respectively, in the (*S*)-MTPA-(*S*)-**2b** environment, while the minor signals at δ = 1.78 ppm and δ = 3.58 ppm belonged to the (*S*)-MTPA-(*R*)-**2b** diastereomer (Fig. 2a). Supporting evidence is also provided by the phenyl group's diamagnetic effect on the proximal groups. Thus in the case of (*S*)-MTPA-(*S*)-**2b** the strong diamagnetic effect of the phenyl ring caused the proximal CH_3 protons to resonate upfield[14a] (Fig. 1a). Indeed, CH_3 protons are found to be more shielded, δ_{CH3} = 1.70 ppm, in comparison with the CH_3 protons of (*S*)-MTPA-(*R*)-**2b** (δ_{CH3} = 1.78 ppm) where the distance between the phenyl and the methyl groups is higher (Fig. 2b). The methoxy protons of the (*S*)-MTPA-(*S*)-**2b** were also found to be more shielded, δ_{OCH3} = 3.54 ppm, when compared with their analogues in (*S*)-MTPA-(*R*)-**2b**, δ_{OCH3} = 3.58 ppm. This is due to the diamagnetic effect of the proximal heteroaryl ring (Fig. 2b). However, in this case the diamagnetic effect of the heteroaryl moiety is lower, as shown by the difference between the δ values as $\Delta\delta_{CH3}$ = 0.08 ppm and $\Delta\delta_{OCH3}$ = 0.04 ppm, due to the larger distance between the OCH_3 group and the heteroaryl moiety.

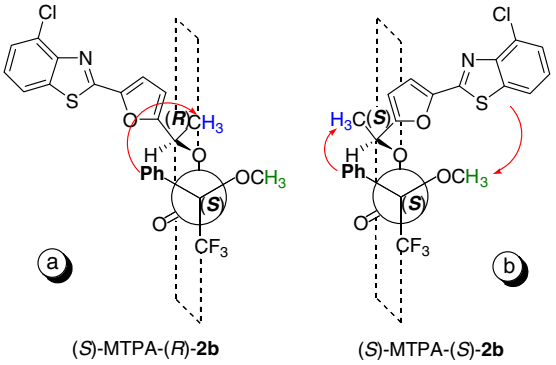


Figure 1. (*S*)-MTPA derivatives of (*R*)-**2b** (a) and (*S*)-**2b** (b).

The esterification of the enantiomerically pure alcohol remained untransformed during the CaL-B-mediated acylation reaction with (*R*)-MTPA chloride, producing the down fielded (*S*)-MTPA-(*S*)-**2b** diastereomer (Fig. 2b), thus confirming the (*S*) absolute configuration predicted by the Kazlauskas empirical rule. The absolute configuration for the rest of the compounds was established by comparing their signs of the specific rotation with (+)-(*S*)-**2b**.

Table 5
Yield, ee and specific rotatory value for the products of CaL-B-mediated kinetic resolutions

Entry	Product	Yield (%)	ee (%)	$[\alpha]_D^{25}$ [c]	Product	Yield	ee (%)	$[\alpha]_D^{25}$ [d]
1[a]	(*S*)-**2a**	49	>99.5	−28.3	(*R*)-**3a**	49	>99.5	+97
2[a]	(*S*)-**2b**	48	98	−40.3	(*R*)-**3b**	49	99	+92.9
3[a]	(*S*)-**2c**	49	99	−18.7	(*R*)-**3c**	49	99	+109.5
4[a]	(*S*)-**2d**	49	>99.5	−12.8	(*R*)-**3d**	47	>99.5	+87.5
5[b]	(*R*)-**2a**	49	>99.5	+31.1	(*S*)-**3a**	48	>99.5	−107
6[b]	(*R*)-**2b**	47	98	+42.7	(*S*)-**3b**	49	99	−97
7[b]	(*R*)-**2c**	48	98	+19.8	(*S*)-**3c**	48	98	−103.4
8[b]	(*R*)-**2d**	50	>99.5	+10.3	(*S*)-**3d**	37	99	−94.3

[a] Products obtained by enzymatic acylation.
[b] Products obtained by enzymatic alcoholysis.
[c] *c* 0.5 mg/mL.
[d] *c* 0.25 mg/mL.

3. Conclusions

An efficient enzymatic kinetic resolution of various furylbenzthiazole-based ethanols *rac*-**2a–d** and their acetates *rac*-**3a–d** has been achieved. Both processes, the enzymatic acylation and the enzymatic alcoholysis were efficient in acetonitrile using CaL-B as a catalyst, affording the highly enantiomerically enriched enantiomers of the target compounds.

The absolute configuration of the obtained products was determined by a detailed ^{1}H NMR study of the Mosher's derivative of *rac*-**2b** and (*S*)-**2b**.

4. Experimental

4.1. Analytical methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz and 75 MHz, respectively. Spectra

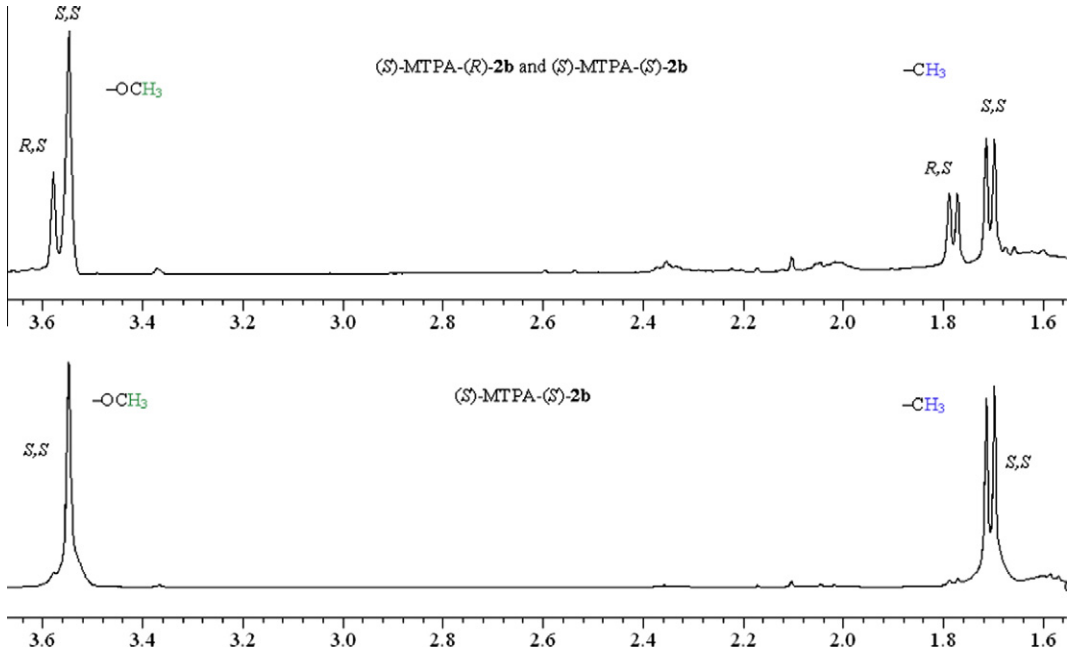


Figure 2. Signals of the CH_3 protons and OCH_3 protons from the ^1H NMR spectra of the (*S*)-MTPA-(*R*) and (*S*)-**2b** and of the (*S*)-MTPA-(*S*)-**2b**.

were recorded at 25 °C in $CDCl_3$. ^1H and ^{13}C NMR spectra were referenced internally to the solvent signal. Electron impact mass spectra (EI-MS) were taken on a VG 7070E mass spectrometer operating at 70 eV. High performance liquid chromatography (HPLC) analyses were conducted with an Agilent 1200 instrument using a Chiralcel OJ-H column (4.6 × 250 mm) and a mixture of *n*-hexane and 2-propanol 80:20 (v/v) as eluent for the enantiomeric separation of *rac*-**2**,**3a–c** and Chiralpak IA-IB tandem columns and a mixture of *n*-hexane and 2-propanol 90:10 (v/v) as eluent for the enantiomeric separation of *rac*-**2**,**3d**. Retention times for (*R*)- and (*S*)-**2**,**3a–d** are presented in Table 6. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F254 sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (63–200 μm). Melting points were determined by the hot plate method and are uncorrected. Optical rotations were determined on a Perkin–Elmer 201 polarimeter and $[\alpha]_D^{25}$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Table 6
Retention times of the enantiomers of *rac*-**2**,**3a–d**

Compound	t_R (min)
(*S*)-**2a**	21.3
(*S*)-**2b**	15.7
(*S*)-**2c**	16.8
(*R*)-**2d**	22.9
(*S*)-**3a**	16.8
(*S*)-**3b**	13.1
(*S*)-**2c**	13.7
(*R*)-**3d**	15.1
(*R*)-**2a**	30.5
(*R*)-**2b**	20.1
(*R*)-**2c**	22.3
(*S*)-**2d**	23.7
(*R*)-**3a**	23.8
(*R*)-**2b**	18.3
(*R*)-**2c**	19.1
(*S*)-**3d**	16.1

4.2. Reagents and solvents

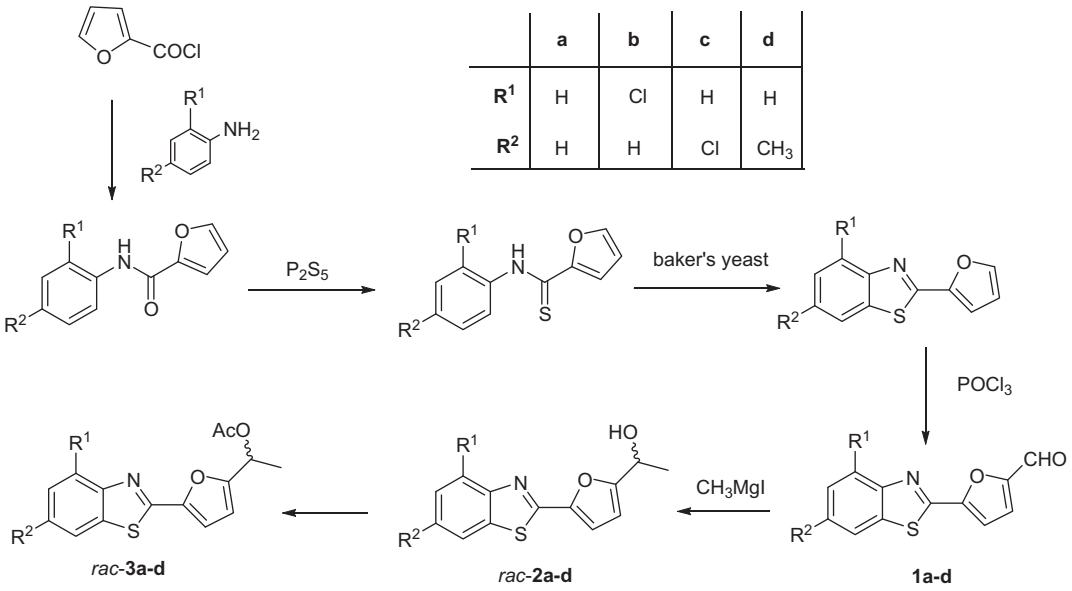
Anilines, 2-furoyl chloride, vinyl acetate, iodomethane, P_2S_5, $POCl_3$ and all other inorganic and organic reagents and solvents were products of Aldrich or Fluka. All solvents were dried and purified by standard methods as required. Novozyme 435 (lipase B from *C. antarctica*), CaL-A (lipase A from *C. antarctica* reticulated with glutaraldehyde), LPS (lipase from *Pseudomonas cepacia*), LAK (lipase from *Pseudomonas fluorescens*), CRL (lipase from *Candida rugosa*), LF (lipase from *Rhizopus oryzae*), CCL (lipase from *Candida cylindracea*) and PPL (lipase from porcine pancreas) were purchased from Novozymes, Fluka and Sigma, respectively. Baker's yeast produced as wet cakes by Budafok Ltd, Hungary was from a local store.

4.3. Synthesis of racemic alcohols and their acetates

The synthesis of racemic secondary alcohols *rac*-**1a–d** and their corresponding acetates *rac*-**2a–d** was performed as shown in Scheme 2. 2-Furan-2-ylbenzothiazole carbaldehydes **1a–d** were prepared as previously described starting from 2-furoyl chloride.[6] Further, using CH_3MgI as Grignard reagent the racemic alcohols **2a–d** were prepared. The synthesis of racemic acetates **3a–d** was achieved by chemical acylation with AcCl.

4.3.1. Synthesis of racemic alcohols rac-2a–d

Into a stirred solution of methylmagnesium iodide, prepared from magnesium (7.4 mmol, 0.177 g) and iodomethane (7.4 mmol, 1.05 g, 0.46 mL) in THF (10 mL), a solution of a heteroaryl-carbaldehyde **1a–d** (6.2 mmol) dissolved in THF was slowly added at room temperature under argon. The resulting mixture was stirred at room temperature for 6 h. After quenching the reaction by slow addition of saturated ammonium chloride solution (10 mL), the organic layer was isolated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed by distillation in vacuo. The crude product was purified by column chromatography using hexane/ethylacetate (1:1, v/v) as eluent.



	a	b	c	d
R^1	H	Cl	H	H
R^2	H	H	Cl	CH_3

Scheme 2. The synthesis of 1-(5-(benzo[*d*]thiazol-2-yl)furan-2-yl) derivatives.

4.3.1.1. 1-(5-Benzo[*d*]thiazol-2-yl)furan-2-yl)ethanol *rac*-2a Yellow solid; yield: 87%; mp 106–107 °C; ^{1}H NMR: 1.62 (1H, d, *J* = 6.7 Hz), 2.1–2.4 (1H, s, br), 4.99 (1H, q, *J* = 6.7 Hz), 6.01 (1H, q, *J* = 6.7 Hz), 6.43 (1H, d, *J* = 3.5 Hz), 7.12 (1H, d, *J* = 3.5 Hz), 7.37 (1H, dd, *J* = 7.8 Hz, *J* = 6.8 Hz), 7.48 (1H, dd, *J* = 6.8 Hz, *J* = 8.2 Hz), 7.87 (1H, d, *J* = 8.2 Hz), 8.04 (1H, d, *J* = 7.8 Hz); ^{13}C NMR: 22.1, 64.3, 108.7, 113.2, 122.2, 123.7, 125.9, 127.2, 134.8, 148.4, 154.2, 158.2, 161.2; HRMS: M^+ found (M^+ calcd for $C_{13}H_{11}NO_2S$: 245.0511): 245.0509; MS: *m/z* (%) = 246 (M+1, 15), 245 (M+, 100), 231 (16), 202 (41), 149 (49), 125 (30), 111 (43), 109 (35), 97 (59), 83 (51), 71 (45), 69 (48), 57 (70), 43 (41).

4.3.1.2. 1-(5-(4-Chlorobenzo[*d*]thiazol-2-yl)furan-2-yl)ethanol *rac*-2b. Yellow solid; yield: 87%; mp 90.5–91; ^{1}H NMR: 1.62 (3H, d, *J* = 6.5 Hz), 2.3–2.5 (1H, s, br), 4.99 (1H, q, *J* = 6.5 Hz), 6.42 (1H, d, *J* = 3.5 Hz), 7.22 (1H, d, *J* = 3.5 Hz), 7.25–7.29 (1H, m), 7.49 (1H, dd, *J* = 1 Hz, *J* = 7.8 Hz), 7.75 (1H, dd, *J* = 1.2 Hz, *J* = 8 Hz); ^{13}C NMR: 21.9, 64.3, 108.8, 113.8, 120.7, 126.2, 127.4, 128.4, 136.3, 148.2, 151.5, 158.9, 161.5; HRMS: M^+ found (M^+ calcd for $C_{13}H_{10}ClNO_2S$: 279.0121): 279.0121; MS: *m/z* (%) = 279 (M+, ^{37}Cl, 0.2), 278 (M+1, ^{35}Cl, 0.1), 321 (M+, ^{35}Cl, 0.6), 59 (2), 58 (38), 57 (2), 44 (2), 43 (100), 42 (7), 39 (4).

4.3.1.3. 1-(5-(6-Chlorobenzo[*d*]thiazol-2-yl)furan-2-yl)ethanol *rac*-2c. Yellow solid; yield: 83%; mp 134–135 °C; ^{1}H NMR: 1.56 (3H, d, *J* = 6.4 Hz), 2.9–3.1 (1H, s, br), 4.97 (1H, q, *J* = 6.4 Hz), 6.56 (1H, d, *J* = 3.4 Hz), 7.23 (1H, d, *J* = 3.4 Hz), 7.53 (1H, dd, *J* = 8.7 Hz, *J* = 1.9 Hz), 7.96 (1H, d, *J* = 8.7 Hz), 8.13 (1H, d, *J* = 1.9 Hz); ^{13}C NMR: 21.4, 62.8, 107.8, 121.6, 123.7, 127.1, 130.2, 135.7, 147.2, 157.9, 162.6; HRMS: M^+ found (M^+ calcd for $C_{13}H_{10}ClNO_2S$: 279.0121): 279.0119; MS: *m/z* (%) = 281 (M+, ^{37}Cl, 7), 280 (M+1, ^{35}Cl, 4), 279 (M+, ^{35}Cl, 25), 266 (^{37}Cl, 8), 264 (^{35}Cl, 25), 107 (5), 77 (5), 58 (26), 43 (100).

4.3.1.4. 1-(5-(6-Methylbenzo[d]thiazol-2-yl)furan-2-yl)ethanol *rac*-2d. Brown solid; yield: 89%; mp 90–91 °C; ^{1}H NMR: 1.61 (3H, d, *J* = 6.7 Hz), 2.47 (3H, s), 2.6–2.8 (1H, s, br), 4.98 (1H, q, *J* = 6.7 Hz), 6.39 (1H, d, *J* = 3.5 Hz), 7.05 (1H, d, *J* = 3.5 Hz), 7.28 (1H, d, *J* = 8.2 Hz), 7.64 (1H, s), 7.89 (1H, d, *J* = 8.2 Hz); ^{13}C NMR: 22.1, 22.2, 64.2, 108.6, 112.8, 121.9, 123.1, 128.8, 134.9, 136.1, 148.4, 152.3, 157.3, 161.1; HRMS: M^+ found (M^+ calcd for $C_{14}H_{13}NO_2S$: 259.0667): 259.0671; MS: *m/z* (%) = 260 (M+1, 1), 259 (M+, 3), 244 (2), 149 (1), 58 (39), 44 (2), 43 (100), 42 (6), 41 (2), 39 (4).

4.3.2. Chemical acylation of *rac*-2a–d

Into the solution of one of the heteroarylethanols *rac*-**2a**–**d** (1 mmol) in dichloromethane (10 mL) were added acetyl chloride (1.5 mmol, 108 μL) and a catalytic amount of 4-*N*,*N*-dimethylamino-pyridine in pyridine (100 μL, 1% solution). After stirring for 30 min at room temperature, the solvent was evaporated in vacuo and the crude product was purified by column chromatography using hexane/ethylacetate (1:1, v/v) as eluent.

4.3.2.1. 1-(5-Benzo[*d*]thiazol-2-yl)furan-2-yl)ethyl acetate *rac*-3a. Yellow solid; yield: 93%; mp 113–113.5 °C; ^{1}H NMR: 1.66 (1H, d, *J* = 6.7 Hz), 2.1 (3H, s), 6.01 (1H, q, *J* = 6.7 Hz), 6.51 (1H, d, *J* = 3.2 Hz), 7.13 (1H, d, *J* = 3.2 Hz), 7.37 (1H, dd, *J* = 8.2 Hz, *J* = 7.2 Hz), 7.48 (1H, dd, *J* =7.2 Hz, *J* = 8.2 Hz), 7.87 (1H, d, *J* = 8.2 Hz), 8.04 (1H, d, *J* = 8.4 Hz); ^{13}C NMR: 19.1, 21.7, 65.7, 111.2, 112.7, 122.2, 123.8, 123.9, 125.9, 126.1, 127.2, 134.9, 149, 154.4, 156.7, 158, 170.8; HRMS: M^+ found (M^+ calcd for $C_{15}H_{13}NO_3S$: 287.0616): 287.0611; MS: *m/z* (%) = 288 (M+1, 2), 287 (M+, 8), 244 (15), 228 (12), 167 (18), 139 (10), 111 (6), 58 (25), 57 (11), 43 (100).

4.3.2.2. 1-(5-(4-Chlorobenzo[*d*]thiazol-2-yl)furan-2-yl)ethyl acetate *rac*-3b. White solid; yield: 95%; mp 84.5–85 °C; ^{1}H NMR: 1.65 (3H, d, *J* = 6.5 Hz), 2.1 (3H, s), 6.01 (1H, q, *J* = 6.5 Hz), 6.52 (1H, d, *J* = 3.2 Hz), 7.25–7.30 (2H, m), 7.49 (1H, dd, *J* = 1.2 Hz, *J* = 7.6 Hz), 7.75 (1H, dd, *J* = 0.8 Hz, *J* = 8 Hz); ^{13}C NMR: 18.9, 21.8, 65.6, 111.3, 113.4, 120.8, 126.3, 127.4, 128.5, 136.4, 148.8, 151.5, 157, 158.8, 170.8; HRMS: M^+ found (M^+ calcd for $C_{15}H_{12}ClNO_3S$: 321.0226): 321.0225; MS: *m/z* (%) = 323 (M+, ^{37}Cl, 10), 322 (M+1, ^{35}Cl, 5), 321 (M+, ^{35}Cl, 28), 280 (^{37}Cl, 28), 278 (^{35}Cl, 65), 171 (25), 169 (37), 135 (26), 58 (30), 57 (21), 43 (100).

4.3.2.3. 1-(5-(6-Chlorobenzo[*d*]thiazol-2-yl)furan-2-yl)ethyl acetate *rac*-3c. Yellow solid; 93%; mp 125–126 °C; ^{1}H NMR: 1.65 (3H, d, *J* = 6.7 Hz), 2.09 (3H, s), 6.05 (1H, q, *J* = 6.7 Hz), 6.72 (1H, d, *J* = 3.4 Hz), 7.27 (1H, d, *J* = 3.4 Hz), 7.55 (1H, dd, *J* = 8.8 Hz, *J* = 2.2 Hz), 7.98 (1H, d, *J* = 8.8 Hz), 8.16 (1H, d, *J* = 2.2 Hz); ^{13}C

NMR: 17.7, 20.1, 64.5, 110.6, 112.5, 121.6, 123.9, 130.5, 135.7, 147.9, 152.7, 156.8, 157.6, 169.3; HRMS: M^+ found (M^+ calcd for $C_{15}H_{12}ClNO_3S$: 321.0226): 321.0229; MS: *m/z* (%) = 323 (M+, ^{37}Cl, 0.4), 321 (M+, ^{35}Cl, 1), 171 (^{37}Cl, 3), 169 (^{35}Cl, 9), 142 (1), 87 (2), 58 (34), 43 (100), 42 (6), 39 (3).

4.3.2.4. 1-(5-(6-Methylbenzo[*d*]thiazol-2-yl)furan-2-yl)ethyl acetate *rac*-3d. Brown solid; yield: 91%; mp 82–83 °C; ^1H NMR: 1.66 (3H, d, *J* = 6.7 Hz), 2.1 (3H, s), 2.47 (3H, s), 6.01 (1H, q, *J* = 6.7 Hz), 6.49 (1H, d, *J* = 3.5 Hz), 7.1 (1H, d, *J* = 3.5 Hz), 7.28 (1H, d, *J* = 8.2 Hz), 7.65 (1H, s), 7.9 (1H, d, *J* = 8.2 Hz); ^{13}C NMR: 19.1, 21.9, 22.2, 65.7, 111.1, 112.3, 121.9, 123.3, 128.8, 135.1, 136.2, 149.1, 152.5, 156.4, 157.1, 170.8; HRMS: M^+ found (M^+ calcd for $C_{16}H_{15}NO_3S$: 301.0773): 301.0772; MS: *m/z* (%) = 302 (M+1, 12), 301 (M+, 65), 259 (23), 258 (100), 242 (83), 226 (14), 216 (6), 150 (6) 93 (3), 43 (2).

4.4. Analytical scale procedure

4.4.1. Analytical scale enzymatic acylation of racemic 1-heteroarylethanols rac-2a–d

In a typical small scale experiment, one of the 1-heteroarylethanols *rac*-**2a**–**d** (0.05 mmol) and vinyl acetate (0.1, 0.2, 0.25, 0.4 mmol) were dissolved in a dry organic solvent (1 mL). After adding lipase (10 mg), the mixture was shaken at 300 rpm at room temperature. Samples (10 μL) were taken at different intervals of time, diluted with the same solvent (100 μL) as the mobile phase for HPLC (see Section 4.1) and analyzed by HPLC.

4.4.2. Analytical scale enzymatic alcoholysis of racemic 1-heteroarylethyl acetates *rac*-3a–d

In a typical small scale experiment, one of the 1-heteroarylethyl acetates *rac*-**3a**–**d** (0.05 mmol) was dissolved in dry organic solvent and lipase (10 mg) and methanol (0.1, 0.2, 0.3, 0.4 mmol) were added into the solution. The mixture was shaken at 300 rpm at room temperature. Samples were taken at different intervals of time, diluted with the same solvent (100 μL) as the mobile phase for HPLC (see Section 4.1) and analyzed with HPLC.

4.5. Preparative scale procedure

4.5.1. Preparative scale enzymatic acylation of racemic 1-heteroarylethanols *rac*-2a–d

A mixture of *rac*-**3a**–**d** (100 mg), vinyl acetate (300 μL) and CaL-B (100 mg) in acetonitrile was shaken at 300 rpm at room temperature. Samples from the reaction mixture (5 μL) were diluted with *n*-hexane/2-propanol (8:2, 100 μL) and analyzed by HPLC. The reactions were stopped by filtering the enzyme at approximately 50% conversions. The solvent was removed in vacuo, and the crude product was purified by column chromatography using *n*-hexane/ethyl acetate (1:1, v/v) as eluent, resulting in the optically active 1-heteroarylethanols (*S*)-**2a**–**d** and 1-heteroarylethyl acetates (*R*)-**3a**–**d**.

4.5.2. Preparative scale enzymatic alcoholysis of racemic 1-heteroarylethyl acetates rac-3a–d

A mixture of *rac*-**3a**–**d** (100 mg), vinyl acetate (300 μL) and CaL-B (100 mg) in acetonitrile was shaken at 300 rpm at room temperature. Samples from the reaction mixture (5 μL) were diluted with *n*-hexane/2-propanol (8:2, 100 μL) and analyzed with HPLC. The reactions were stopped by filtering the enzyme at approximately 50% conversions. The solvent was removed in vacuo, and the crude product was purified by column chromatography using *n*-hexane/ethyl acetate (1:1, v/v) as eluent, resulting in the optically active 1-heteroarylethanols (*S*)-**2a**–**d** and 1-heteroarylethyl acetates (*R*)-**3a**–**d**.

MS, NMR and IR spectra of the optically active products were indistinguishable from those of their racemates. Data on yield, enantiomeric composition and specific rotation of the products are shown in Table 5.

4.6. Preparation of the Mosher's esters

Into the solution of racemic 1-heteroarylethanol *rac*-**2b** or enantiomerically pure 1-heterorarylethanol (*S*)-**2b** (20 mg, 0.071 mmol) in CH_2Cl_2 (2 mL), 4-*N*,*N*-dimethylamino-pyridine in pyridine (100 μL, 1% solution) was added, followed by the addition of (*R*)-MTPA-Cl (35 mg, 0.14 mmol). The reaction mixture was stirred for 24 h at room temperature. The solvent was further removed in vacuo, and the product was purified by column chromatography using *n*-hexane-ethylacetate (1:1, v/v) as eluent.

Acknowledgements

L.C.B. is grateful for grants from the Romanian National Council of Scientific Research of Higher Education (BD, Cod CNCSIS: 384) and the Hungarian Academy of Science (Hungarian Science Abroad Scholarship Programe, MTA HTMTÖP). We thank also Professor Mircea Dărăbanţu for useful discussions on the stereochemistry topics of the manuscript.

References

1. (a) Caner, S.; Groner, E.; Levy, L. *DDT* **2004**, *9*, 105–110; (b) Francotte, E.; Lindner, W. *Chirality in Drug Research*; Wiley-VCH: Weinheim, 2006. pp 13–18.
2. (a) Andreas, S.; Bommarius, B.; Riebel, R. *Biocatalysis*; Wiley-VCH, 2004. pp 2–14; (b) Liese, A.; Seelback, K.; Wandrey, C. *Industrial Biotransformations*; Wiley-WCH, 2006. pp 10–43.
3. (a) Magdolen, P.; Zahradník, P.; Foltínová, P. *Pharmazie* **2000**, *55*, 8; (b) Su, X.; Vicker, N.; Trusselle, M.; Halem, H.; Culler, M. D.; Potter, B. L. V. *Mol. Cell. Endocrinol.* **2009**, *301*, 169–173; (c) Su, X.; Vicker, N.; Ganeshapillai, D.; Smith, A.; Purohit, A.; Reed, J. M.; Potter, B. L. V. *Mol. Cell. Endocrinol.* **2006**, *248*, 169–173; (d) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209; (e) Onitsuka, S.; Nishino, H.; Kurosawa, K. *Tetrahedron Lett.* **2000**, *41*, 3149; (f) Alagoz, O.; Yilmaz, M.; Pekel, A. T. *Synth. Commun.* **2006**, *36*, 1005; (g) Lipshut, B. H. *Chem. Rev.* **1986**, *86*, 795; (h) Racane, L.; Kralj, M.; Suman, L.; Stojkovic, R.; Tralic-Kulenovic, V.; Karminski-Zamola, G. *Bioorg. Med. Chem.* **2010**, *18*, 1038–1044.
4. Tralic-Kulenovic, V.; Racane, L.; Kaminski-Zamola, G. *Spectrosc. Lett.* **2003**, *36*, 43–50.
5. Zajac, M.; Hrobarik, P.; Magdolen, P.; Foltinova, P.; Zahradnik, P. *Tetrahedron* **2008**, *64*, 10605–10618.
6. (a) Paizs, C.; Tosa, M.; Majdik, C.; Tähtinen, P.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 619–627; (b) Paizs, C.; Toşa, M. I.; Majdik, C.; Mişca, R.; Irimie, F. D. *Roum. Biotechnol. Lett.* **2001**, *6*, 325–331.
7. Kamal, A.; Azhar, A. M.; Krishajni, T.; Malik, M. S.; Azeeza, S. *Coordin. Chem. Rev.* **2008**, *252*, 569–592.
8. (a) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331–3351; (b) Toşa, M. I.; Pilbák, S.; Moldovan, P.; Paizs, C.; Szatzker, G.; Szakács, G.; Novak, L.; Irimie, F. D.; Poppe, L. *Tetrahedron: Asymmetry* **2008**, *19*, 1844–1852; (c) Bencze, L. C.; Paizs, C.; Toşa, M. I.; Vass, E.; Irimie, F. D. *Tetrahedron: Asymmetry* **2010**, *21*, 443–450; (d) Chojnacka, A.; Obara, R.; Wawrzenczyk, C. *Tetrahedron: Asymmetry* **2007**, *18*, 101–107.
9. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
10. Jing, Q.; Kazlauskas, R. J. *Chirality* **2008**, *20*, 724–735.
11. (a) Nagy, V.; Tőke, E. R.; Keong, L. C.; Szatzker, G.; Ibrahim, D.; Omar, I. C.; Szakács, G.; Poppe, L. *J. Mol. Catal. B: Enzym.* **2006**, *39*, 141–148; (b) Bosch, B.; Meissner, R.; Berendes, F.; Rainhard, K. US2005/0153404A1.
12. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
13. Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663–2669.
14. (a) Baskar, B.; Pandian, N. G.; Priya, K.; Chadha, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3961–3966; (b) Chen, H.; Nagabandi, S.; Smith, S.; Goodman, J. M.; Plettner, E. *Tetrahedron: Asymmetry* **2009**, *20*, 449–456.
15. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519; (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143; (c) Merckx, E. M.; Vanhoeck, L.; Lepoivre, J. A.; Alderweireld, F. C.; Van Der Veken, B. J.; Tollenaere, J. P.; Raymaekers, L. A. *Spectr.: Int. Journal.* **1983**, *2*, 30; (d) Doesburg, H. M.; Petit, G. H.; Merckx, E. M. *Acta Crystallogr., Sect. B* **1982**, *38*, 1181; (e) Oh, S. S.; Butler, W. H.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 4499.