BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS

INVESTIGATION OF RESOLUTION OF ALCOHOLS

Ph.D. thesis

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1. INTRODUCTION AND AIMS

The asymmetric molecules prepared on the general chemical synthesises arise as racemic compounds. The racemic compound is a mixture with 1:1 proportion of two enantiomers which are in reflection relationship. The effect of these two enantiomers of a racemic compound is different for the living organisms so it is very important to examine the effect of the certain enantiomer separately. The preparation of the chiral molecule in enantiopure form is playing more and more important role in numerous fields, especially in chemical, pharmaceutical and pesticide research and manufacture and this requirement necessitates the research of different methods of resolution and selective synthesis.

Since Pasteur made the first resolution with the sorting out manually the ammonium tartarate crystals in the middle of the XIX. century the preparation of optically active molecules has undergone an explosive development - like the other area of science. Nowadays the most prevalent method among of the methods for preparation of optically active molecules is the chemical resolution *via* diastereoisomeric salt formation. In the last decades the part of biocatalysis has become important and indispensable in several aspects.

In course of my work I studied the possibilities of the resolution of different racemic alcohol compounds and the purification of various mixtures of enantiomers with enzymes and chemical reagents.

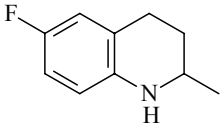
2. SUMMARY OF NEW SCIENTIFIC RESULTS

Model compounds

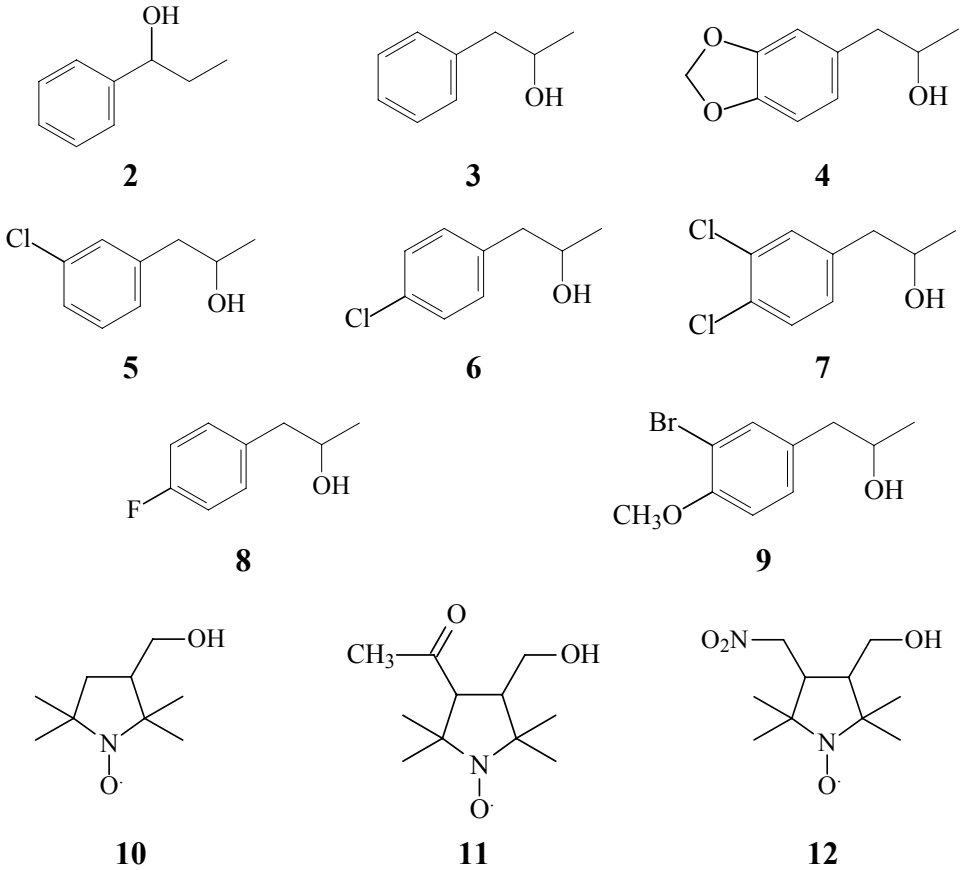
Our research group has been dealing with resolution in the Budapest University of Technology and Economics at the Department of Organic Chemical Technology for a long time. At the beginning of my work during the resolution of the racemic (6-fluoro-2-methyl)-1,2,3,4-tetrahydroquioline (FTHQ) (**1**) *via* diastereoisomeric salt formation (**Scheme 1**) we observed a very interesting phenomenon: the reverse influence of the kinetic and thermodynamic control for the chiral recognition.

Latching on the researches my challenge was the studying of resolutions achievable under kinetic and thermodynamic control. My model compounds were the racemic 1-phenyl-1-propanol (**2**), 1-phenyl-2-propanol (**3**), 1-benzo[1,3]dioxole-5-yl-2-propanol (**4**), 1-(3-chlorophenyl)-2-propanol (**5**), 1-(4-chlorophenyl)-2-propanol (**6**), 1-(3,4-dichlorophenyl)-2-propanol (**7**), 1-(4-fluorophenyl)-2-propanol (**8**), 1-(3-bromo-4-methoxyphenyl)-2-propanol (**9**), and the racemic 3-

(hydroximethyl)-2,2,5,5-tetramethyl-pyrrolidine oxide (**10**), *transz*-3-(hydroximethyl)-4-(methoxycarbonil)-2,2,5,5-tetramethyl-pirrolidine oxide (**11**), *transz*-3-(hydroximethyl)-4-(nitromethyl)-2,2,5,5-tetramethyl-pirrolidine oxide (**12**) (**Scheme 2**).



Scheme 1: (6-Fluoro-2-methyl)-1,2,3,4-tetrahydroquioline (FTHQ) (**1**)



Scheme 2: Model compounds

2.2. The influence of the kinetic and thermodynamic control on the resolution of Flumequin intemedier[1]

During the early investigations we found that respectively the *(R)*- and *(S)*-enantiomer crystallize alike in the diastereoisomeric salt depending on the solvent. Further investigations were elaborated in the two chosen solvents – methanol and ethyl acetate – and the resolution agent was di-*p*-tolyl tartaric acid in amount of half equivalent. We observed that the enantiomeric

excess of the *(S)*-enantiomer crystallized in the diastereoisomeric salt increases continuously in advance of the time using methanol as solvent. We worked up the crystallized diastereoisomeric salt after 5 minutes, 4 days and 3 weeks and we found that the enantiomeric excess and the yield were increased; the system went on the thermodynamical equilibrium.

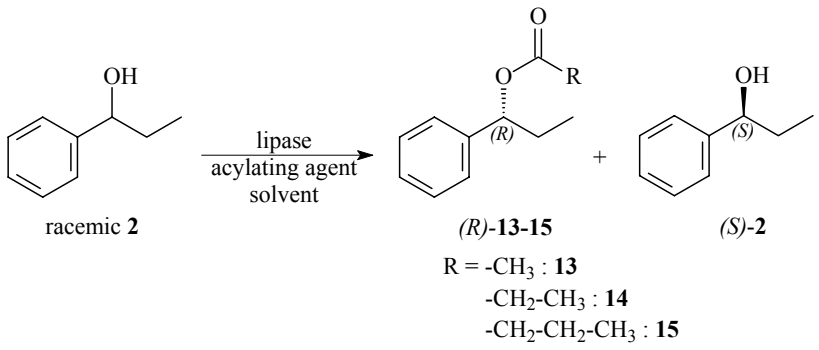
Making the resolution in ethyl acetate firstly the less stable diastereoisomeric salt containing the *(R)*-enantiomer crystallized. Working up this diastereoisomeric salt after 5 minutes and then 4 days further crystallization were observed by the decrease of the enantiomeric excess of the mixture of enantiomers. However working up the diastereoisomeric salt after 3 weeks the mixture of enantiomers containing the more stable *(S)*-enantiomer in small excess was obtained. In pursuance of resolution such kinetic effects like this was not described in the literature yet.

2.3. Separation of the enantiomers of alcohols by biological method

2.3.1. Lipase-catalyzed kinetic resolution of phenyl propanols

2.3.1.1. Lipase-catalyzed kinetic resolution of 1-phenyl-1-propanol (**2**) by acylation

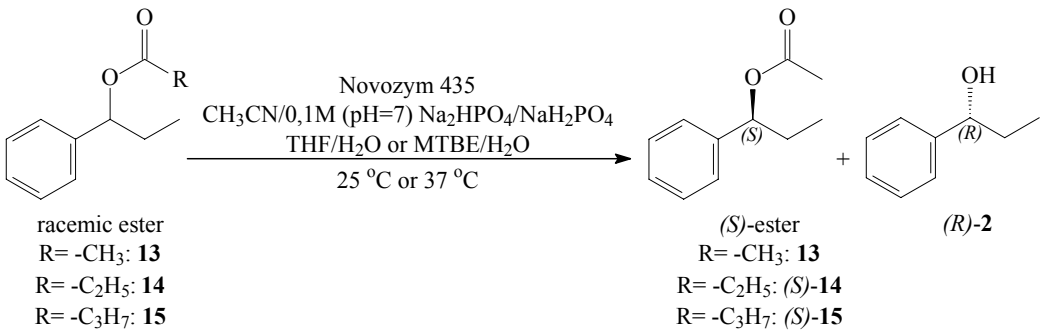
The best enantiomer selectivity was achieved with vinyl acetate acylating agent in the selective acylation of the racemic 1-phenyl-1-propanol (**2**) using Amano PS-C and Novozym 435 enzyme preparations (**Scheme 3**). With the changing of the solvent better enantiomer selectivity and increase of the reaction time were observed in hexane. Using different acylating agents like vinyl propionate and vinyl butyrate hexane was used as solvent and increasing the size of the acyl group the increase of the enantiomeric selectivity was obtained in the investigations.



Scheme 3: Lipase-catalyzed kinetic resolution of the racemic 1-phenyl-1-propanol (**2**) by acylation

2.3.1.2. Lipase-catalyzed kinetic resolution of 1-phenyl-1-propanol esters (**13**-**15**) by hydrolysis

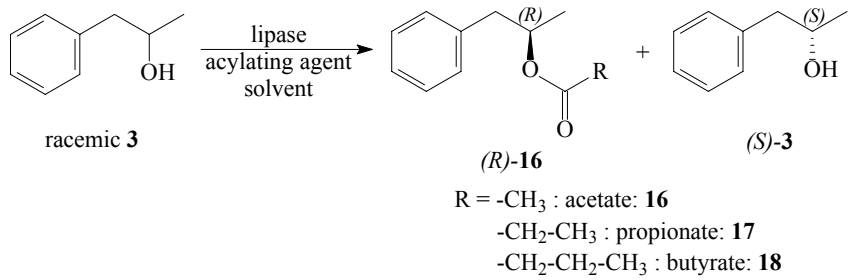
Investigating the selective hydrolysis of 1-phenyl-1-propanol esters (**13**-**15**) the best enantiomeric selectivity was achieved using Novozym 435 enzyme preparation (**Scheme 4**). Among the tested solvents and reaction temperatures better enantiomeric selectivity was observed in room temperature and water/methyl-*terc*-buthyl-ether system. When the size of the acyl group was increased the enantiomeric selectivity changed too: the best enantioseparation was obtained using propionate (**14**) as staring compound, which has a chain one more methylene group than the acetate has. On the other hand the obtained results by the hydrolysis of the butyrate (**15**) which has two more methylene groups than the acetate has was similar to the obtained enantiomeric selectivity of the hydrolysis of the acetate (**13**).



Scheme 4: Selective hydrolysis of racemic 1-phenyl-1-propanol esters (**13**-**15**)

2.3.2.2. Lipase-catalyzed kinetic resolution of 1-phenyl-2-propanol (**3**)[2]

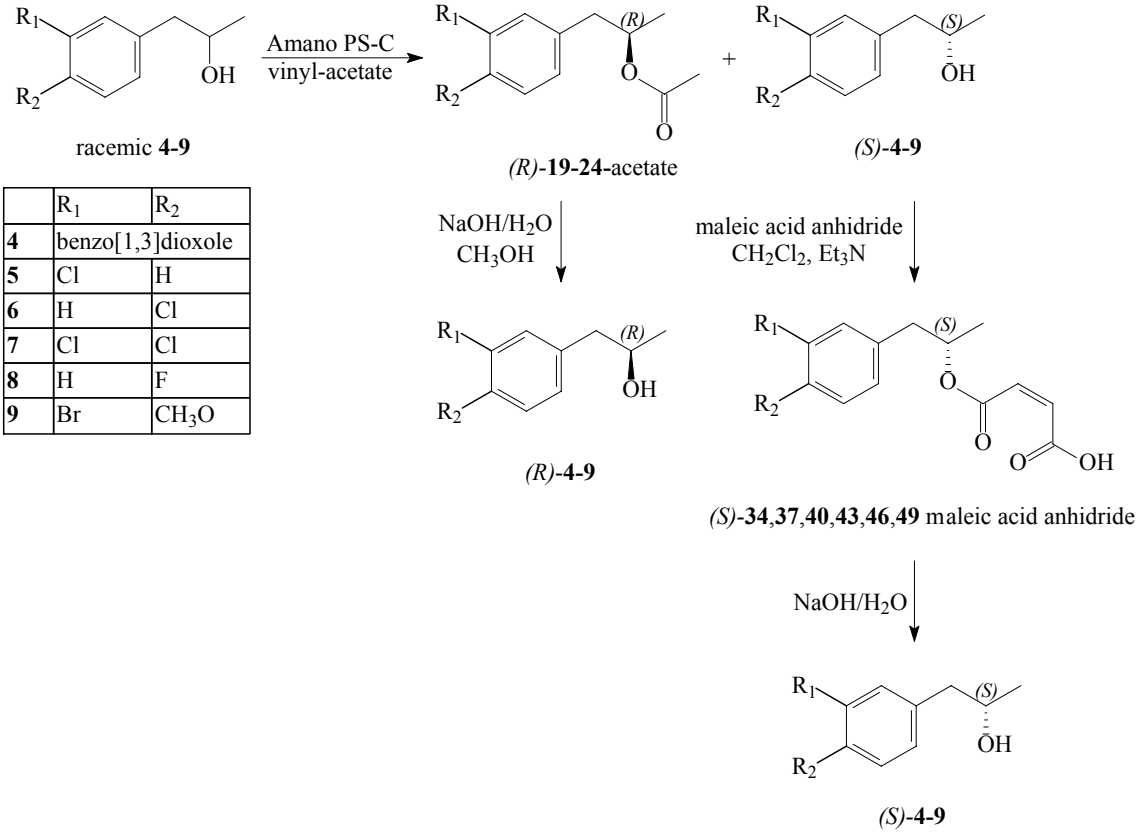
The selective acylation of the racemic 1-phenyl-2-propanol (**3**) was elaborated with the same reaction conditions (lipase, solvent, acylating agent, reaction temperature) as with the 1-phenyl-1-propanol (**2**) were (**Scheme 5**). The best enantiomeric selectivity was obtained by using Amano PS-C and hexane seemed better among the investigations with different solvents. Hexane was used as solvent in further investigations with acylating agent containing acyl groups with growing chain and I found that the size of the acyl group does not influence the enantiomeric selectivity at a significant rate.



Scheme 5: Selective acylation of the racemic 1-phenyl-2-propanol (**3**)

2.3.2.2. Lipase-catalyzed kinetic resolution of substituted 1-phenyl-2-propanol derivatives (**4-9**)[2,3,8]

The separation of the enantiomers of the 1-phenyl-2-propanol derivatives substituted in positions 3 and/or 4 was successful with lipase-catalysed selective acylation using Novozym 435 enzyme preparation. The separation of the arisen acetate was achieved from the unreacted alcohol with chemical method *via* formation of maleic acid monoester (**Scheme 6**) and the purification of the mixtures of enantiomers was investigated with lipase-catalyzed kinetic re-resolution, too.



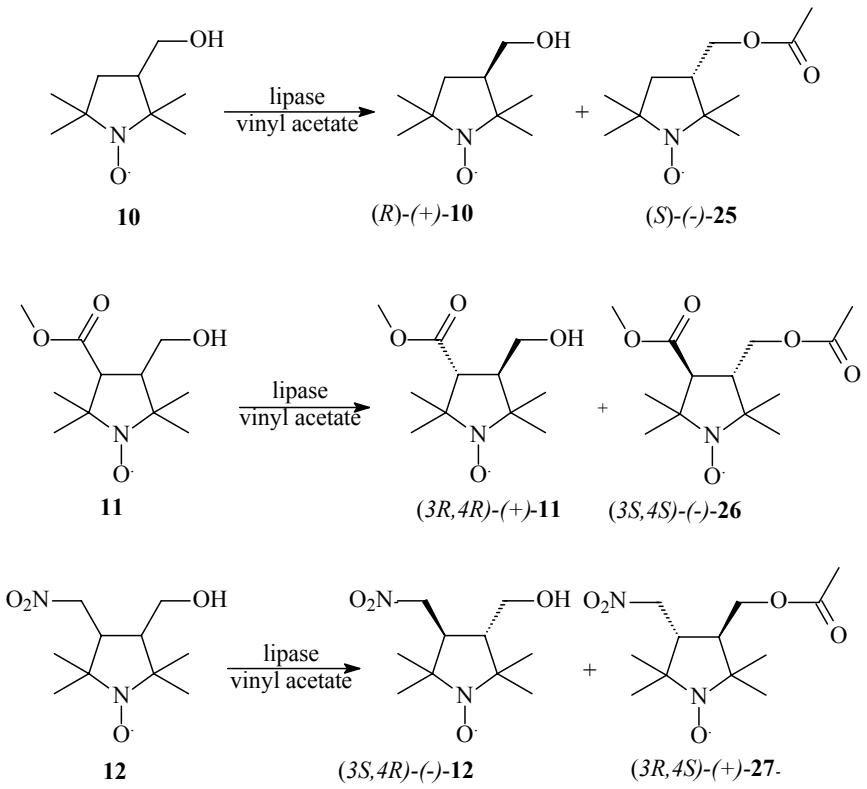
	R_1	R_2
4	benzo[1,3]dioxole	
5	Cl	H
6	H	Cl
7	Cl	Cl
8	H	F
9	Br	CH_3O

Scheme 6: Lipase-catalysed selective acylation of substituted 1phenyl-2-propanol derivatives (**4-9**) using Amano PS-C lipase preparation

The position and the number of the substituents in the aromatic ring have various affects on the enantiomeric selectivity in the selective acylating reaction of racemic **4**-**9** alcohols. The best result was obtained in case of **4** alcohol containing a methylene dioxide substituent in the positions number 3 and 4 while the separation was similar but a little bit weaker in the reactions of **5**, **7**, **8** and **9** alcohols substituted in position number 3 and disubstituted in positions number 3 and 4. The worst selectivity was obtained in the acylation of **6** alcohol substituted in position number 4.

2.4. Lipase-catalysed kinetic resolution of different tetramethyl pirrolidine oxide derivatives[4]

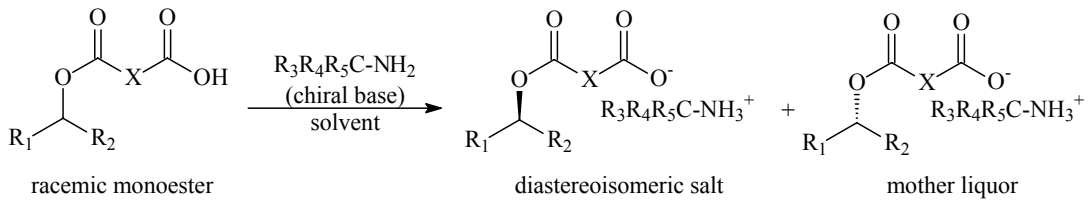
The separation of the enantiomers of the 3-(hydroxyl-methyl)-2,2,5,5-tetramethyl-pirrolidine oxides (**10**-**13**) containing no substituent, methoxy-carbonil and nitro-methyl groups in position number 4 was successfully achieved *via* lipase-catalysed kinetic resolution (**Scheme 7**). There is no example for the separation of the enantiomers with the above mentioned compounds with enzymatic method in the literature. The enantiomers were obtained with moderate enantiomeric excess in the reactions, which then were purified in lipase-catalysed kinetic re-resolution and recrystallization, too.



Scheme 7: Selective acylation of different tetramethyl pirrolidine oxide derivatives (**10**-**12**)

2.5. Separation of the enantiomers of different alcohols by chemical method[2,5]

First, the maleic acid, the succinic acid and the phthalic acid monoesters **(28-51**) of the **2-9** alcohols were synthesised for the chemical resolution *via* diastereoisomeric salt formation (**Scheme 8**) which is practicable under thermodynamic control (**Table 1**).

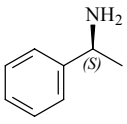
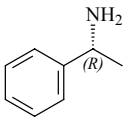
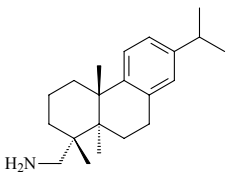
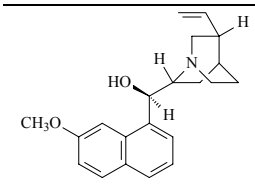
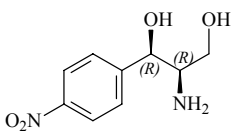
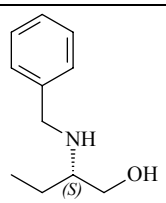
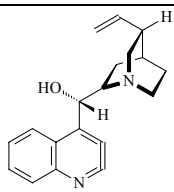
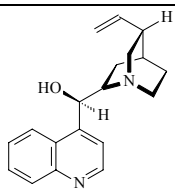
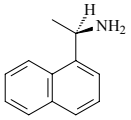


Scheme 8: Chemical resolution *via* diastereoisomeric salt

Table 1: Monoesters of the racemic **2-9** alcohols

	R_1	**R_2**	**X = CH=CH**	**Y (%)**	**X = CH_2-CH_2**	**Y (%)**	**X=** 	**Y (%)**
2	H	H	**28**	91	**29**	94	**30**	91
3	H	H	**31**	99	**32**	97	**33**	96
4	benzo[1.3]dioxole		**34**	98	**35**	86	**36**	96
5	Cl	H	**37**	98	**38**	96	**39**	96
6	H	Cl	**40**	~100	**41**	94	**42**	97
7	Cl	Cl	**43**	99	**44**	97	**45**	99
8	H	F	**46**	92	**47**	84	**48**	92
9	Br	CH_3O	**49**	98	**50**	98	**51**	98

Table 2: Chiral basises

	**52**		**53**		**54**
	**55**		**56**		**57**
	**58**		**59**		**60**

The resolving agents were various chiral basises such as the *(S)-(-)*-1-phenylethylamine (**52**), *(R)-(+)*-1- phenylethylamine (**53**), (+)-dehydroabiethylamine (**54**), quinine (**55**), *(R,R)-(-)*-1-(4-nitrophenyl)-2-amino-1,3-propanediole (**56**), *(S)-(+)*-2-benzylaminobuthanol (**57**), cinchonine (**58**), cinchonidine (**59**), and *(R)-(+)*-1-(1-naphtyl)-ethylamine (**60**) (**Table 2**). The solvents were ethyl acetate, methanol, diethyl ether, diisopropyl ether and the mixtures of the above mentioned solvents.

I established that the separation of the enantiomers is influenced by the place of the hydroxyl group and the place, number and quality of the substituents in the aromatic ring equally. The maleic and the succinic acid monoesters (**28**, **29**) prepared from the unsubstituted **2** alcohol were successfully resolved but only the maleic acid monoesters (**31**, **34**) synthesised from the unsubstituted **3** alcohol and the **4** alcohol containing methylene dioxide substituent in the places number 3 and 4 were successfully separated for the two enantiomers.

Besides the enantiomers of maleic acid monoesters (**37**, **43**, **49**) the succinic acid and/or the phthalic acid monoesters (**39**, **44**, **50**, **51**) of **5**, **7**, and **9** alcohols substituted in the place number 3 and disubstituted in the places number 3 and 4 were successfully separated but the best result was obtained with the maleic acid monoester in case of each alcohols. Finally both the succinic and the phthalic acid monoester (**41**, **42**) of **6** alcohol substituted in the place number 4 were successfully resolved but no result was obtained with the maleic acid monoester (**40**).

Finally the various mixtures of enantiomers were investigated respectively with re-resolution using the appropriate resolving agents and recrystallization in course of monoesters and alcohols with solid state.

3. PUBLCATIONS

3.1. Published articles on the subject of the dissertation

1. József Bálint, Gabriella Egri, Violetta Kiss, Antal Gajáry, Zoltán Juvancz and Elemér Fogassy: Unusual phenomena during the resolution of 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ): thermodynamic-kinetic control; *Tetrahedron: Asymmetry*, **2001**, *12*, 3435-3439.
2. Violetta Kiss, Gabriella Egri, József Bálint, István Ling, József Barkóczi and Elemér Fogassy: Kinetic and chemical resolution of different 1-phenyl-2-propanol derivatives; *Tetrahedron: Asymmetry*, **2006**, *17*, 2220–2234.
3. Z. Juvancz, V. Kiss, J. Schindler, J. Bálint: Use of achiral derivatization to increase selectivity and reverse the order of elution of enantiomers on chirasil-dex; *Chromatographia*, **2004**, *60*, S161-163.
4. József Bálint, Violetta Kiss, Gabriella Egri, Tamás Kálai, Ádám Demeter, Mária Balog, Elemér Fogassy and Kálmán Hideg: Kinetic resolution of 1-oxyl-3-hydroxymethyl-2,2,5,5-tetramethylpyrrolidine derivatives by lipase-catalyzed enantiomer selective acylation; *Tetrahedron: Asymmetry*, 15, **2004**, 671-679.
5. Violetta Kiss, Gabriella Egri, József Bálint, Elemér Fogassy: Enantioseparation of secondary alcohols by diastereoisomeric salt formation; *Chirality*, 18, **2006**, 1–5.

3.2. Other articles on the subject of the dissertation

6. Violetta Kiss and Elemér Fogassy: Resolution of different phenylisopropanol derivatives; PhD Students: 2nd Conference of PhD Students at Faculty of Chemical Engineering, *Periodica Polytechnica Chemical Engineering*, 49/1, **2004**, 55-56.
7. Tamás Horváth**,** Violetta Kiss and Elemér Fogassy: Resolution of racemic 1-phenyl-1-propanol; MSc Students: Conference of MSc Students, *Periodica Polytechnica Chemical Engineering*, 47/2, **2003**, 132-133.

3.3. Patent on the subject of the dissertation

8. József Barkóczy, István Ling, József Bálint, Gabriella Egri, Violetta Kiss, Elemér Fogassy: Pharmaceutical intermediates and a process for the preparation thereof, WO 2006/013399 A1, International publication date: 09. February, **2006**.

3.4. Posters on the subject of the dissertation

9. Kiss Violetta, Egri Gabriella, Bálint József: Fenil-izopropanol származékok reszolválásának vizsgálata; **2. Doktoráns Konferencia**, Budapesti Műszaki és Gazdaságtudományi Egyetem, Vegyészmérnöki Kar, 2004. november 24.
10. Kiss Violetta, Dr. Egri Gabriella, Dr. Bálint József, Dr. Fogassy Elemér: 1-Fenil-2-propanol reszolválási lehetőségei; **MKE Vegyészkonferencia**, Hajdúszoboszló**,** 2003. június 26-28**.**

3.5. Publications not fitted in the subject of the dissertation

11. Elemér Fogassy, Mihály Nógrádi, Dávid Kozma, Gabriella Egri, Emese Pálovics, Violetta Kiss: Optical resolution methods; *Biomol. Chem.*, **2006**, *4*, 3011-3030.
12. Fogassy Elemér, Schindler József, Kiss Violetta, Pálovics Emese: Kiralitás és a szerves kémia néhány összefüggése; *Magyar Kémiai Folyóirat*, 109-110, **2004**, 64-70.
13. József Bálint, Gabriella Egri, Mátyás Czugler, József Schindler, Violetta Kiss, Zoltán Juvancz and Elemér Fogassy: Resolution of alpha-phenylethylamine by its acidic derivatives; *Tetrahedron: Asymmetry*, 12, **2001**, 1511-1518.