Antioxidáns hatású természetes eredetű vegyületek szintézise

Doktori (PhD) értekezés tézisei

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Synthesis of natural compounds with antioxidant properties

PhD theses

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Természettudományi Kar

Debrecen, 2005

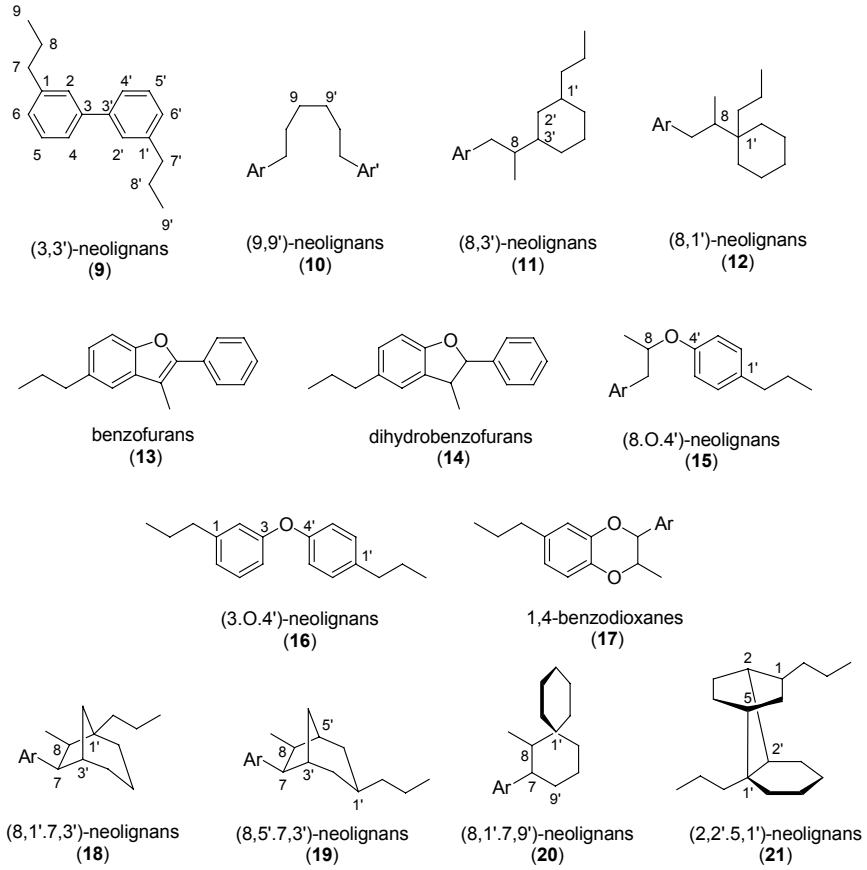
„Soha ne úgy gondolj tanulmányaidra, mint kötelességre, hanem mint irigylésre méltó lehetőségre, megismerni a szépség felszabadító erejét a szellem birodalmában saját kedvedre és a közösség hasznára, amelyhez későbbi munkád tartozik.”

Albert Einstein

1. Antecedents and aims

Naturally occurring plant products have been used for treatment of diseases since centuries. Usage of these compounds have renaissance, however, in many cases exact structure of molecule possessing the pharmacological activity is not known, therefore the structure determination and exploration of structure-biological activity relationship of such a compound are very important research fields of organic and pharmaceutical chemistry.

Neolignans is one of the most important groups of naturally occurring natural products of biological activity. On the basis of their structures these can be divided into more than fifteen classes and in which further subclasses can also be distinguished. Their classification -similar to lignans- is defined by bond linking of two C_6-C_3 units. The most important classes are the followings (Scheme 1):



Scheme 1

These compounds of significant different structures possess a wide range of biological activity. In course of my work 2,3-dihydrobenzo[b]furan-, and 8.O.4'-neolignan- and 1,4-benzodioxan-type neolignans (**14,15,17** resp.) have been synthesized and in the case of 8.O.4'-neolignans their antioxidant property was also examined.

2. Applied methods

The macro, semi macro and micro methods of modern preparative organic chemistry were applied in the synthetic work. Reactions were monitored by thin layer chromatography; the isolation and

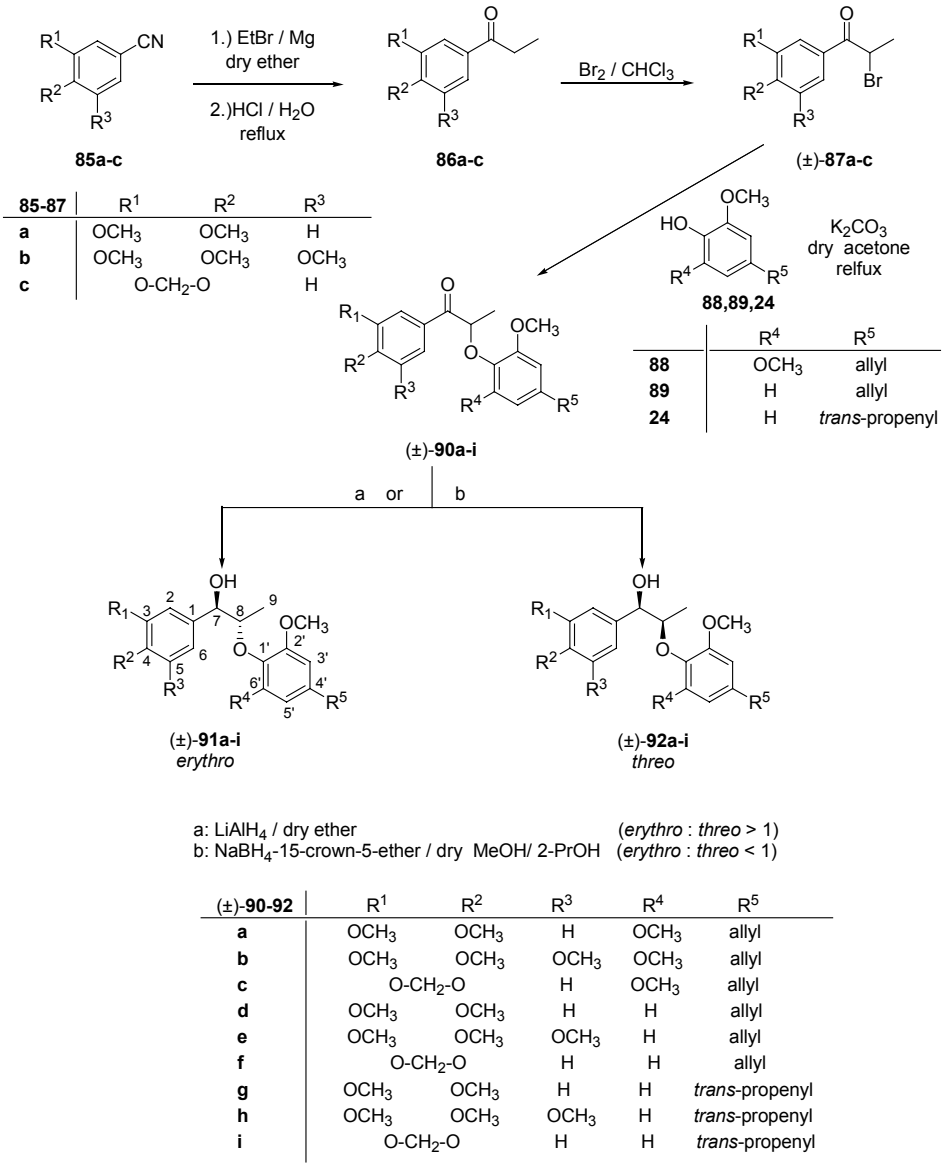
purification of the crude products were carried out by column chromatography. Melting point, optical rotation, ^{1}H and ^{13}C NMR and CD spectroscopy measurements were applied for the identification and characterization of the prepared compounds. Assay of superoxide anion generation was assessed spectrophotometrically by measuring the reduction of cytochrome C in a microassay and an ELISA reader. In these experiments 8.O.4'-neolignans or Vitamin E at a final concentration of 25 μM were added. The samples were incubated for 10 min in a micro-plate incubator, and the cell suspension was added into each well. The cells were stimulated by phorbol myristate acetate (PMA) and the plate was incubated for 15 min at 37°C and then cytochrome C reduction was measured by spectrophotometer at 550 nm.

3. New results

3.1. Synthesis and study of antioxidant properties of 8.O.4'-neolignans

Radical scavenging activities of flavonolignans belong to polyphenols family has been reported in literature but interestingly this property of 8.O.4'-neolignans has not been examined yet. On the basis of their structure one can be expected that they have antioxidant property similar to 2,3-dihydrobenzo[b]furan and 1,4-benzodioxane type flavonolignans isolated from *Silybum marianum*. In order to continue our work on the field of the synthesis and biological study of O-heterocyclic compounds of natural origin *erythro*-**91a-d,g** and *threo*-**92g,h** 8.O.4'-naturally occurring neolignans as well as their derivatives (**91e,f,h,i; 92a-f,i**) have been synthesized and their effect on the superoxide anion ($O_2^{\cdot-}$) release by human polymorphonuclear leukocytes (PMNLs) has also been studied.

According to the literature racemic α-bromo propiophenon derivatives [(±)-**87a-c**] were synthesized from the appropriate nitrile derivatives **85a-c** by Grignard reaction followed by bromination. These compounds were treated with **88,89,24** phenols in present of potassium carbonate in acetone at 56ºC to give the appropriate ketones (±)-**90a-i**, whose stereocontrolled reduction could be achieved by lithium aluminium hydride yielded *erythro*-(±)-**91a-i** alcohols as a major products (Scheme 2).



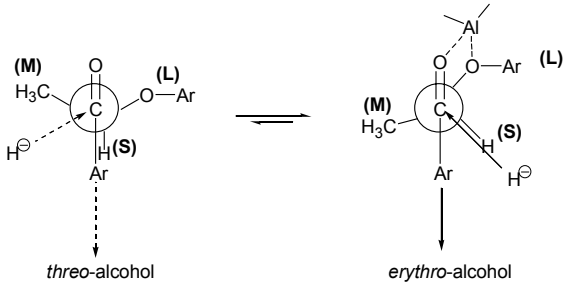
85-87	R^1	R^2	R^3
a	OCH_3	OCH_3	H
b	OCH_3	OCH_3	OCH_3
c	O-CH_2-O		H

	R^4	R^5
88	OCH_3	allyl
89	H	allyl
24	H	*trans*-propenyl

(±)-**90-92**	R^1	R^2	R^3	R^4	R^5
a	OCH_3	OCH_3	H	OCH_3	allyl
b	OCH_3	OCH_3	OCH_3	OCH_3	allyl
c	O-CH_2-O		H	OCH_3	allyl
d	OCH_3	OCH_3	H	H	allyl
e	OCH_3	OCH_3	OCH_3	H	allyl
f	O-CH_2-O		H	H	allyl
g	OCH_3	OCH_3	H	H	*trans*-propenyl
h	OCH_3	OCH_3	OCH_3	H	*trans*-propenyl
i	O-CH_2-O		H	H	*trans*-propenyl

Scheme 2

Separation of these compounds from the *threo*-derivatives [(±)-**92a-i**] was performed by preparative TLC. The stereoselectivity of the reduction could be changed by using so called „naked" hydride reagent prepared *in situ* from $NaBH_4$ and 15-crown-[5]-ether. According to Cram's rule and *threo*-alcohols were formed as a major product in every case (Scheme 3).

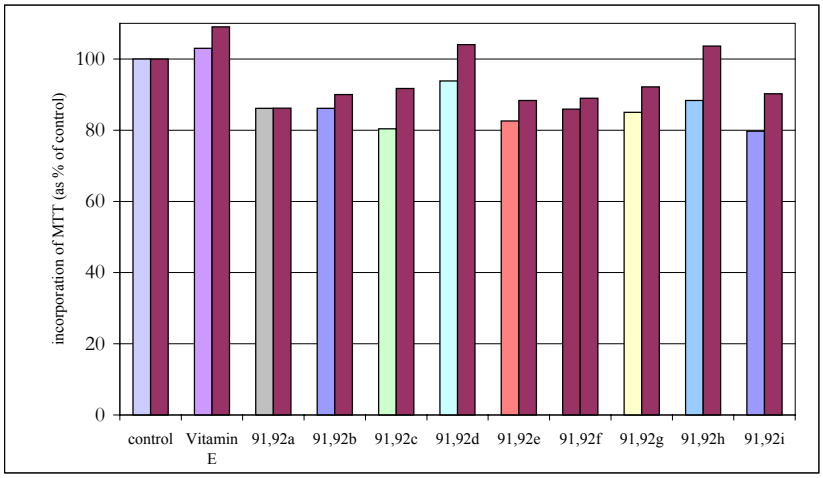


Scheme 3

The inhibitory activity of these compounds on the superoxide anion ($O_2^{\cdot-}$) release by PMNLs have been tested and the structure-activity relationship was also studied. It is well known that in human

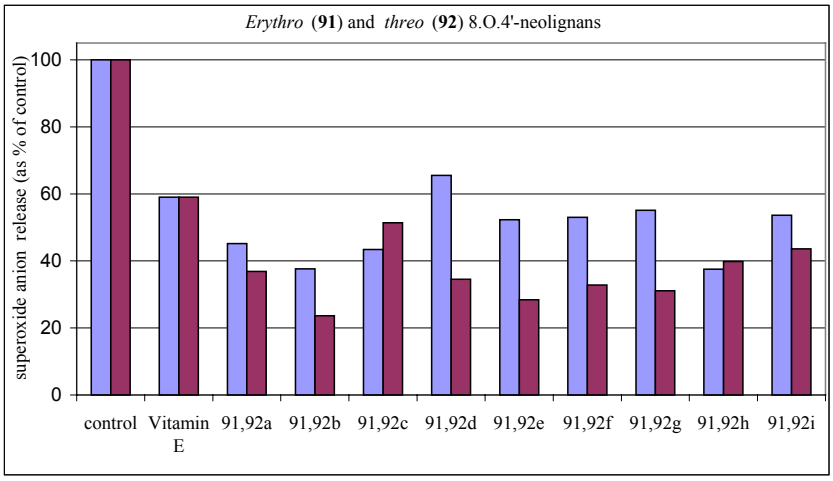
circulation system the PMNLs generate $O_2^{\cdot-}$ in the presence of PMA due to its influence on protein kinase C (PKC) and NADPH oxidase (reduced nicotinamide adenine dinucleotide phosphate oxidase) enzymes.

The incorporation of 3-(4,5-dimethyltiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into cells has clearly shown that the racemic **91,92a-i** 8.O.4'-neolignans are not toxic in 25μM concentration. It is also noteworthy that the incorporation of MTT was reduced only by 20-25% in 100μM concentration therefore the inhibition of $O_2^{\cdot-}$ release exclusively belong to antioxidant activity of our compounds (Scheme 4).



Scheme 4

The $O_2^{\cdot-}$ release of PMNLs were reduced significantly by all compounds (**91,92a-i**) in 25μM a 25-70% inhibition has been observed (10 min after the stimulation) and the antioxidant capacity of these compounds has been found to be measurable after 30 minutes after stimulation and its change in time has also suggested that there is a relationship between the structure of the molecule and its antioxidant activity. Furthermore, a significant difference between scavenging activity of the *erythro*- and *threo*-alcohols could be observed (Scheme 5).



Scheme 5

The values of $O_2^{\cdot-}$ release clearly indicated that exception of **92c** all further compounds belonging to the *threo* series of 8.O.4'-neolignans possess significantly higher activity on the inhibition of oxidative burst of PMNLs, than their *erythro* stereoisomers. Remarkable that in the case of **92a,b,e,f,g** the inhibition were higher than 60% and the highest inhibitory activity was found in the case of **92b**. This result is in full harmony with our earlier results suggesting that the inhibitory activity of molecules in $O_2^{\cdot-}$ release of human PMNLs can be influenced by its lipid solubility. Thus, the higher lipid solubility, i.e. presence of more methoxy groups in the molecule, might enhance the binding of the molecule into the cell membrane where $O_2^{\cdot-}$ is formed by membrane-bound NADPH oxidase. The significant difference between the inhibition value of **92e** and **92h** referred the binding of the molecule into the cell membrane in the case of molecule with allyl side chain is favourable. It is also known, the biological effect of a racemate can be significantly different to its enantiomers. Since the antioxidant activity of racemic **92a-i** *threo* neolignans has been found to be comparable with that of Vitamin E so it was obvious to study the activity of their enantionomers as well. Therefore we have investigated the resolution and enantioselective synthesis of these compounds in detail.

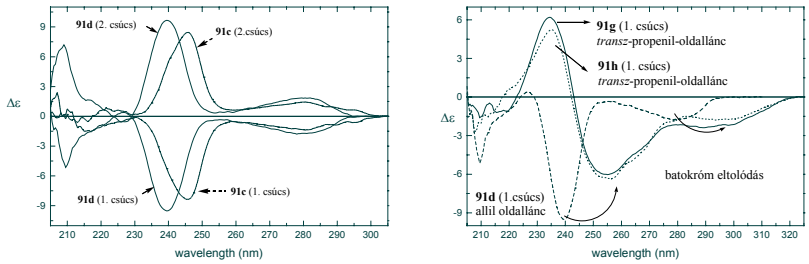
3.2. Resolution and enantioselective synthesis of 8.O.4' neolignans

The resolution of racemic *erythro*- and *threo*-alcohols was performed by HPLC on chiral stationer phase (Chiralcel OD). The optimized chromatographic conditions (*n*-hexane : 2-propanol = 90:10 v= 0.9, 0.5 ml/min) provided baseline separation most of the racemates (Table 1).

Compound	t_R1	k'1	t_R2	k'2	α	R_s
91a	20.81	3.94	21.77	4.17	1.06	0.91
92a	29.84	6.08	-	-	-	-
91b	17.38	3.13	18.43	3.37	1.08	0.95
92b	22.49	4.34	32.93	6.82	1.57	5.32
91c	10.08	1.39	13.29	2.16	1.55	5.33
92c	14.40	2.42	17.39	3.13	1.29	3.49
91d	20.81	3.94	26.84	5.37	1.36	4.18
92d	24.84	4.90	37.92	8.00	1.63	6.28
91e	17.97	3.27	-	-	-	-
92e	19.75	3.69	25.76	5.11	1.39	3.43
91f	10.97	1.60	12.89	2.06	1.28	3.24
92f	14.68	2.48	-	-	-	-
91g	23.60	4.60	31.76	6.54	1.42	4.71
92g	27.31	5.48	36.25	7.6	1.39	3.67
91h	21.65	4.14	28.48	5.76	1.39	3.98
92h	23.11	4.48	30.25	6.18	1.38	4.00
91i	12.68	2.01	17.60	3.18	1.58	6.17
92i	15.35	2.64	16.15	2.83	1.07	1.07
91j[a]	19.75	3.11	20.93	3.36	1.03	1.42
92j[a]	19.79	3.12	21.52	3.48	1.12	1.84
91jOAc[a]	11.47	1.39	12.77	1.66	1.20	2.24
92jOAc[a]	12.13	1.53	-	-	-	-
91fOAc	8.46	0.76	8.84	0.84	1.10	0.99
92fOAc	8.93	0.86	9.53	0.99	1.15	1.27

Table 1

The application of online HPLC-CD detection the LC/CD spectra of our compounds (except **91e,92a,92f**) were recorded on 230 and 245nm. The flow was stopped on the maxima of the CD signal and CD spectra of compounds were recorded in range 200-350 nm, so an unambiguous determination of absolute configuration was become possible (Scheme 6).

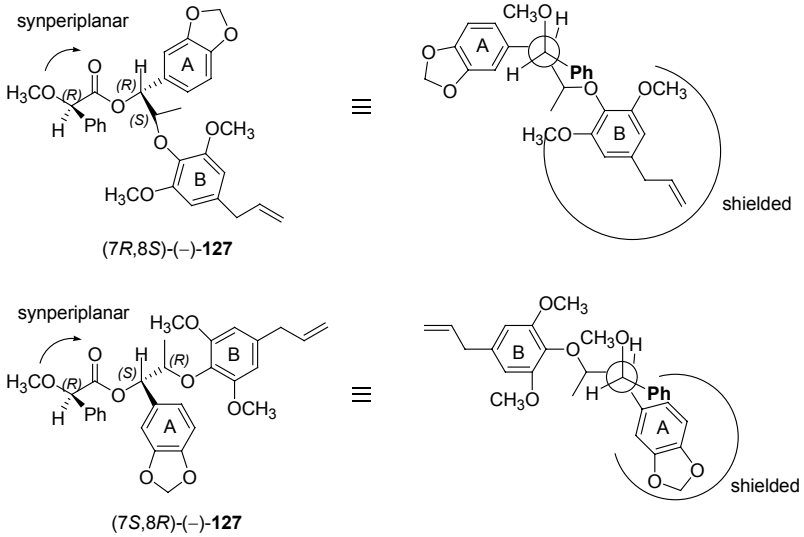


Scheme 6 A B

A: LC/CD spectra of the first and second eluted enantiomers of **91d** (continuous lines) and **91c** (dotted lines). B: LC/CD spectra of the *erythro*-8.O.4'-neolignans **91g** (continuous line) and **91h** (dotted line) compared with that of **91d** (broken line).

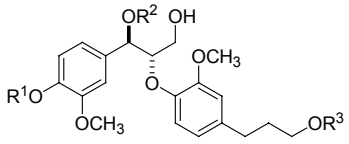
Either Horeau's or Mosher's method using ^{1}H-NMR spectroscopy has been already published in the literature for the determination of the absolute configuration of 8.O.4' neolignans. We have supposed that the preparative application of Mosher's method makes possible not only the synthesis of **91a-i** and **92a-i** neolignans in enantiomeric pure form but the ^{1}H and ^{13}C-NMR examination of their diastereomers obtained with *R*-(-)-α-methoxyphenyl acetic acid can provide further data to the determination of their absolute configuration.

Diastereomers of *erythro*- and *threo*-neolignans **91c,92c,e,i** were prepared with *R*-(-)-α-methoxyphenyl acetic acid (**125**) whose separation could be achieved without difficulties by column chromatography (Scheme 7).



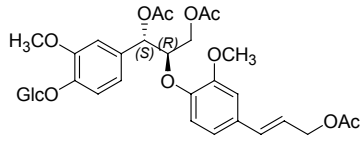
Scheme 7

The CD data of these compounds revealed that there is a simple relationship between the absolute configuration of *erythro*- and *threo*-8.O.4'-type neolignans and their chiroptical properties. A positive (negative) Cotton-effects within the ^1L_a and ^1L_b bands of benzene chromophore containing substituted ring A derives from 7*R*,8*S* (7*S*,8*R*) in the *erythro*-series. In the *threo*-series the same relationship is valid in the case of absolute configuration of 7*R*,8*R* (7*S*,8*S*). On the basis of this rule the absolute configuration of some naturally occurring neolignans have been revised (Scheme 8).



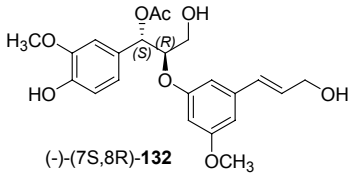
(-)-**129**,(-)-**130**

129: R_1 = Glc, R_2 = H, R_3 = H; CD nm (Δε): **239 (1.94)**
130: R_1 = H, R_2 = H, R_3 = Glc; CD nm (Δε): **239 (1.76)**



(-)-(7S,8R)-**131**

CD (EtOH) nm (Δε): 220 (-2.36), **228 (-3.60)** 235 (-1.75), 250 (-0.27).



(-)-(7S,8R)-**132**

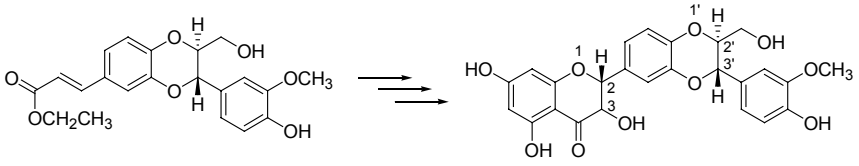
CD (EtOH) nm (Δε): 224 (-2.42), **230 (-3.75)**, 240 (-2.03), 254 (-0.25).

Scheme 8

Thus, the absolute configuration of (-)-**129** and (-)-**130** 8.O.4'-neolignan derivatives isolated from the leaves of *Lonireca graciliper* var. g*landulosa Maxim* by Matsuda and Kikuchi must be changed (7*S*,8*R*→7*R*,8*S*), as well as the configuration of (-)-**131** *erythro*-8.O.4'-neolignan and (-)-**132** 8.O.3'-neolignan containing *trans* propenyl side chain on ring B derivatives isolated from *Arum italicum* by Greca and his co-workers could be corrected (7*R*,8*S*→7*S*,8*R*) (Scheme 8).

3.3. Enzyme catalysed resolution of 2-hydroxymethyl-1,4-benzodioxanes

Recently we have shown that (±)-**77b** 1,4-benzodioxane derivative is a suitable starting material for the synthesis of hepatoprotective silybin-A, -B in racemic form (**77b** → **60a**) (Scheme 9). Since the configuration of chirality centres in the 1,4-benzodioxane ring remained unchanged in these transformation, so it was obvious intensively to deal with the resolution of (±)-**77b** whose enantiomers could be served as a starting material for the synthesis of (+)-silybin-A, and -B.



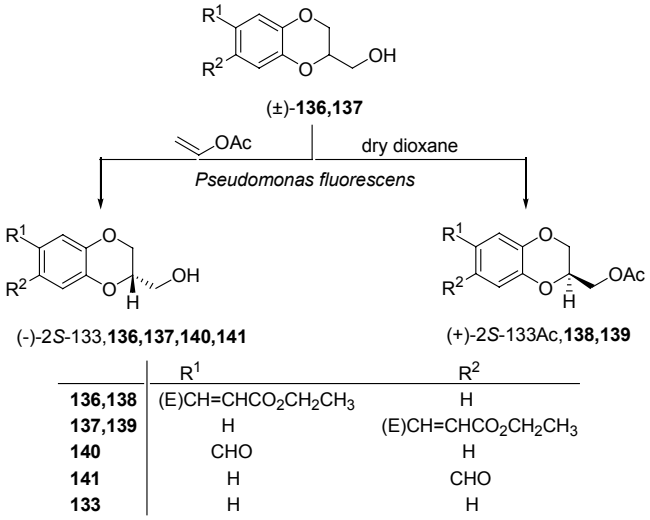
(±)-**77b**

(+)-**60a** 2R,3R,2'S,3'S (silybin-B)
(+)-**60b** 2R,3R,2'R,3'R (silybin-A)

Scheme 9

On the basis of our recent results we supposed that the availability of eneantiomers [(-)**77b** and (+)-**77b**] could be ensured by *Pseudomonas fluorescens* lipase enzyme catalyzed kinetic resolution. Surprisingly (±)-**77b** 1,4-benzodioxane derivative was not substrate of this enzyme, although in the case of 2-hydroxymethyl-1,4-benzodioxane (**133**) the remained alcohol (-)-**133** could be obtained in optically pure form (ee=99%). In order to get more information about the active site of this enzyme, the enantioselective acylation of a series of 1,4-benzodioxane derivatives (**136,137,140,141,142,143,158**) were studied.

The TLC monitoring of these transformations has shown that the acylations of **136** and **137** esters in dry dioxane by vinyl acetate took place [**136**→ (+)-**138**, **137**→ (+)-**139**] significantly slower than in the case of 2-hydroxymethyl-1,4-benzodioxane (**133**) [(±)-**133** → (+)-**133Ac**: conversion: 62%, time: 13.5 hours)] (Scheme 10).

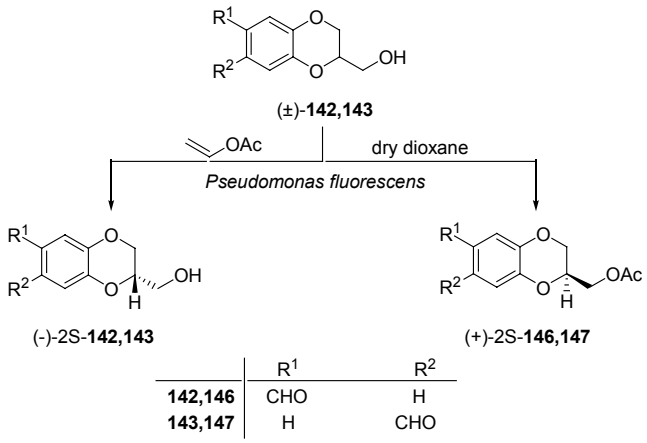


	R^1	R^2
136,138	(E)CH=CHCO$_2$CH$_2$CH$_3$	H
137,139	H	(E)CH=CHCO$_2$CH$_2$CH$_3$
140	CHO	H
141	H	CHO
133	H	H

Compound	Time (hour)	Conversion (%)	Alcohol (**136,137**) ee (%)	Acetate (**138,139**) ee (%)	**E**
136,138	214	45	71	79	14
137,139	214	52	52	75	11

Scheme 10

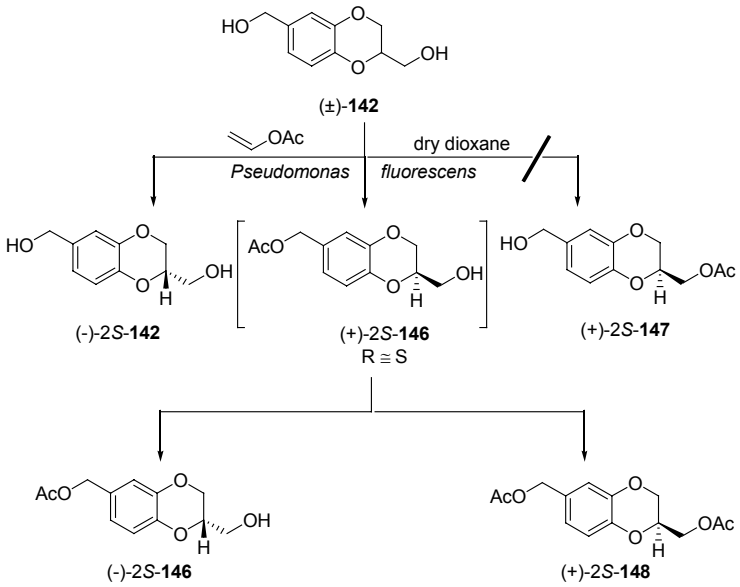
Namely, 45% conversion was reached only after 214 hours. The remained alcohols [(-)-**136,-137**] could be easily separated from the appropriate acetyl derivatives by column chromatography. Their absolute configurations were determined by chemical correlation and their optical purities were determined on Chiralcel OJ column by HPLC. In order to study the steric effect of the side chain of aromatic ring the resolution of **140** and **141** aldehydes were also studied (Scheme 11).



Compound	Time (hour)	Conversion (%)	Alcohol (**142,143**) ee (%)	Acetate (**146,147**) ee (%)	**E**
142	97	45	65	75	14
143	97	48	73	57	7,7

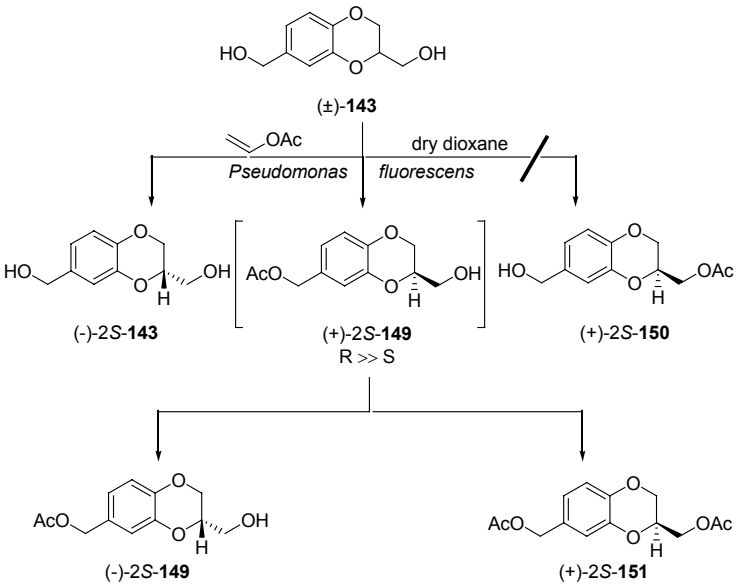
Scheme 11

The data given in Scheme 11 clearly show that the steric effect of R^1 substituent does not have influence to the enzyme chiral recognition. Even in the case of R^2 substituent only a slightly influence could be recognized. Further interesting information could be obtained about the topology of the enzyme active site by the kinetic resolution of bis-hydroxymethyl-1,4-benzodioxanes [(±)-**142**, (±)-**143**] as well (Scheme 12 and 13).



Compound	Time (hour)	Conversion (%)	Alcohol (**142**) ee (%)	Monoacetate (**146**) ee (%)	Diacetate (**148**) ee (%)	**E**
142	167	67	11	75	67	-
(±)-**146**	167	50	-	76	61	9,2

Scheme 12



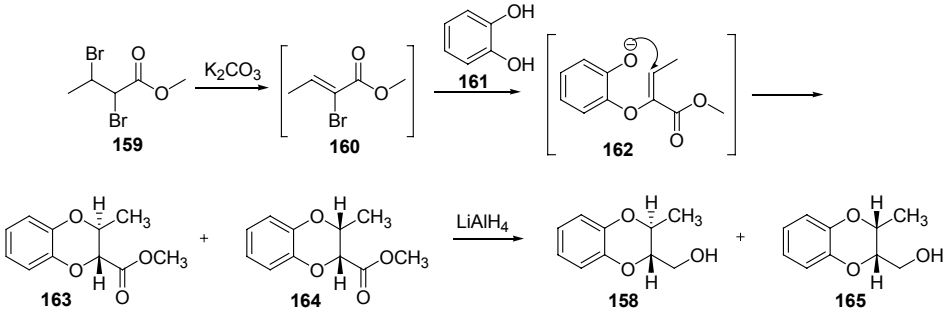
Compound	Time (hour)	Conversion (%)	Alcohol (**143**) ee (%)	Monoacetate (**149**) ee (%)	Diacetate (**151**) ee (%)	**E**
143	167	66	33	42	87	-
(±)-**149**	167	55	-	97	59	15

Scheme 13

On the one hand these experiments also confirmed our earlier results obtained in cases of aldehydes (±)-**140,141** and on the other hand they have pointed out the increasing of the distance between the active site of the enzyme and the chiral centre of the molecule the recognition of the enzyme significantly has fallen.

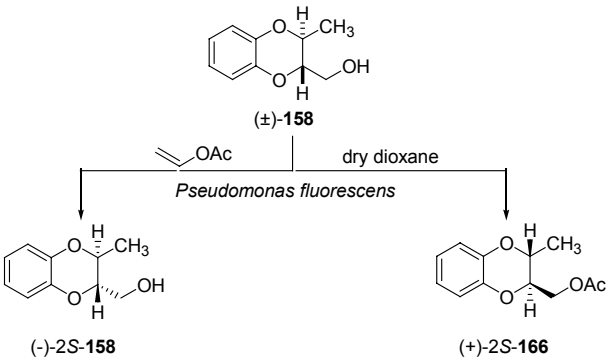
The absolute configurations (*S*) of our compounds were determined by the chiroptical rule published by us earlier [(^1L_b-CD (-) → heteroring helicity M → absolute configuration *S*)]. The optical purities of compounds were determined by HPLC on chiral stationer phase (Chiralcel OJ).

From the above mentioned results conclusion could be draw that the bulky 4-hydroxy-3-metoxyphenyl group at C-3 of 1,4-benzodioxane ring has prevent the formation of enzyme-substrate complex [(±)-**77a** → (+)-**134** or (±)-**77b** → (+)-**135**]. Therefore it was also obvious to examine the steric effect of the substituent in this position. For this purpose *trans*-2-hydroxymethyl-3-methyl-1,4-benzodioxane (**158**) was prepared according to the literature shown on Scheme 14.



Scheme 14

In the case of *trans* compound (**158**) its 25% conversion was reached after 168 hours. Although this fact has confirmed the formation of enzyme-substrate complex but it has also clearly shown that the steric effect of the substituent at this position is characteristically determining (Scheme 15).



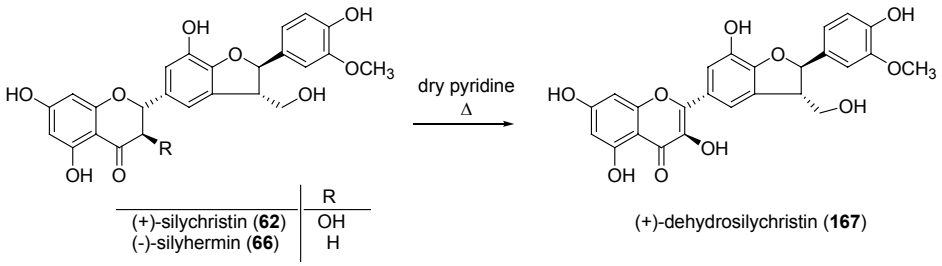
Compound	Time (hour)	Conversion (%)	Alcohol (**158**) ee (%)	Acetate (**166**) ee (%)	**E**
158	168	25	23	12	1.5

Scheme 15

On the basis of the comparison of our results with those of the literature a conclusion could be drawn that (i) different polarity and steric effect of substituents at aromatic ring could not be prevent the formation of enzyme-substrate complex and in all case (ii) the enantiomer of *R* configuration was acylated faster and (iii) the degree of selectivity highly depended on the substituent. The much largest substituent effect was observed in the case of at position C-3. In this case the replacement of hydrogen atom to methyl group shifted the equilibrium E+S $\rightleftharpoons$ ES to the direction of substrate; moreover, in the presence of a bulky aryl group the enzyme-substrate complex was formed not at all.

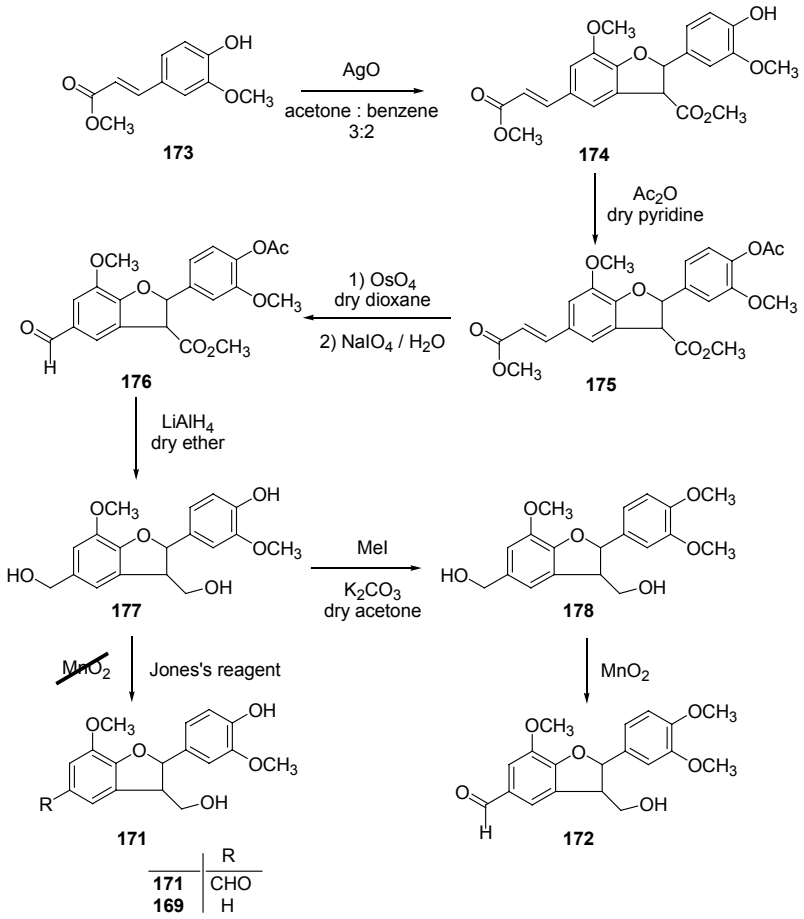
3.4. Enzyme catalysed resolution of 3-hydroxymethyl-benzo[b]furans and determination of absolute configuration of (+)-silychristin

The 3-hydroxymethyl-2,3-dihydrobenzo[b]furan skeleton is a building block of numerous flavano- and neolignan derivatives, and this moiety can be recognized in one of the active component of Legalon®, in (+)-silychristin (**62**) and in its 3-dezoxyderivatives, in (+)-silyhermin (**66**) as well. Starting from aldehyde derivative **80** the synthesis of the last mentioned compound in racemic form was performed by our research group. It seemed to be very obvious to use this sequence for the total synthesis and the determination of absolute configuration of these compounds.



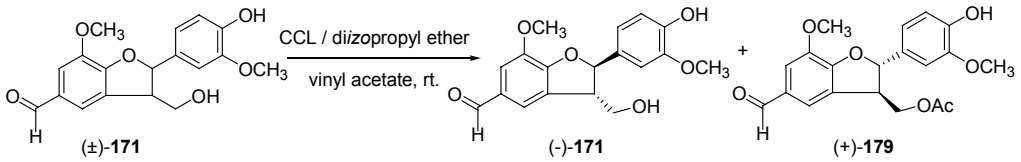
Scheme 16

On the basis of our recent results it was also obvious that the preparation of **171** 2,3-dihydrobenzo[b]furan aldehyde derivative can be achieved by the kinetic enzymatic resolution. This compound [(±)-**171**] and its methyl ether [(±)-**172**] were prepared by our method starting from methyl ferulate (**173**) (Scheme 17).



Scheme 17

The conditions of enzyme catalysed kinetic resolution optimized for 2,3-dihydrobenzo[b]furan derivative (±)-**169** was used in cases of (±)-**171** and (±)-**172**. The transformation was monitored by HPLC.

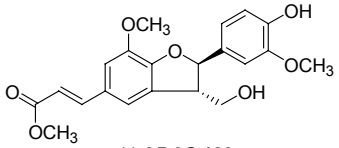


(±)-**171** (-)-**171** (+)-**179**

Compound	Time (hour)	Conversion (%)	Alcohol (-)-**169,171** ee (%)	Acetate (+)-**170,179** ee (%)	**E**
(±)-**169**	96	52	84	84	36
(±)-**171**	30	37	23	63	5,5

Scheme 18

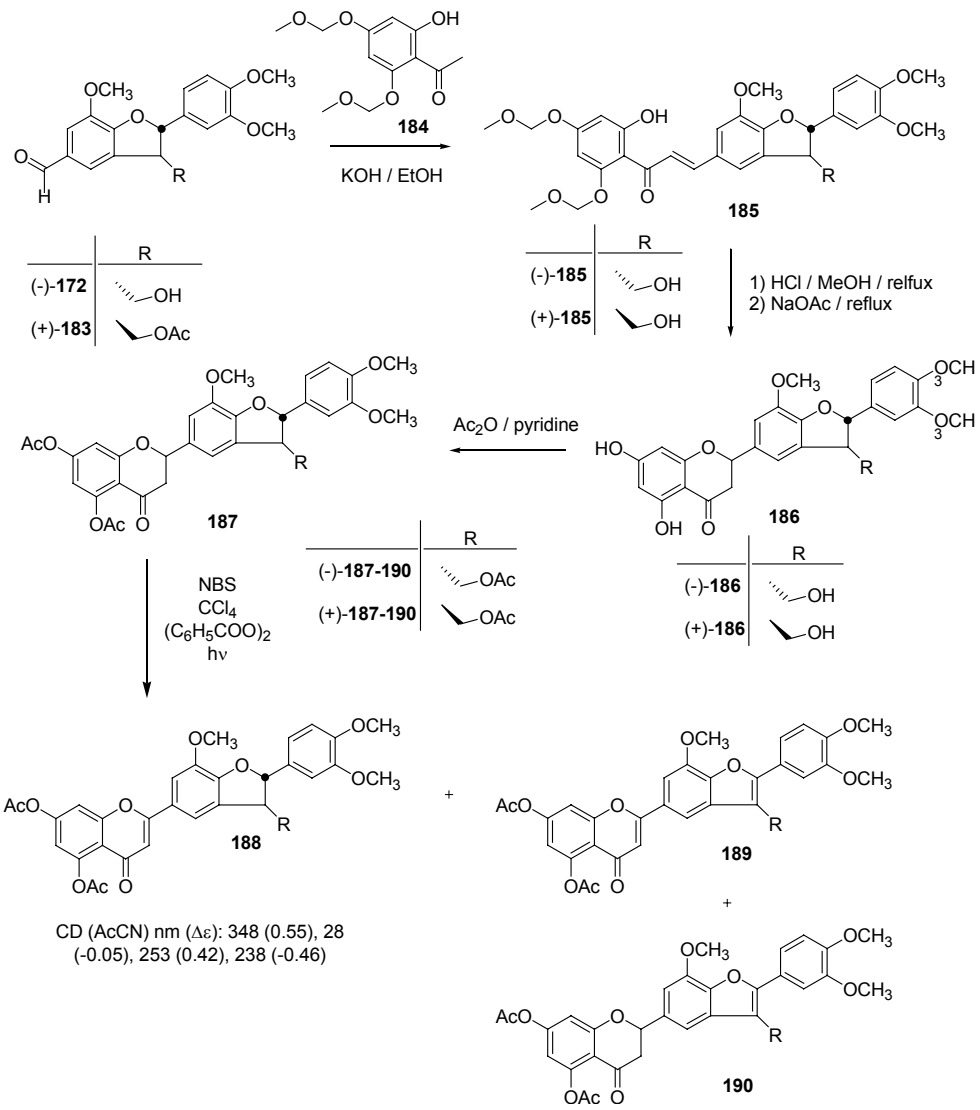
These experiments showed that the enzyme surprisingly lost its activity at 30-40% conversion (30-40 hours). The remained laevorotatory alcohol was separated from the dextrorotatory acetyl derivative by column chromatography and the optical purities and the absolute configuration of these compounds were determined by the chemical correlation with (-)-2*R*,3*S*-**180** ester derivative isolated from *Ziziphus jujuba* (Scheme 19).



(-)-2*R*,3*S*-**180**
[α]= -81 (c= 0.10, $CHCl_3$),
CD (CH_2Cl_2): $|\Theta|_{376}$+806, $|\Theta|_{363}$0,$|\Theta|_{327}$-9884,
$|\Theta|_{276}$0,$|\Theta|_{255}$-4780,$|\Theta|_{246}$0,$|\Theta|_{234}$+9695

Scheme 19

These data have clearly shown the introduction of formyl group at 2,3-dihydrobenzo[b]furan skeleton significantly has influenced the substrate binding at the active site of the enzyme. Thus, the preparation of **171** aldehyde derivative in optically pure form was not successful. Due to this fact the realization of the total synthesis of (+)-silychristin (**62**) and (+)-silyhermin (**66**) had to be given up but the determination of absolute configuration of (+)-silychristin (**62**) by chiroptical spectroscopy could be achieved by using aldehyde derivative **172** of 30-40% optical purity. Thus, suitable model compounds [(+)- and (-)-**188**] could be prepared by the route shown in Scheme 20 staring from the corresponding aldehydes [(+)- and (-)-**172**].



Scheme 20

The comparison of the CD data of (+)-**188** flavone derivative with those of dehydrosilychristin (**167**) has unambiguously indicated that its absolute configuration is not 2*R*,3*R*,2'*R*,3'*S* as reported by Zanarotti but it is 2*R*,3*R*,2'*S*,3'*R*.

4. Publikációk / Publications

Az értekezés alapjául szolgáló közlemények / Papers underlying the Theses

1. Kónya, K.; Varga, Zs.; Antus, S. Antioxidant properties of 8.O.4'-neolignans. *Phytomedicine*, **2001**, *8*, 454-459
2. Kónya, K.; Varga, Zs.; Antus, S. Egyszerű szintézisút az antioxidáns tulajdonságú 8.O.4'-típusú neolignánok előállítására. *Magyar Kémikusok Lapja*, **2002**, *108*, 273-275
3. Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. Enantiomeric separation of racemic neolignans on Chiralcel OD and determination of their absolute configuration with online circular dichroism. *Journal of Chromatographic Science*, **2004**, *42*, 478-483
4. Kónya, K.; Kurtán, T.; Kiss-Szikszai, A.; Juhász, L.; Antus, S. A General CD Method for the Configurational Assignment of *erythro*-8.O.4'-Neolignans. *Arkivoc*, **2004**, *xiii*, 72-78 (http://arkat-usa.org)
5. Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. Kinetic resolution of 2-hydroximethyl-1,4-benzodioxanes. *Tetrahedron Asymmetry*, (közlemény összeállítás alatt)
6. Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. Revision of absolute configuration of (+)-silychristin possessing liver protective activity. *Tetrahedron Letters*, (közlemény összeállítás alatt)

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Előadások / Oral lectures

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2. Kónya, K.; Juhász, L.; Antus, S. Kísérletek 4',8-típusú neolignánok enantioszelektív szintézisére. MTA Flavonoidkémiai Munkabizottság előadóülése (Debrecen, 1998. november 2-3.)
3. Kónya, K. Kísérletek 8.O.4'-típusú neolignánok enantioszelektív előállítására. Országos Diákköri Konferencia (Veszprém, 1999. április 7-9.)
4. Kónya K.; Czompa, A.; Újhelyi, L.; Kiss, A.; Balla, J.; Kakuk, Gy.; Antus, S.; Varga, Zs. A silybin hatása a protein kináz C transzlokációjára, a NADPH-oxidáz aktivitására és az apoptózisra

a PMA stimulálta humán neutrofilekben. Gyógynövények kutatása és felhasználása 2002 (Kecskemét, 2002. november 13-15.)

5. Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. O-heterociklusos vegyületek kinetikus rezolválása. MTA Flavonoidkémiai Munkabizottság Tudományos Előadóülése (Budapest, KKKI, 2003. december 3.)

6. Juhász, L.; Kónya, K.; Kurtán, T.; Antus, S.; Kinetikus rezolválás az O-heterociklusok körében. Elméleti Szerveskémiai Munkabizottsági ülés (Budapest, KKKI, 2005. január 27.)

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2. Kónya, K.; Varga, Zs.; Antus, S. 8,4'-Oxyneolignán származékok hatása a neutrofilek PMA stimulálta szuperoxidanion ($O_2^{\cdot-}$) termelésére. (MÉT, Szeged, 2001. június 6-8.)

3. Kónya, K.; Kiss-Szikszai, A. Synthesis, HPLC and Antioxidant Properties of 8.O.4'-Neolignans. XXII Corso Avanzato in Chimica Farmaceutica e Seminario Nazionale per Dottoranti "E. Duranti" (Italy, Urbino, 2002, július 1-5.)

4. Kónya, K.; Antus S.; Varga Zs.; Kiss-Szikszai, A. 8.O.4'-Neolignanok szintézise, HLPC-s tulajdonságaik és antioxidáns hatásuk vizsgálata. Gyógynövények kutatása és felhasználása 2002 (Kecskemét, 2002. november 13-15.)

5. Kónya, K.; Kiss-Szikszai, A.; Antus, S. Hidroximetil-1,4-benzodioxán származékok enzim katalizáltkinetikus rezolválása. Vegyészkonferencia 2003 (Hajdúszoboszló, 2003. június 26-28.)

6. Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. Enzyme catalyzed kinetic resolution of Hydroxymethyl-1,4-benzodioxane derivatives. 9th International Conference on Circular Dichroism in Chemistry and Life Sciences (ELTE Kongresszusi Központ, Budapest, 2003. augusztus 31.– szeptember 4.)

7. Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. Enzyme catalyzed kinetic resolution of hydroxymethyl-1,4-benzodioxane derivatives. First German-Hungarian Workshop (Hannover, Leibnizhaus, 2004. július 5-6.)

8. Kurtán, T.; Kónya, K.; Juhász, L.; Antus, S. Lipase-catalysed kinetic resolution of hydroxymethyl-1,4-benzodioxanes and dihydrobenzo[b]furans. XXIst Europian Colloquium on Heterocyclic

Chemistry (Sopron, 2004. szeptember 12-15.)

9. Kónya, K.; Kiss-Szikszai, A.; Compa A.; Antus, S. Újabb adatok a *Pszeudomonas fluorescens* aktív centrumának topológiájáról. Vegyészkonferencia 2005 (Hajdúszoboszló, 2005. június 28-30.)