Synthesis of heteroaryloxy-phenoxypropionic acid derivatives of potential herbicide activity and deoxygenation of O-heterocyclic compounds

Doktori (Ph. D.) értekezés tézisei

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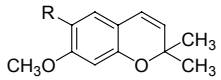
Szerves Kémiai Tanszék, Debreceni Egyetem,
Debrecen, 2003

1. Introduction and the aim of the dissertation

According to reliable estimates, biotic factors, i.e., animalm pests, microorganisms and weeds, diminish the yield of agricultural produce by 35 %. Even in the past, mankind could not accept a loss of 35 %, and will be able to afford it still less in the future. The saving of perishable agricultural produce is no longer an economic, but a fundamental humanitarian problem. Industrialisation and the ensuing massive rural exodus result in shortage of agricultural labour; hence, herbicides application with large-scale technology has become the only possible way of killing weeds.

Since 1970's increasing use of phenoxyacetic as herbicide has resulted to grow of monocotyledonous grass in the cereal and corn. as Bearded wheat grass (*Agropyron repens),* and Guinea-grass *(Sorgum halepense*). The hardness of protection of the environment, the aim of decrease of quantity of herbicides during the protection and to save the earth led to challenge to development of efficient, selective annual and grass weed-controls.

The disadvantage and danger of using of insecticides were reported in the 1960's. It was proved that lots of insecticides had toxic, carcinogenic and mutative side-effects. These factors and stringency of protection of environment changed the way of development of insecticides: the use controll instead of pest-killing. Bowers and his co-workers reported in the middle of 1970's that they isolated two compounds from *Ageratum houstonianum*, which caused antijuvenile hormon activity (precocious metamorphosis). These two compounds were proved to be 2,2-dimethyl-7-methoxy-2H-chromene (Precocene-1, **1a**, P-1) and 2,2-dimethyl-6,7-dimethoxy-2H-chromene (Prekocene-2, **1b**, P-2).



1a,b

1

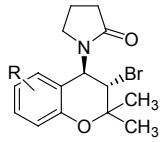
a
b

R

H
CH_3O

1

Such a new benzopyranoid is Cromakalim (**2**) [R = 6-CN].



2

My research programme was to synthesize of a new 2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propanamide derivatives of potential herbicide activity. In the course of my work I also elaborated a new way of preparing of 2,2-dimethylchromene-4-on derivatives. I also examined the deoxygenation of different flavanoid derivatives contain one, two or three hydroxyl group(s).

2. Applied methods

In the course of our work, macro, semi-micro and micro preparative organic methods have been used. The reaction were monitored by thin-layer chromatography. The isolation and purification of the products were carried out by crystallization or by column chromatograhy. The prepared products were identified and characterized by H-NMR, C-NMR, MS and HPLC.

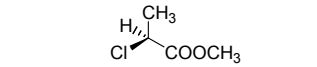
3. New results of the dissertation

3.1. Synthesis of optically active 2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propanamide derivatives of potential herbicide activity

Since the recognition of the auxin action of phenoxy acids extensive research has been undertaken to elucidate the relationships between the biological activity and the chemical structure of this group of compounds.

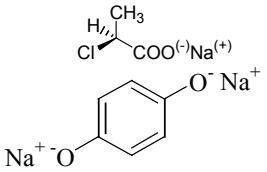
Accordingly, to have the growth hormone effect the molecule must contain a ring system in which at least one double bond is present, it must contain a side chain with a carboxyl group substituent, and the carboxyl group of the molecule and the ring must be separated from each other by at least one carbon atom. It was proved that the herbicide activity of the (hetero)aryloxy-phenoxypropanoates belong to the acid formula instead of ester. We though that the amide derivatives of ethyl-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propanoate (Fenoxaprop-etil) [Whip® (producer: Hoechst-Roussel] (**3b**) could have been patented.

One of the way to prepare of the ethyl-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propanoate (**3b)** was to react disodium salt of hydoquinone (**4**) with methyl-S-(-)-2-chloropropanoate (**5**).



NaOH

- CH_3OH

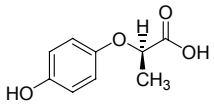


N_2 / 40 ^oC

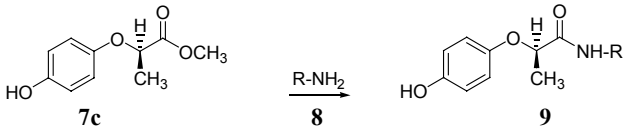
S-(-)-**5**

S-(-)-**6**

4



The optical purity of these esters were not only controlled by its optical rotary but were also checked by H NMR spectroscopy using of chiral shift-reagent, tris[3-trifluoromethylenehydroxymethylene-D-camphorate]europium (III); $Eu(tfc)_3$. In the next steep we tried to prepare optically active amide (**9**) derivations by the reaction of methyl-R-(+)-(4-hydroxy-phenoxy)-propionate (**7c**) with aliphatic primary amines (**8**). We hoped that 6 mol-equivalent of amines (**8**) in net could furnish the desired amides (**9**) without racemization.

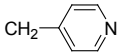


8,9
R

8,9
R

a

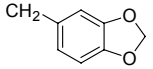
f



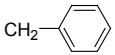
b

g

c



h



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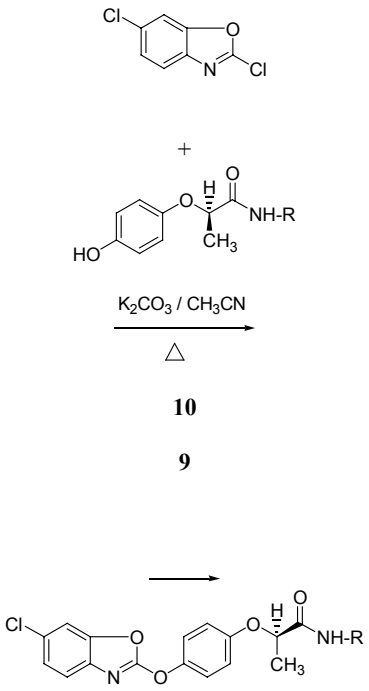
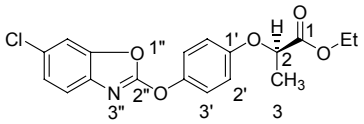
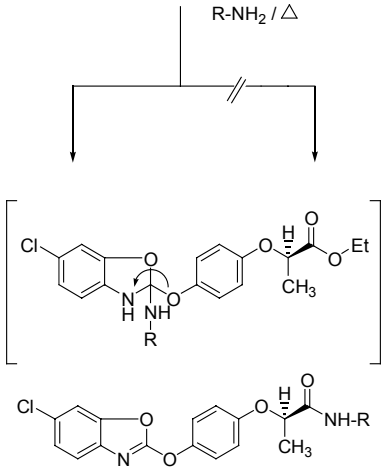


R-(+)-11

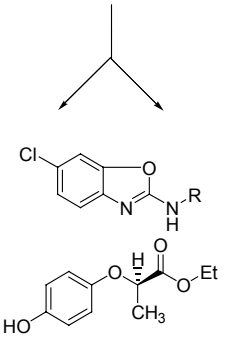
The desired (benzoxazolyloxy-phenoxy)-propanamide derivatives (R-(+)-**11**) were prepared in good yields, (65 – 88 %) and the optical purity of these were high (ee % > 98). We tried to prepare the above amides (**11**) by the direct amidation of ethyl-R-(+)-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propionate (**3b**) with aliphatic primary amines (**8**). It has been known from the literature that the direct amidation of ethyl-R-(+)-2-[4-(5-trifluoromethylpyridyloxy)-phenoxy]-propionate (**12**) with amines (**8**) furnished R-(+)-2-[4-(5-trifluoromethylpyridyloxy)-phenoxy]-propanamides (**13**).



3b



16
11



15
7b

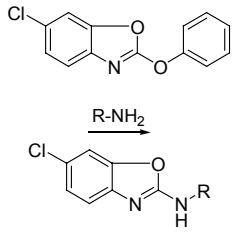
Carbon atom
Net charge
Nukleophile superdelocalizability

2”
0,1888
1,37260

1
0,3641
1,09021

Table 1. Net charge and nucleophile superdelocalizability of **39b** ester

2-Phenoxy-6-chlorobenzoxazole (**17**) was prepared by the reaction of 2,6-dichlorobenzoxazole (**10**) with phenol (**16**) in acetonitrile using potassium-carbonate and **17** was furnished in 86 % yield. We reacted the 2-phenoxy-6-chlorobenzoxazole (**17**) with 2 molekvivalent amines (**8**) in toluene and the desired **15** products were prepared in high yield (87 – 92 %). We also found that the reaction of **17** with 6 mol-equivalent amines (**8**) could have done at room temperature and also furnished the **15** amines in excellent yields and purity (Table 2.).

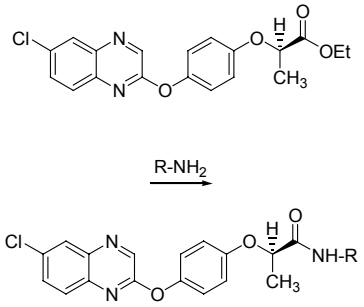


17
8
15

15

The importance of our elaborated method was to prepare the biological importance of **15** in easy way. The literature methods have lots of disadvantages to prepare **15** products from o-aminophenol (**18**). These ways needed to use toxic reagents (i. e. phosgene, bromocyan etc.).

The reaction of **14** ester with 6 mol-equivalent cyclopropylamine (**8b**) showed to furnished one product after 2 hours, which was proved to be cyclopropylmethyl-R-(+)-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propanamide (**19b**).



R-(+)-14

8

19

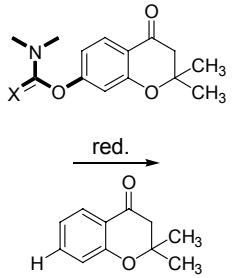
The background of this reaction was also explained by CAChe-programme.

Carbon atom **Net charge** **Nukleofil superdelocalizability**
2”
0,075
1,16416
1
0,360
0,96026

These data showed that the nucleophilic attack of amines (**8**) could have done at ester

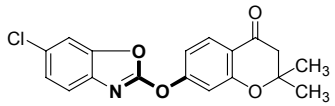
Both systems could only be used for preparing susbstituted 2,2-dimethylchromane-4-ones if the starting phenol like resorcin type. In this case the products are mainly 7-hydroxy-, or 7-alkoxy-2,2,-dimethylchromane-4-ones. If the starting phenol is not resorcin-type, we could get a complicated reaction products from which the isolation of the desired 2,2-dimethylchromane-4-ones (**21**) are hard or impossible. Remove of hydroxyl group of substituted 2,2-dimethylchromane-4-ones (**20**) would lead to such a products, which could not be prepared from the starting phenols.

The second aim of my work was to find a new way of preparing of the biological importance of 2,2-dimethylchromane-4-one derivatives (**21**). The deoxygenation methods of phenolic hydroxyl group are mainly based on the catalytic hydrogenation reaction, in which the carbon – oxygen bond is activated the following structure.



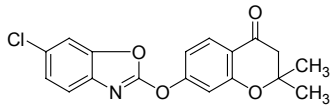
X = NH, O, S, N=N-

As this structure could be found in the 22,-dimethyl-7-(6'-chloro-2'-benzoxazolyloxy)-chromane-4-one (**23**), therefore we tried to prepare 2,2,-dimethylchromane-4-one (**21a**) by catalytic hydrogenation of **23**

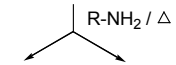


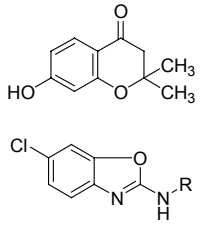
23

The catalytic hydrogenation was carried out in ethanol with palladium charcoal (Pd-C) at 5 bar pressure. We experienced that the desired 2,2-dimethylchromane-4-one (**21a**) was formed in 38 % yield but the starting material (**23**) was also reacted with ethanol to formed 2-ethoxy-6-chlorobenzoxazole (**25**) beside the hydrolitic product, the 7-hydroxy-2,2-dimethylchromane-4-one (**20**) in 35 % yield. As the **25** product was formed in the above reaction, this forced us to investigate the reaction of **23** with aliphatic primary amines (**8**).



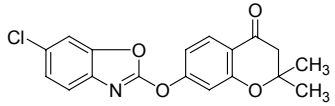
23





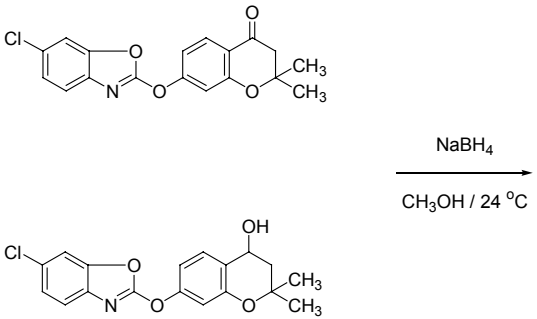
20a
15

The reaction was monitored by TLC and we experienced that the reaction time was short and two products were formed.. After working-up the reaction mixture, we isolated the 2-(N-substituted)-amino-6-chlorobenzoxazoles (**15**) and 7-hydroxy-2,2-dimethylchromane-4-one (**20a**). We tried to cleavage the carbon – oxygen bond of **23** by nickel chloride / sodium borohydride system.



23

In this case we also get a complicated reaction mixture and we isolated the desired **21a** product in 27 % yield. It is worth mention that the reduction of carbonyl group of **23** was not detected, so the 2,2-dimethyl-7-(6'-chloro-2'-benzoxazolyloxy)-chromane-4-ol (**27**) was not formed. This was also experienced concerning **28** – **30** starting products.



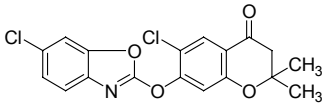
23

27

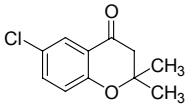
Starting material

Products

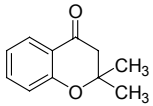
Ratio (GC %)



28

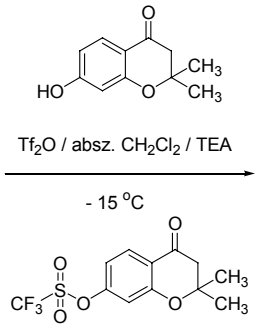


34



21a

Table 1. has shown that the carbonyl group did not react and the phenolic hydroxyl group was removed *via* their benzoxazolyl derivatives with sodium borohydride. It was also experienced that the carbonyl group played role in the cleavage of carbon – oxygen bound. This table also shows that the reaction of **30** formed less deoxygenated products than in the case of **29**, and only the hydrolized product (**43**) was observed in the case of **33**. These results have showed that the activity effect of benzoxazolyl group was not enough to use for general deoxygenation of hydroxyl group(s). It has been known from the literature that the deoxygenation of phenolic hydroxyl group cold be done *via* their trifluoromethanesulfonate (triflate) ester derivatives. The cleavage of triflic group could be done with the use of palladium acetate / tripenylphosphine / formic acid / triethylamine complex system. We tried to use this system for removing of the hydroxyl group of 7-hydroxy-2,2-dimethylchromane-4-one derivatives (**20a**). 7-(Trifluoromethanesulfone)-2,2-dimethylchromane-4-one (**45a**) was prepared in 92 % yield from 7-hydroxy-2,2-dimethylchromane-4-one (**20a**) with the reaction of trifluoromethanesulfonic anhydride (triflic anhydride) in dichloromethane in the presence of triethylamine at minus 15 ^{o}C.

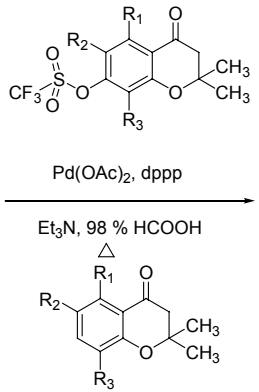


20a

45

The solid **45** was than solved in dimethylformamide and triphenylphosphine, triethylamine, palladium acetate and formic acid was added to this. This reaction mixture was stirring at 60 ^{o}C

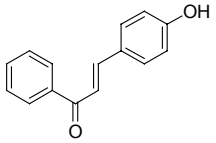
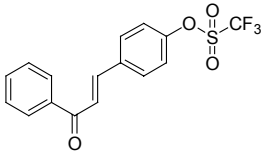
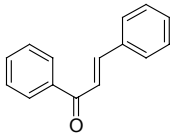
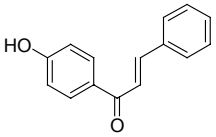
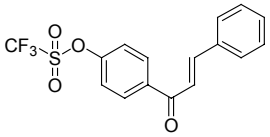
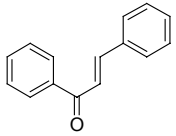
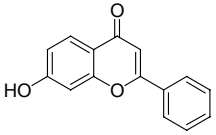
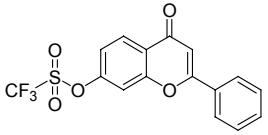
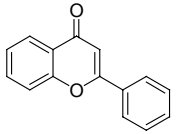
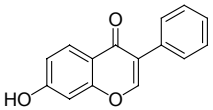
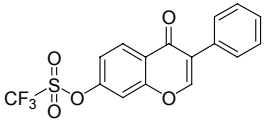
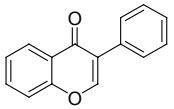
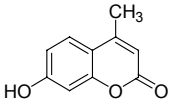
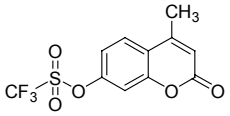
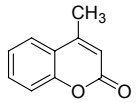
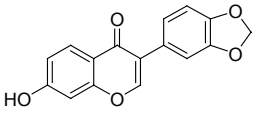
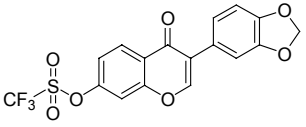
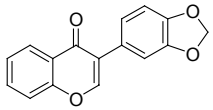
We also examined the remove of hydroxyl group of 7-hydroxy-6-chloro-2,2-dimethylchromane-4-one (**45b**). We used the standard method for preparing of **45b**. Deoxygenation of **45b** showed that it was easily transformed (30 minutes) and two products were formed. The main product was 7-hydroxy-6-chloro-2,2-dimethylchromane-4-one (**20b**) and we also isolated the target 6-chloro-2,2-dimethylchromane-4-one (**21b**) in 61 % and 28 % yield, respectively. It has been known from the literature that the speed of the reduction steep of aryltriflate depends on the stability of the palladium (0) catalyst generated from palladium acetate. Therefore the triphenylphosphine was changed to 1,3-diphenylphosphino-propane (dppp) and we repeated the above reaction. Monitoring of the reaction by TLC showed that the speed of the reaction was increased (15 minutes). The starting **45b** material formed again two products but the products ratio was changed. In this case the main product was 6-chloro-2,2-dimethylchromane-4-one (**21b**) but 7-hydroxy-6-chloro-2,2-dimethylchromane-4-one (**20b**) was also formed in 70 % and 28 % yield, respectively. This experiment showed that the use of dppp increased the speed of the reduction of starting material (**45b**) and the side reaction – the hydrolysis - was decreased. We examined the usability of this system for the deoxygenation of different 7-hydroxy-2,2-dimethylchromane-4-one derivatives (**20**). The results have been summarized in Table 2.

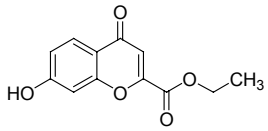


45a-g

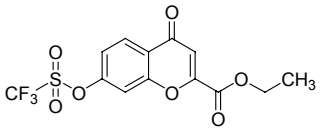
					20,21,45
R_1	**R_2**	**R_3**	**Reaction time (minutes)**	**Yield (%)**	
					a
H	H	H	50	93	
					b
H	Cl	H	15	70	
					c
CH_3	H	H	20	90	
					d
H	H	CH_3	30	91	
					e
CH_3O	H	H	70	14	

Reduction of **51-55** triflates showed that the remove of hydroxyl group of these *via* their triflate ester could have done and formed the appropriate deoxygenated products (**56-60**) in good to high yields (Table 3.).

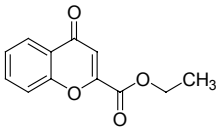
Starting material	Triflate product (yield %)	Reduction product (yield %)
 **46a**	 **51a** (95,1 %)	 **56** (83,0 %)
 **46b**	 **51b** (94 %)	 **56** (83,0 %)
 **47**	 **52** (78 %)	 **57** (85,2 %)
 **48**	 **53** (89,7 %)	 **58** (90,6 %)
 **49**	 **54** (91,7 %)	 **59** (94,7 %)
 **50a**	 **55a** (73,2 %)	 **60a** (90,5 %



50b



55b (65,6 %)

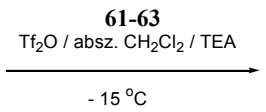


60b (79,1 %)

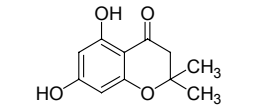
Table 3. Deoxygenation of flavonoid derivatives contain one hydroxyl group

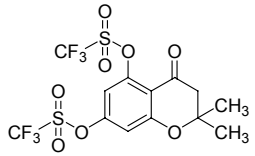
3.3.2. Deoxygenation of flavonoid derivatives contain two hydroxyl groups

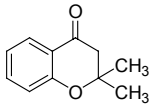
We also examined the remove of hydroxyl groups of one of the representative of isoflavonoid (**61**), chroman-4-one (**62**) and cumarine (**63**) derivatives. The appropriate triflate derivatives (**64**-**66**) were prepared by the standard method. During this reaction we experienced that the reaction of 5,7-dihydroxy-2-methyl-isoflavon (**61**) with triflic anhydride formed the 7-triflate derivative (**64**) as the main product in 67,9 % yield. This result showed that there was a difference of reactivity of the C-5 and C-7 hydroxyl group of compound **61**, therefore we managed to isolate the **64** triflate as the main product but the ditriflate derivative of **61** was also formed as minor product in 25 % yield. The reason of this experience may be that the C-7 hydroxyl group of **61** has higher acidity than the C-5 hydroxyl group so the monoester derivative (**64**) could easily be formed. The two other starting materials have no showed this difference result and formed the ditriflate derivatives (**65**,**66**), (Table 4).



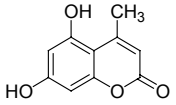
Starting material	Triflate product (yield %)	Reduction product

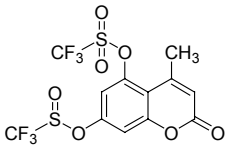


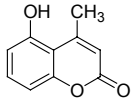




62
65 (85,1 %)
21a (75,3 %)





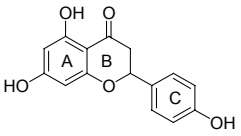


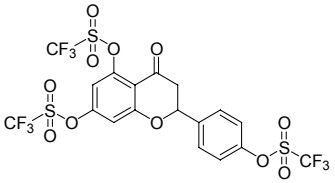
63
66 (74,5 %)
68 (89,9 %)

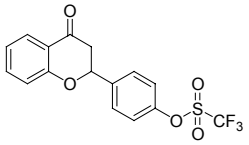
Table 4. Deoxygenation of flavonoid derivatives contain two hydroxyl groups

We carried out the deoxygenation process as we did before

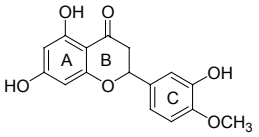
Starting material
Triflate product
(yield %)
Reduction product
(yield %)



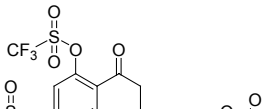




69
71 (78,6 %)
73 (67 %)



70



List of publications

1) **J. Kövér**, T. Tímár, J. Tompa, Novel and efficient synthesis of 6-chloro-2-(substituted amino)benzoxazoles, *Synthesis*, **1994**, *11*, 1124 – 1126

2) **J. Kövér,** T. Tímár, S. Antus, A novel method for deoxygenation of hydroxybenzopyranoids *via* their 2-benzoxazolyloxy derivatives, *Flavonoids and Bioflavonoids* **1995**, Akadémiai Kiadó, Budapest, 317 – 321, 1996

3) **J. Kövér**, L. Szilágyi, S. Antus, J. Tompa, T. Gunda, Synthesis of optically active 2-[4-(6-chloro-2-benzoxazolyloxy)phenoxy]propionamide derivatives of potential herbicide activity, *J. Heterocyclic. Commun*., **2002**, *Vol. 8. No. 3*, 237 -242

Lectures and posters

1) **J. Kövér,** T. Tímár, S. Antus, A novel method for deoxygenation of hydroxybenzopyranoids *via* their 2-benzoxazolyloxy derivatives, International Bioflavonoid Symposium, Bécs, 1995 (P)

2) **J. Kövér,** S. Antus, Deoxygenation of 2,2-dimethylchromane-4-one *via* their trifluoromethanesulfonate derivatives, 10th Hungarian Medicinal Plant Conference – „Research and application of Medicinal Plant", Kecskemét, 2002 (E)