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**PREPARATION OF THE CYCLOALKANOINDOLE SCAFFOLD WITH  
PERICYCLIC REACTION; EXAMINATION, OPTIMIZATION OF THE  
REACTION; PREPARATION OF DERIVATIVES**

PhD Thesis

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2013

## 1. Introduction, goals

My research was started in the Dr. Lajos Novák's research group, at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, under the direct supervision of Dr. Gábor Hornyánszky in 2003.

Due to the development of the modern society the population is getting older and often show the sign of demencia in old age.

Acetylcholine has an important role in the brain's neurotransmission. However as a result of the selective necrosis in some part of the brain (cerebral Cortex, hippocampus) the ratio of the acetylcholine is decreased.

One of the most important research directions dealing with the inhibition of the acetylcholine esterase enzyme (AChE) which can maintain a constant level of the disease. The enzyme decreases the level of the neurotransmitter resulting a cholinerg deficit via the quick metabolism of the acetylcholin generating by natural way in the brain.

### Physostigmine and Phenserine like AChE blockers

The muscle-paralyzing effect of the African Calabar bean (*Physostigma venesonum*) has been already known by the native tribes. This effect is due to the AChE blocking activity of the plant's alkaloid, the *Physostigmin* (**1**) by carbamoylating the enzyme.

### Figure 1

Several derivatives of the *Physostigmine* as a lead molecule have been synthesized. Among these the (-) *Phenserine* (**2**) shows outstanding biological and pharmacokinetic features. The in vitro assays of the (-)*Phenserine* (**2**) are verified the double effect of the molecule. Besides enzyme inhibition it decreases the production of the neurotoxic amyloid protein by 30%. However, the clinical studies have not provided the required results.

Then the focus was shifted to the enantiomer of **2**, to the (+)*Phenserine* (**3**, Posiphen®).

(+)*Phenserine* (**3**) shows less binding activity on the AChE enzyme, but it highly decreases the synthesis of the APP (Amyloid Precursor Protein).

That way the proper intensity of the AChE inhibition can be reached with a larger dose and less APP level. (+)*Phenserin* (**3**) has been successfully applied in stem cell therapy in the case of animals.

Positive experience about the Posiphen®'s (**3**) clinical studies was announced by the inventors in 2010.

My goal was to synthesize *Phenserine* analogs without heteroatom in the C ring. The required tricyclic scaffold can be achieved by aza-Claisen rearrangement and subsequent spontaneous ring closure of substituted *N*-cycloalkenyl anilines (**4a-c**) or their *N*-methyl derivatives (**5a,b**).

Figure 2

During my work the methoxy containing analog has been synthesized. New work up was developed to prevent the decomposition of the molecule, which was then easily interconvertible into the proper carbamate derivative.

Bromine and chlorine substituted cycloalkanoindoles were also prepared. From these compounds new derivatives were prepared using cross-coupling reaction.

The mechanism of the rearrangement and the ring closure was modeled by computational chemistry. New reaction mechanism was proposed based on these information what was favorable both in kinetic and thermodynamic sense, too.

## 2. Preparation of methoxy and halogen containing cikloalkanoindole analogs

In the case of the methoxy substituted *N*-cycloalkenyl-*N*-methyl anilines the product of the ring closure decomposed.

The decomposition was minimalized and the proper cyclized product was isolated when the weakly acidic silica gel was changed to aluminum oxide gel.

The products were easily obtained from the separated cyclic compounds (**18**). Beyond the cycloalkane containing five numbered derivatives, a six and a seven numbered phenylcarbamate derivatives were successfully prepared (**10**, **11**, **12**).

Figure 3

In the case of the bromine substituted analog the bromine was eliminated under the circumstances of the ring closure and the cycloalanoindole derivative (**7**) was isolated. The molecule required for the cross-coupling was prepared with the application of *N*-bromo-succinimide (Figure 4).

Figure 4

The experiments were extended to the 4-bromoaniline and 5-bromoindole to investigate their behavior under the ring closure circumstances. However, the bromine was eliminated only in the case of the indole derivatives.

Partial charge distribution of the bromine or carbon atoms were calculated at these molecules focusing to the 4th position.

There was not significant difference between the aniline and the indole derivatives. Concluding that the reaction is going with radical mechanism what is frequent at bromine compounds.

In the case of chlorine substituent this phenomenon was not observed further confirming our hypothesis. The cyclic product (**14**) was observed at lower temperature (140-150°C) (Figure 5), but this molecule was not suitable for the coupling reaction.

Figure 5

### 3. Mechanism verification by computational chemistry

Based on the previously proposed mechanism a [3,3]-sigmatropic rearrangement (**16**) was taken place followed by a rearomatization. The ring was closed by the stabilization of the *exo* double bond (**17**) (Figure 6).

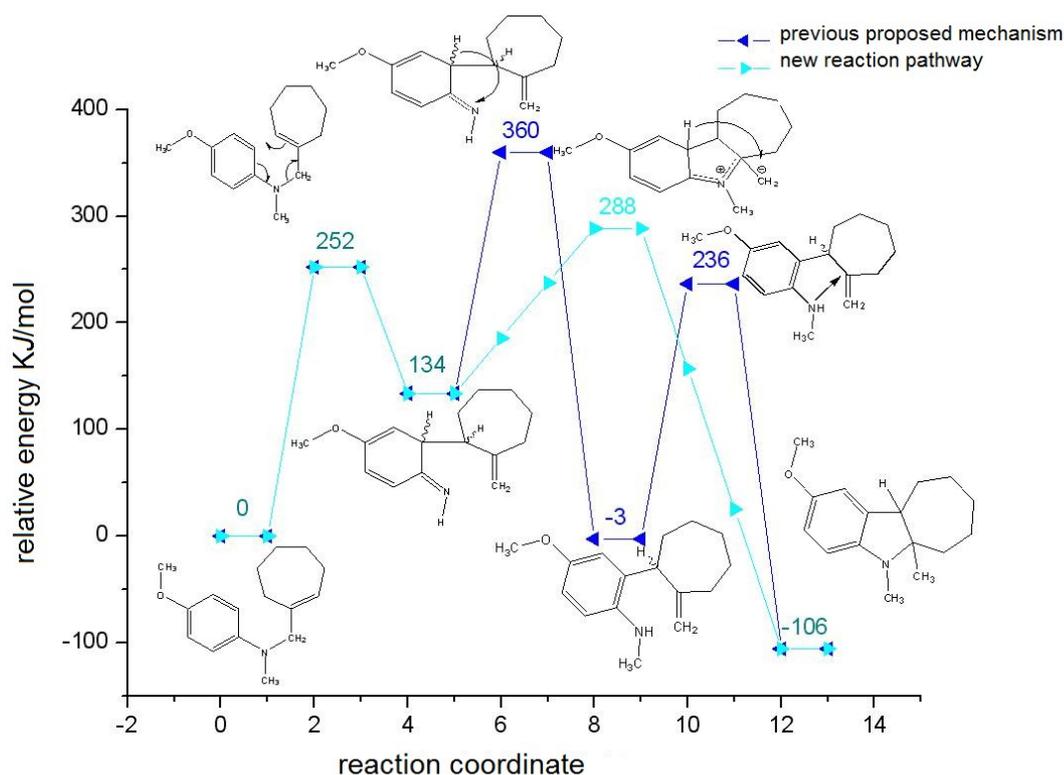
Quantum chemical methods was used for the deeper understanding of the reaction mechanism.

Figure 6

Thus the reaction consists of three elementary steps and the activation energy required for the rearrangement seemed to be high as well. These results prompted us to work on a new mechanism proposal.

Figure 7

According to our hypothesis the first sigmathropic rearrangement was followed by a subsequent Alder pericyclic reaction. This statement we underlined by quantum chemical calculations as well (Scheme 1).



Scheme 1

We were able to discover a kinetically favoured (lower activation energy) as well as thermodynamically favoured (one less elementary step) reaction pathways.

In accordance with our results the activation energy of the reaction was further decreased with the application of catalyst.

#### 4. Optimization of ring-closure reaction

In our earlier experiments ring-closure reactions were performed in the presence of catalytic amount of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . The favored reaction temperature is 170-180°C, whilst higher or lower reaction temperature would result in the decrease of ring-closed products.

The product (**7b**) can easily be extracted from ionic liquid that enables monitoring the reaction via gas chromatographic analysis.

This gave us the opportunity to investigate the effect of concentration of the reaction mixture, manner of dosage, amount as well as the concentration of the catalyst and reaction temperature on the outcome of reaction.

Taking these experiences into account we can conclude, that higher temperature, concentrated reaction mixture and usage of catalyst, which was added to the mixture in one portion, facilitates the ring formation reaction. Therefore, I completed the reaction with the following reaction conditions (Table 1): 500 mg starting material was dissolved in 500 mL ionic liquid at 185-190°C, and the catalyst diluted at 1:1 ratio was added to the mixture in one portion. This resulted the best performance (68% yield).

Temperature	Time	<b>5a</b>	<b>7a</b>	<b>9a</b>	Side-products
°C	Minute	GC %	GC %	GC %	GC %
190	5	0	68	4	28

Table 1

Application of ionic liquids provide the possibility of easier work up of the reaction and the development of environmental benign synthesis method.

The ring-closure reaction proceeded in ionic liquid as well as in sulfolane using microwave irradiation.

Neat conditions provided unexpected results. We were able to isolate the product (**7a**), although with lower yield. It is surprising, because according to our previous experiments thermic and neat conditions resulted in unsuccessful reaction (Table 2).

	neat	sulfolane	Ionic liquid (BMIM-BF <sub>4</sub> )
	GC% ( <i>cis/trans</i> )	GC% ( <i>cis/trans</i> )	GC% ( <i>cis/trans</i> )
Thermic	—	26 / 14	34 / 9,3
Microwave	10 / 5,4	17,2 / 8,5	18,1 / 7,6

Table 2

Thermic conditions initiated decomposition and elimination of the catalyst.

## 5. Cross-coupling reactions

We aimed to synthesize further derivatives, consequently we performed Suzuki coupling reaction starting from previously synthesized halogen derivatives.

#### Figure 8

In the first two cases coupling reactions worked well if *p*-nitrophenylboronic acid was used as the coupling agent, although the expected product could only be isolated with significantly lower yield. Due to the nitro group's deactivation effect the yield dropped down to one third.

During the course of Suzuki coupling we observed that the size of the C ring had no significant effect on the outcome of reaction.

## 6. Thesis points

- 1) I worked out and applied a new synthetic plan for the production of two different methoxy-group containing tricyclic scaffolds (carbasole and octahydrocyclohept[*b*]indole). These products were used in the synthesis two new Phenserine analogues containing 6- and 7-member cycloalkane rings.<sup>1</sup>
- 2) I proposed a new mechanism for the ring-closure reaction of substituted *N*-cycloalkenyl-*N*-methylaniline analogs. The new hypothesis was supported by quantum chemical calculations as well. In the course of reaction an aza-Claisen pericyclic reaction was followed by a subsequent Alder-ene-type reaction. The number of elementary steps has been reduced and the activation energy need were also decreased, which resulted in a kinetically and thermodynamically favored reaction.<sup>3</sup>
- 3) I investigated and optimized the effect of parameters on the ring-closure reaction of *N*-cycloalkenyl-*N*-methyl-aniline and its 4-methoxy derivative. I also investigated the ring-closure reaction of *N*-cycloalkenyl-*N*-methyl-aniline under microwave irradiation. In this case the carbasole scaffold was synthesized under neat condition – which was not possible earlier under thermic one.<sup>4</sup>
- 4) I observed an unexpected reaction during the ring formation of 4-bromo-cycloalkenyl-*N*-methylaniline derivatives. Debromination was observed under these conditions, thus we assumed that the reactions go via radical mechanism. Under similar conditions aniline derivatives (4-bromoanilin, 4-bromo-2-methylaniline and 4-bromo-*N,N*,2-trimethylaniline) were stable, whilst 5-bromoindole derivatives underwent debromination.
- 5) I synthesized six, new, presumably APP synthesis blocking agents with the application of palladium catalyzed cross-coupling reaction. These compounds were built up with the combination of three different arylboronic acids (4-fenoxyphenylboronic acid, 4-trifluoromethylphenylboronic acid and 3-nitrophenylboronic acid) and two different tricyclic scaffold containing bromo substituent (carbasole and octahydrocyklohept[*b*]indol).<sup>2</sup>

## 7. PhD dissertation is based on the following publications:

1. Kiraly I., Hornyanszky G., **Kupai K.**, Novak L.: Synthesis of cycloalkanoindoles, the carba analogs of *physostigmine*  
*Heterocycles* **2008**, *75*, 43-56.

IF: 1,014

2. **Kupai K.**, Hornyanszky G., Banoczi G., Novak L.: Facile synthesis of cycloalkanoindole derivatives by aza-Claisen rearrangement  
*Monatshefte für Chemie - Chemical Monthl.* **2012**, *143*, 1663-1669.

IF: 1,532

3. **Kupai K.**, Hornyanszky G., Banoczi G., Kolonits P., Novak L.: A Convenient Method For The Preparation Of Cyclohepta[*b*]indole Derivatives  
*Central European Journal of Chemistry* **2012**, *10*, 91-95.

IF: 1,073

4. **Kupai K.**, Hornyanszky G., Novak L.: Investigation of the preparation of cycloalkanoindole derivative in ionic solvent  
*Periodica Politechnica* **2013**

IF: 0,27

K. Kupai, G. Hornyanszky, L. Novak, Budapest, *Doktoráns Konferencia*, 2009, előadás

K. Kupai, I. Kiraly, G. Hornyanszky, L. Novak, Marosvásárhely, *XV. Nemzetközi Vegyészkonferencia*, 2009, presentation

K. Kupai, I. Kiraly, G. Hornyanszky, L. Novak, Kolozsvár, *XIV. Nemzetközi Vegyészkonferencia*, 2008, presentation

K. Kupai, I. Kiraly, G. Hornyanszky, L. Novak, Hajdúszoboszló, *Vegyészkonferencia*, 2008, poster

K. Kupai, G. Hornyanszky, L. Novak, Budapest, *Doktoráns Konferencia*, 2006, presentation

## 8. Further publications

A. Tomin, G. Hornyanszky, K. **Kupai**, Zs. Dorko, L. Urge, F. Darvas, L. Poppe, Lipase-catalyzed kinetic resolution of 2-methylene-substituted cycloalkanols in batch and continuous-flow modes, *Process Biochem.*, **2010**, *45*, 859-863.

IF: 2,444

A. Tomin, K. Kupai, G. Hornyanszky, L. Poppe, Sopron, *Centenárium Vegyészkonferencia*, 2007 poster

G. Hornyanszky, I. Kiraly, K. Kupai, L. Novak, Sopron, *Centenárium Vegyészkonferencia*, 2007, presentation