Budapest University of Technology and Economics

Faculty of Chemical Technology and Biotechnology

1,3-DIPOLAR CYCLOADDITIONS AND 1,5-ELECTROCYCLISATIONS OF AZOMETHINE YLIDES

PhD thesis

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2008.

1. Introduction

My research work was supervised by Dr. Miklós Nyerges at the Budapest University of Technology and Economics, Department of Organic Chemistry and Technology. I investigated pericyclic reactions, mainly cycloadditions and electroyclisations of azomethine ylides. My goals were to explore new reactions and application methods of these types of ylides.

The presented chemical transformations could help the chemists to synthesize complicated structures of biological active molecules easily.

2. Literature background

2.1 Synthesis of pyrrol containing alkaloids

Nowadays, the isolation and synthesis of natural products have considerable importance, because several molecules possess promising biological activities.

During my researches, I dealt with the preparation of lamellarine, ningalin and lukianol alkaloid intermediates. This research field requires the development of new and effective synthesis methods. For this reason, several research groups prepared new strategies for the synthesis of pyrrol containing alkaloids. Joined to this effort my results were utilized to the preparation of these natural products.

2.1.1 Lamellarine alkaloids

The building up of the azepin sturcture by 1,7-eletrocyclisation can be regarded as a starting point to the synthesis of lamellarines. In the course of 1,7-electrocyclizations, several azepin derivatives have been prepared by our

research group.[1] In further experiments we found that changes in the substitution pattern of the isoquinoline side chain promote the formation of a product with pyrrolo[2,1-*a*]isoquinoline frame in an 1,5-eletrocyclization reaction instead of azepin derivatives. The observed phenomenon thus beneficial for the formation of lamellarine analogues.

New lamellarine synthesis was developed as an alternative way of the afore-mentioned method by our research group. The basis of the investigations was given by a previous research at the Budapest University of Technology and Economics, the Department of Organic Chemical Technology. Bende et al. studied 1,3-dipolar cycloadditions in which compounds with pyrrolo[2,1-*a*]isoquinoline frames were synthesized from the reactions of the corresponding ylides and dipolarofiles.[2] We supposed that further transformations of on the 1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline molecule will lead to simple and quick synthetic ways for the creation of lamellarine frames.

2.1.2 Lukianol and ningalin alkaloids

The preparation of the key intermediates of lukianol and ningalin alkaloids were carried out owing to our previous experiences of the electrocyclisation reactions of β-phenylcinnamonaldehyde. We found significant differences between the reactivity of ester-stabilized and non-stabilized azometin-ylides during the electrocyclisations of azometin-ylides containing α,β:γ,δ conjugations, originated from β-phenylcinnamonaldehyde.[3] As a

[1] Nyerges, M.; Somfai, B.; Tóth, J.; Tőke, L.; Dancsó, A.; Blaskó, G.; *Sythesis* **2005**, 12, 2039.
Nyerges, M., Virányi, A.; Tóth, J.; Blaskó, G., Tőke, L.; *Synthesis* **2006**, 8, 1273.
Tóth, J.; Dancsó, A., Blaskó, G.; Tőke, L.; Groundwater, P. W.; Nyerges, M.; *Tetrahedron* **2006**, 62, 5725.

[2] Bende, Z., Simon, K.; Tóth, G.; Tőke, L.; Weber, L.; *Liebigs Ann. Chem.* **1982**, 924.
Bende, Z.; Tőke, L.; Weber, L.; Tóth, G.; Janke, F.; Csonka, G.; *Tetrahedron*, **1984**, 40, 69.

[3] Arany, A.; Groundwater, P. W.; Nyerges, M.; *Tetrahedron Lett.*; **1998**, 39, 3267.
Groundwater, P. W.; Garnett, I., Morton, A. J.; Shariff, T., Coles, S. J.; Hursthouse, M. B.; Nyerges, M., Anderson, R. J., Bendell, D., McKillop, A., Zhang, W.; *J. Chem. Soc., Perkin Trans*. 1, **2001**, 2781.
Groundwater, P. W., Shariff, T, Arany, A.; Hibbs, D. E., Hursthouse, M. B.; Garnett, I., Nyerges, M.; *J. Chem.*

consideration of the afore-mentioned reactions and the substituent dependent electrocyclisations recognised during the synthesis of lamellarines, azomethine ylides generated by stilbenic aldehyde were investigated with the aim of the synthesis of so-called Furstner intermediate.

2.2 Molecules with oxazolidine fragment

During my research, I synthesized molecules, which contain oxazolidine fragments too. The oxazolidine derivatives were synthesized via three-component one-pot reactions, developed by our research group.[4] My goal was to widen the applicability of these reactions, which can result worthy intermediates and druglike molecules.

3. Experimental methods

The „classical" preparative organic chemistry and separation methods were applied in the synthetic work.

Thin layer chromatography was applied to monitor reactions. Crystallization, column chromatography were used for the purification of the crude products. Spectroscopic methods (IR, ^{1}H and ^{13}C NMR, MS) were applied for the verification of the new structures of the synthesized compounds.

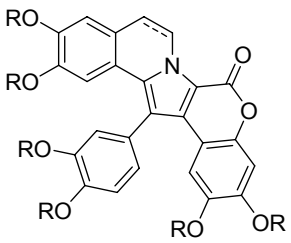
Soc., Perkin Trans. 1, **1998**, 2837.
Groundwater, P. W., Shariff, T., Arany, A.; Hibbs, D. E., Hursthouse, M. B.; Nyerges, M.; Tetrahedron Lett. **1998**, 39, 1433.

[4] Nyerges, M.; Fejes, I.; Virányi, A.; Groundwater, P. W.; Tőke, L.; *Synthesis*, **2001**, 10, 1479.

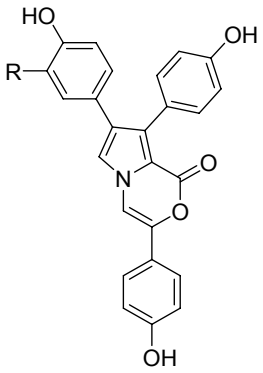
4. Results

My research work could be divided into two parts:

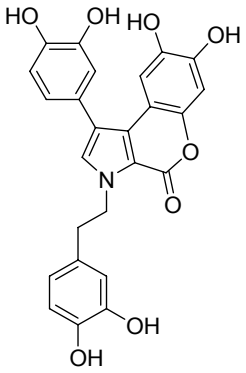
4.1 The synthesis of lamellarines and other pyrrol containing alkaloid intermediers.



lamellarines



lukianol A R=H
lukianol B R= I



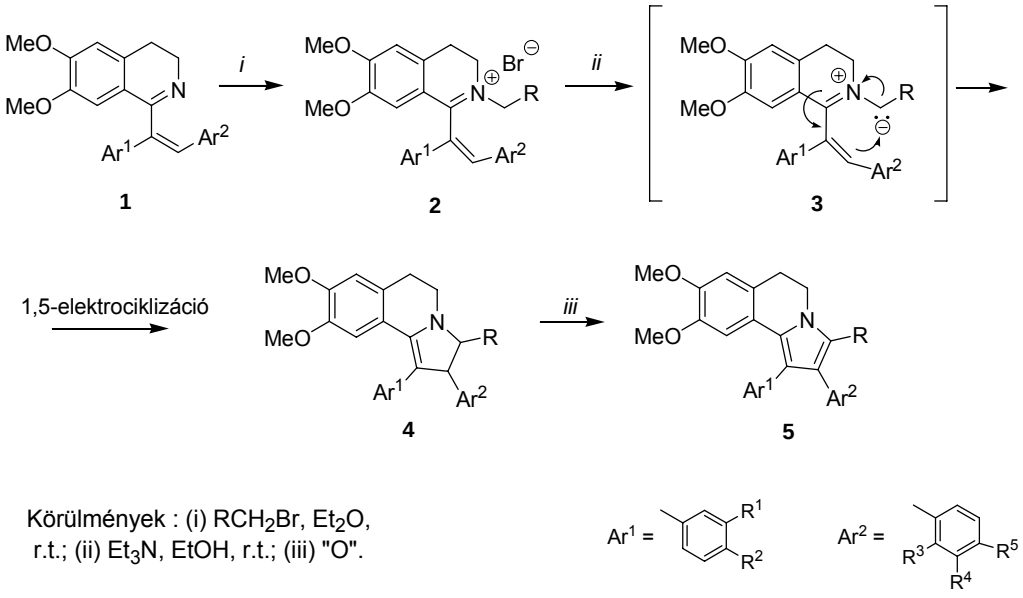
ningalin B

4.2 Preparation of oxazolidine derivatives by 1,3-dipolar cycloaddition.

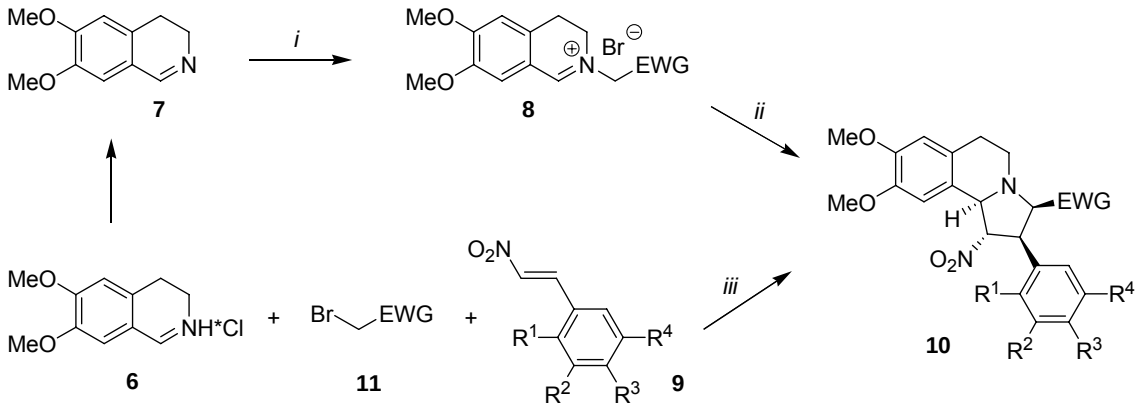
4.1.1 Lamellarine alkaloid analogues were prepared by new 1,5-electrocyclisations of stabilised α,β:γ,δ-unsaturated azomethine ylides formed with deprotonation of iminium salts.

The **1** dihydroisoquinoline that is required for the electrocyclisation reaction was synthesized in four step. From **1** a quaternery salt was formed by the correspondent alkylation agent. After the dehydrohalogenation of **2** quaternery salt, a **3** ylide was formed, which was stabilised in an 1,5-electrocyclisation process. As a result of this reaction a **5** pyrrolo[2,1-*a*]isoquonoline was isolated, which was formed by the oxidation of **4** pyrroline intermediate.

Reacting the **2** isoquinolinium salts with triethylamine in dichloromethane in the presence of manganese dioxide, resulted a clean and fast formation of **5** utilizing a one-pot, sequential dehyrohalogenation-electrocyclisation-oxidation process as a key step.



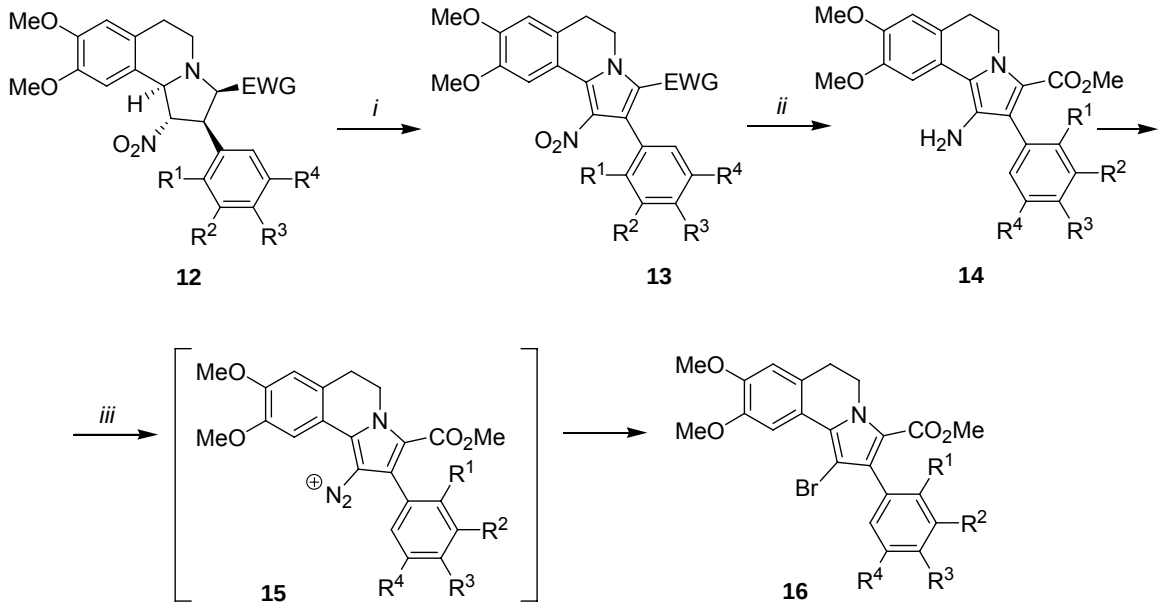
4.1.2 Alternatively to the above synthesis, the **10** dihydropyrrolo[2,1-*a*]isoquinoline skeleton was prepared by [3+2] cycloaddition as key step. Instead of the traditionally three step synthesis – base liberation, alkylation, cycloaddition - **10** was realized directly from **6** using a one step method.



Körülmények: (i) EWG-CH_2Br, Et_2O, r.t.; (ii) **9**, Et_3N, EtOH, r.t.; (iii) Et_3N, EtOH, r.t.

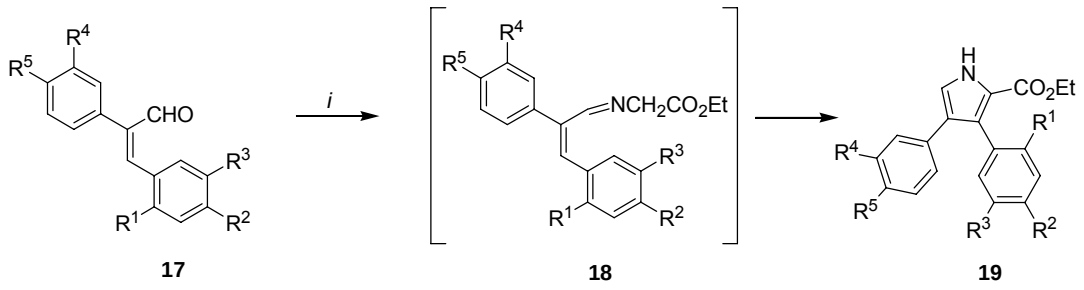
A new method was developed to the aromatisation of **10** cycloadduct. The oxidation reaction was performed by NBS at room temperature. As a limitation of this method, in the case when the aromatic ring has two or more electron-donating substituents, the concomitant bromination of the 2-aryl substituent was

observed, which can be avoided by applying lower reaction temperature. Finally, the lamellarine intermediates, the 2-aryl-1-bromo-8,9-dimethoxy-5,6-dihydro[2,1-*a*]isoquinoline (**16**) were preapared in two steps. After the reduction of the compound **13**, the **14** amino-pyrrol compound was transformed into the desired **16** lamellarine intermediate by *i*-pentyl-nitrite and bromophorm.



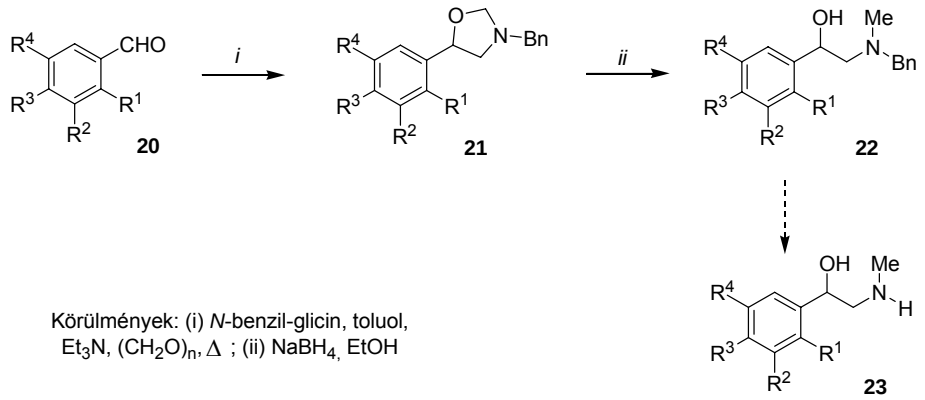
Körülmények: (i) NBS, $CHCl_3$, r.t.; (ii) $Na_2S_2O_4$, EtOH, H_2O, Δ ; (iii) *i*-pentil-nitrit, $CHBr_3$, 120°C.

4.1.3 Azomethine ylides containing extended conjugation, generated from **17** stilbenic aldehydes were examined. Surprisingly, the non-stabilised azomethine ylides generated from **17** aldehydes did not take part in 1,5-electrocyclisation reactions. Despite, an unexpected 1,5-electrocyclisation was occurred with the **18** ester-stabilised azomethine ylides if **17** contained electron-donating groups. As a result, the formal total synthesis of the lukianol and ningalin alkaloids were performed.



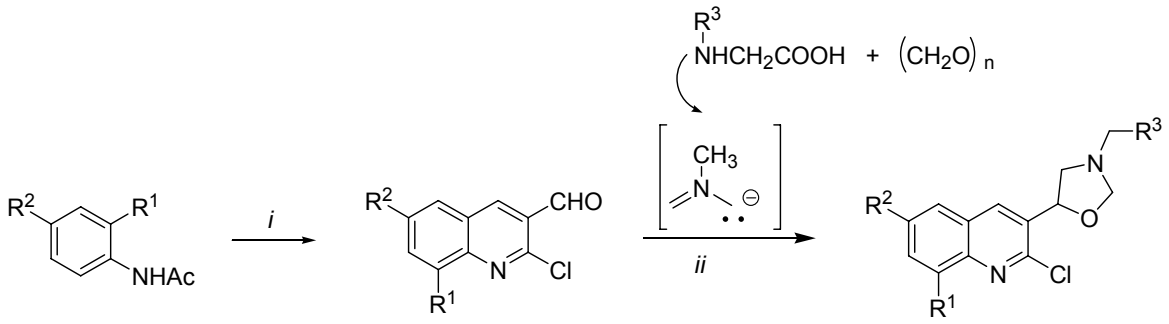
Körülmények: (i) $NH_2CH_2CO_2Et$, Et_3N, xilol,Δ

4.2.1 5-Aryl-3-benzyloxazolidines (**21**) were synthesized by the thee-component domino reaction of formaldehyde, *N*-benzylglycin and **20** aromatic aldehyde. In all cases the formaldehyde and the *N*-benzylglycine served as a component for the non-stabilised azomethine ylide generation, and the oxazolidine ring was created in a 1,3-dipolar cycloaddition of the azomethine ylide to the C=O double bond of the **20** aromatic aldehyde. Subsequently, the oxazolidine ring was subjected to a reductive ring opening process, which resulted 2-(*N*-benzyl-*N*-methylamino)-1-arylethanols (**22**). Further valuable **23** synthetic intermediates could be formed by the removal of the benzyl group.



Körülmények: (i) *N*-benzil-glicin, toluol, Et_3N, $(CH_2O)_n$,Δ ; (ii) $NaBH_4$, EtOH

This method was used for the preparation of new, quinoline containing heterocycles. As a result of the reaction, **26** quinoline-3-yl-1,3-oxazolidine derivatives were prepared.



24 **25** **26** R^3 = Me, Bn

Körülmények: (i) $POCl_3$, DMF, 90°C, (ii) toluol, 110°C.

5. Thesis

1. Dihydropyrrolo[2,1-*a*]isoquinoline derivatives were prepared by 1,5-electrocyclisation reaction of azomenthine ylides generated by a deprotonation method. As a result of this newly developed method, lamellarine alkaloid analogues were synthesized.[5]

2. The skeleton of lamellarine analogues were achieved also by [3+2] cycloaddition. A new, multi component, one-pot method was processed to the preparation of 1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline derivatives, proceeded from dihydroisoquinolinium hydrocloride salts.[6]

3. A new oxidation method was processed to the transformation of pyrrolidines to pyrroles by *N*-bromosuccinimide. With this method, dihydropyrrolo[2,1-*a*]isoquinolines were easily prepared.[7]

[5] Tóth, J.; Nedves, A.; Dancsó, A.; Blaskó, G., Tőke, L., Nyerges, M., *Synthesis*, **2007**, 7, 1003.
[6] Nyerges, M.; Somfai, B.; Tóth, J.; Tőke, L.; Dancsó, A.; Blaskó, G.; *Sythesis* **2005**, 12, 2039.
[7] Tóth, J.; Váradi, L.; Blaskó, G.; Dancsó, A., Tőke, L.; Nyerges, M., *Synlett*, **2007**, 8, 1259.

4. A new lamellarine alkaloid intermiediate was synthesized in two steps proceeded from 2-aryl-8,9-dimethoxy-1-nitro-dihydropyrrolo[2,1-*a*]isoquinlines.

5. A new 1,5-electocyclisation reaction of ester-stabilised azomethine ylides was discovered by the reaction of ester-stabilised azomethine ylides, generated from (Z)-2,3-diarylprop-2-enals. In the case when the stilbenic aldehyde contained electron-donating substituents, 3,4-diarylpyrrol-2-carboxilate derivatives were synthesized.

6. The formal total synthesis of lukianol A and B, as well as ningalin B were achieved by 1,5-electrocyclisations of ester-stabilised azomethine-ylides generated from (Z)-2,3-diarylprop-2-enals in a new pathway.

7. Different 5-aryl-3-benzyloxazoilidine and quinoline-3-yl-1,3-oxazolidine derivatives were prepared.[8] In all cases, the formaldehyde and the sarcosine (or *N*-benzylglycine) served as a component for the non-stabilised azomethine ylide generation, and the oxazolidine ring was created by a 1,3-dipolar cycloaddition of the azomethine ylide to the C=O double bond of the aromatic aldehyde. β-Amino-alcohol intermediates were synthesized by the ring opening process of 5-aryl-3-benzyloxazolidine.

6. Applications

I didn’t make efforts to utilize my results in preparation of products which have industrial significance, however, I pointed out some simply preparation process for alkaloids, which have physiological importance.

[8] Tóth, J., Blaskó, G.; Dancsó, A.; Tőke, L.; Nyerges, M.; *Synthetic Commun*., **2006**, 36, 3581.

The variety of the reactions completed with simple reagents under mostly mild circumstances are the most important results of my research work, which contributes to the improvement of this research field and widens the toolbar of the preparative organic chemistry.

7. Publications

7.1 Related publications to the PhD

1. Nyerges, M., Somfai, B.; Tóth, J.; Dancsó, A.; Blaskó, G.; Tőke, L.
   A novel one-pot, three component access to hexahydro-pyrrolo[2,1-*a*]isoquinolines by an alkylation - dehydrohalogenation - 1,3-dipolar cycloaddition sequence
   Synthesis **2005**, 2039. (IF: 2,400)

2. Nyerges, M.; Virányi, A.; Tóth, J.; Blaskó, G.; Tõke, L.
   Synthesis of New β-Carboline Derivatives via 1,7-Electrocyclisation of Azomethine Ylides
   Synthesis **2006**, 1273. (IF: 2,333)

3. Nyerges, M., Tóth, J.; Dancsó, A.; Blaskó, G.; Tőke, L.
   1,7-Electrocyclization Reactions of Stabilised α,β:γ,δ-Unsaturated Azomethine Ylides *Tetrahedron* **2006**, *62,* 5725. (IF: 2,817)

4. Tóth, J.; Dancsó, A.; Blaskó, G.; Tőke, L.; Nyerges, M.
   Synthesis of New Quinoline Derivatives
   Synthetic Communication **2006**, 3581. (IF: 1,001)

5. Tóth J.; Nedves, A.; Blaskó G.; Dancsó, A.; Tőke L.; Nyerges, M.
   Synthesis of Pyrrolo[2,1-*a*]isoquinolines by a Tandem 1,5-Electrocyclisation – Oxidation Process
   Synthesis **2007**, 1003. (IF: 2,257)

6. Tóth J.; Váradi L.; Blaskó G.; Dancsó, A.; Tőke L.; Nyerges, M.
   Novel oxidation of substituted pyrrolidines by *N*-bromosuccinimide – Rapid synthesis of pyrrolo[2,1-*a*]isoquinolines
   Synlett **2007**, 1259. (IF: 2,763)

7. Nyerges, M.; Tóth, J.; Groundwater, P.W.
   1,7-Electrocyclisation of Azomethine Ylides: Scope and Synthetic Aspects
   Synlett **2008**, 1269. (IF: 2,763)

7.2 Presentations

1. Tóth, J. Nyerges, M., Tőke, L., Dancsó, A.
   Synthesis of lamellarine alkloids; oral lecture
   Confrence of the Alkaloid Chemistry Comittie of the Hungarian Academy of Science, Hungary, Balatonfüred, 15-16, May, 2006.

2. Tóth, J., Nyerges, M.
   Electrocyclization reactions of stabilized α,β:γ,δ-unsaturated azomethine ylides-concise construction of the lamellarin skeleton; poster presentation
   European Cheimcal Societies, 13th FECHEM Conference on Heterocycles in Bioorganic Chemistry,Hungary, Sopron 28-31, May, 2006.

3. Tóth, J., Váradi, L., Tőke L., Nyerges, M.
   Oxidation of pyrrolidine derivatives by *N*-bromosuccinimide; poster presentation
   Centenary Chemist Conference, Hungary, Sopron, 29 May- 1 June, 2007.

4. Tóth, J., Nedves, A., Gáber, Sz., Tőke, L., Nyerges, M.
   Synthesis of lamellarine alkaloid analogues; poster presentation
   Centenary Chemist Conference, Hungary, Sopron, 29 May- 1 June, 2007.

5. Tóth, J., Tőke, L., Nyerges, M.
   Synthesis of heterocyclic compounds by pericyclic reactions; poster presentation
   PhD Student Conference - Budapest Uiniversity of Technology and Economics, Faculty of Chemical Technology and Biotechnology; Hungary, Budapest, 8, February, 2008.

6. Tóth, J., Nyerges, M., Tőke, L.
   Formal total synthesis of lukianol A and related pyrrol alkaloids via 1,5-electrocyclic reaction of azomethine ylides; oral lecture
   Confrence of the Alkaloid Chemistry Comittie of the Hungarian Academy of Science, Hungary, Balatonfüred, 13-14, May, 2008.

7. Tóth, J., Nyerges, M.
   1,5-electrocyclisation of azomethine yilides – Concise construction of the Lamellarin; poster presentation
   XIth Belgian Organic Synthesis Symphosium; Belgium, Gent, 13-18, July, 2008.