Ph.D. Thesis

Syntheses and transformations of carbamatoalkylnaphthols prepared via modified Mannich reactions

Renáta Csütörtöki

Supervisor:
Prof. Dr. Ferenc Fülöp

Institute of Pharmaceutical Chemistry
University of Szeged

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A. INTRODUCTION AND AIMS

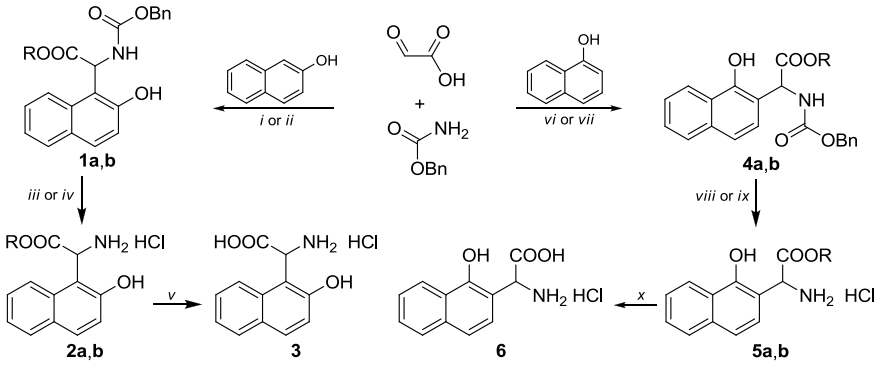
The Mannich reaction is one of the most frequently applied multicomponent reaction in organic chemistry. One of its special variants is the modified three-component Mannich reaction (mMR), in which the electron-rich aromatic compounds are 1- or 2-naphthol.

Since one of the most important areas of application of aminonaphthols prepared via mMRs is the synthesis of new heterocycles, my Ph.D. work focused on the synthesis of novel trifunctional aminonaphthol derivatives. I therefore set out to prepare hydroxynaphthyl-substituted glycines as new α-amino acid derivatives by starting from 1- or 2-naphthol. As the newly prepared aminononaphthol derivatives contain one chiral centre, the separation of their enantiomers was a further aim.

In order to extend the series of naphthoxazino-fused heterocyclic ring systems (naphth[1,2-*e*][1,3]oxazino[1,3]benzoxazines and naphth[1,2-*e*][1,3]oxazinoisoquinolines) during my Ph.D. work, the syntheses of naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline and the ring-anellation analogue naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazoline derivatives were planned. Another goal was the conformational analysis of the newly prepared naphth[1,2-*e*][1,3]oxazinoquinazolines by means of NMR spectroscopy and accompanying molecular modelling.

B. RESULTS AND DISCUSSION

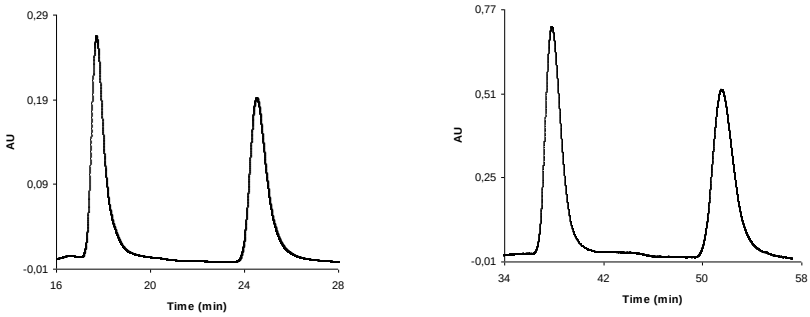
1. Hydroxynaphthyl-substituted glycine derivatives **2a** and **5a** were successfully prepared from 2- or 1-naphthol, glyoxylic acid and benzyl carbamate in MeOH via a mMR in the presence of *p*-TSA, followed by removal of the protecting group. Acidic hydrolysis of **2a** and **5a** resulted in the expected α-amino acids **3** and **6**. The optimized reaction conditions were extended by starting from EtOH. Benzyloxycarbonyl-protected ethyl esters **1b** and **4b** were isolated in lower yields as compared with those of methyl esters **1a** and **4a** (Scheme 1).



Reagents, conditions and yields: (*i*) *p*-TSA, MeOH, reflux, 26 h, 69%; (*ii*) *p*-TSA, EtOH, reflux, 94 h, 34%; (*iii*) Pd/C, H_2, MeOH, r.t., 1 h, HCl–EtOH, 75%; (*iv*) Pd/C, H_2, EtOH, r.t., 1.5 h, HCl-EtOH, 72%; (*v*) R = Me, 5% aq. HCl, reflux, 2 h, 82%; (*vi*) MeOH, reflux, 36 h, 53%; (*vii*) EtOH, reflux, 97 h, 27%; (*viii*) Pd/C, H_2, MeOH, r.t., 1 h, HCl–EtOH, 84%; (*ix*) Pd/C, H_2, EtOH, r.t., 1.5 h, HCl–EtOH, 69%; (*x*) R = Me, 10% aq. HCl, reflux, 4 h, 88%.

Scheme 1

2. The enantiomers of **2a** and **5a** were successfully separated on analytical and semi-preparative HPLC columns (Fig. 1). Their absolute configurations were determined by CD analysis supported by TDDFT CD calculations, which revealed that the absolute configuration of the second-eluting enantiomer of **2a** was *S* and of the first-eluting enantiomer of **5a** was *S*.

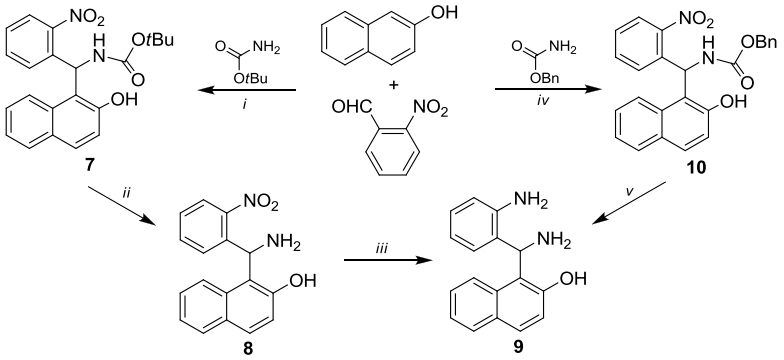


a **b**

Fig. 1. a) Chromatogram of **2a**. *Conditions*: Chiralcel OD-H; *n*-hexane–2-PrOH = 70/30 (v/v); detection at 230 nm; flow rate 0.5 mL/min.

b) Chromatogram of **5a**. *Conditions*: Chiralcel OD-H; *n*-hexane–2-PrOH = 85/15 (v/v); detection at 230 nm; flow rate 0.5 mL/min.

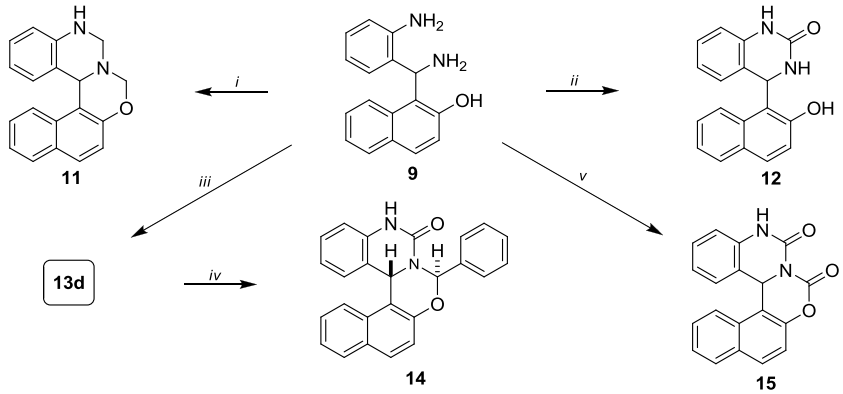
3. A new, highly functionalized aminonaphthol derivative, 1-(amino(2-aminophenyl) methyl)-2-naphthol (**9**), was synthetized through two synthetic pathways. The reaction of 2-naphthol, 2-nitrobenzaldehyde and *tert*-butyl carbamate led to the formation of nitro derivative **7**. After the removal of the protecting group and reduction of the NO_2 group, the desired trifunctional aminonaphthol derivative **9** was obtained. The reaction pathway was simplified when *tert*-butyl carbamate was replaced by benzyl carbamate (Scheme 2).



Reagents, conditions and yields: (*i*) 80 ºC, 47 h, 53%; (*ii*) 99% TFA, r.t., 10 min, 10% Na_2CO_3, 90%; (*iii*) Pd/C, H_2, MeOH, r.t., 1.5 h, 68%; (*iv*) 80 ºC, 32 h, 76%; (*v*) Pd/C, H_2, MeOH, r.t., 2 h, 69%.

Scheme 2

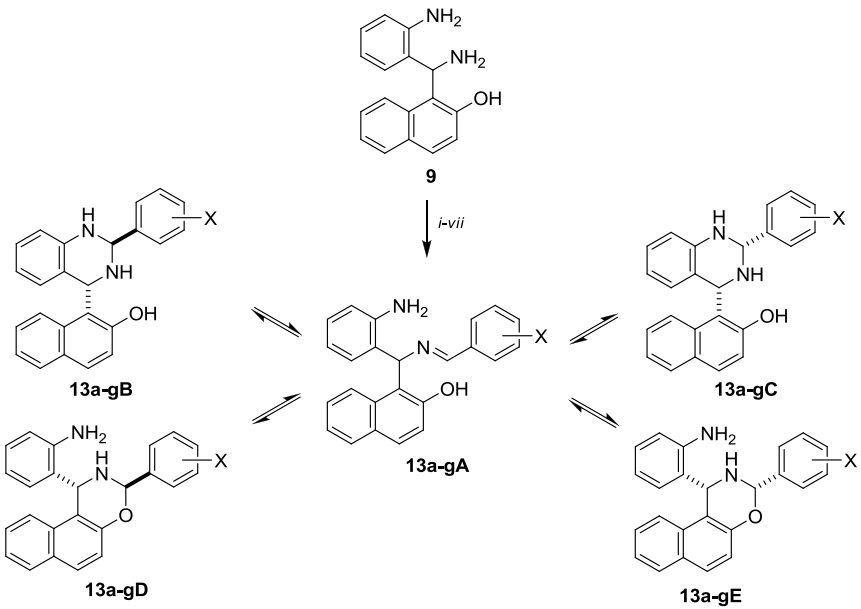
The aminonaphthol derivative (**9**) thus obtained was converted in a ring closure reaction with formaldehyde to 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline (**11**). The ring closure reaction of the starting diamine with phosgene and/or benzaldehyde led to the formation of new naphthoxazinoquinazolinone derivatives (**12**, **14** and **15**; Scheme 3).



Reagents, conditions and yields: (*i*) 2 equiv. 30% aq. CH_2O, $CHCl_3$, r.t., 1.5 h, 40%; (*ii*) 0.5 equiv. $(COCl_2)_3$, 5 equiv. Na_2CO_3, toluene, r.t., 45 h, 40%; (*iii*) 1.1 equiv. PhCHO, MeOH, r.t., 24 h, 88%; (*iv*) 4 equiv. $(COCl_2)_3$, 10 equiv. Na_2CO_3, toluene, r.t., 6.5 h, 31%; (*v*) 4 equiv. $(COCl_2)_3$, 10 equiv. Na_2CO_3, toluene, r.t., 8.5 h, 67%.

Scheme 3

4. Products **13a-g** obtained via the condensation of **9** with substituted benzaldehydes can potentially furnish five-component tautomeric mixtures in CD_2Cl_2 at 300 K. We succeeded in detecting three of the five components: one epimeric quinazoline (**B**) and two epimeric naphthoxazines (**D** and **E**, Scheme 4). The influence of aryl substituents on the tautomeric composition could be described in terms of the Hammett-Brown parameter (σ^+). It can be concluded that electron-donating substituents increase the proportion of the quinazoline form (**B**), while electron-withdrawing substituents prefer the naphthoxazine forms (**D** and **E**, Table 1).



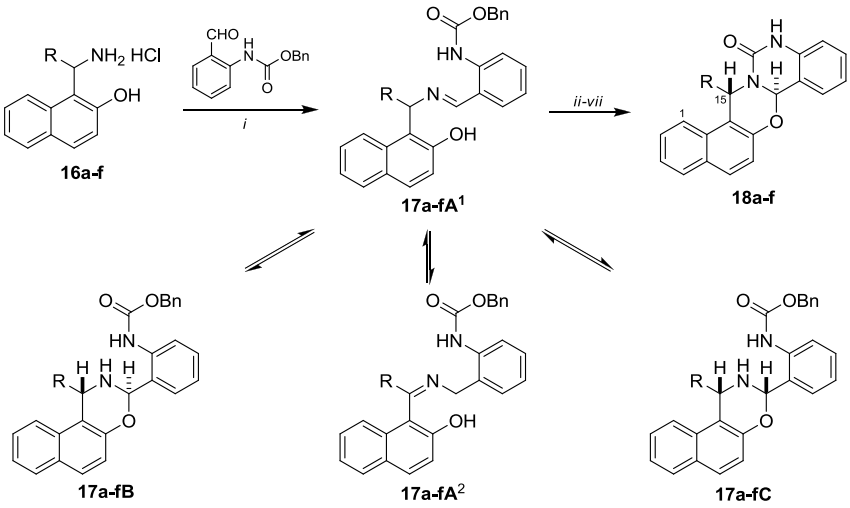
Reagents, conditions and yields: (*i*) *p*-NO_2-PhCHO, MeOH, r.t., 24 h, **13a**: 77%; (*ii*) *m*-Cl-PhCHO, MeOH, r.t., 24 h, **13b**: 52%; (*iii*) *p*-Cl-PhCHO, MeOH, r.t., 24 h, **13c**: 63%; (*iv*) PhCHO, MeOH, r.t., 24 h, **13d**: 88%; (*v*) *p*-Me-PhCHO, MeOH, r.t., 24 h, **13e**: 66%; (*vi*) *p*-OMe-PhCHO, MeOH, r.t., 24 h, **13f**: 90%; (*vii*) *p*-NMe_2-PhCHO, MeOH, r.t., 24 h, **13g**: 57%.

Scheme 4

Table 1. Proportions (%) of the tautomeric forms (**A**, **B**, **C**, **D** and **E**) in tautomeric equilibrium for compounds **13a-g** (CD_2Cl_2, 300 K)

X	σ^+	**A** (%)	**B** (%)	**C** (%)	**D** (%)	**E** (%)
p-NO_2	0.79	-	79.1	-	5.8	15.1
m-Cl	0.40	-	80.6	-	5.5	13.9
p-Cl	0.11	-	82.0	-	5.3	12.7
H	0.00	-	84.5	-	4.8	10.7
p-Me	-0.31	-	85.2	-	4.5	10.3
p-OMe	-0.78	-	87.0	-	4.1	8.9
p-NMe_2	-1.70	-	88.6	-	3.5	7.9

5. The syntheses of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives (**18a** and **18c**) were achieved by the solvent-free heating of benzyloxycarbonyl-protected intermediates (**17a** and **17c**) with MeONa. Compounds **17a** and **17c** were synthetized by the reactions of substituted aminonaphthol derivatives (**16a** and **16c**) with benzyl *N*-(2-formylphenyl)carbamate. This synthetic pathway was extended to the preparation of naphthoxazinoquinazolinones containing different aryl substituents at position 15 (*p*-Cl-Ph: **18b**, *p*-OMe-Ph: **18d**, 1-Nph: **18e**, and 2-Nph: **18f**). During the reaction of **17b-f** with MeONa, the formation of two diastereomers is possible; the diastereomeric ratio was therefore checked by NMR spectroscopy on the crude product. The NOE measurements on purified **18b-f** indirectly proved the *trans* arrangement of H-15 and H-7a (Scheme 5).



R = H: **a**; *p*-Cl-Ph: **b**; Ph: **c**; *p*-OMe-Ph: **d**; 1-Nph: **e**; 2-Nph: **f**

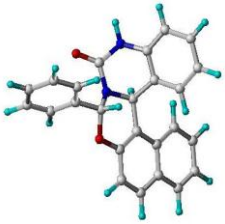
Reagents, conditions and yields: (*i*) Et_3N, EtOH, r.t., 2-4 days; (*ii*) MeONa, 174 °C, 10 min, **18a**: 70%; (*iii*) MeONa, 179 °C, 20 min, **18b**: 61%; (*iv*) MeONa, 152 °C, 30 min, **18c**: 54%; (*v*) MeONa, 154 °C, 40 min, **18d**: 60%; (*vi*) MeONa, 203 °C, 15 min, **18e**: 74%; (*vii*) MeONa, 165 °C, 20 min, **18f**: 51%.

Scheme 5

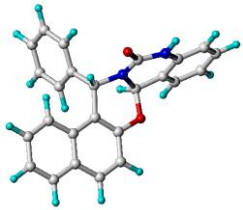
6. In solution at 300 K, **17a-f** can furnish three-component tautomeric mixtures containing diastereomeric ring forms (**B** and **C**) besides the chain form (**A**). When the NMR spectra of **17a-f** were recorded in DMSO, the spectra of **17b-d**,**f** revealed the presence of a new

tautomeric chain form ($\mathbf{A^2}$) besides the *trans* ring form **B** and the chain form $\mathbf{A^1}$. The reason for the formation of $\mathbf{A^2}$ may be the possibility of conjugation of substituent R (aryl) with the C=N double bond, which is supported by the lack of $\mathbf{A^2}$ in **17a** and **17e**. In **17a** there is no aromatic ring, while for **17e** the hindered rotation of the 1-naphyl ring restricts the conjugation. The amount of $\mathbf{A^2}$ increases, while those of **B** and $\mathbf{A^1}$ decrease as the duration of standing in DMSO becomes longer.

7. Compounds **11**, **14** and **18a-f** were studied in all the configurations at the DFT level of theory with respect to the preferred conformers and conformational equilibria. The experimental NMR parameters obtained were in general agreement with the theoretical findings. The conformational study of phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-10-one (**14**) revealed that the oxazine ring proved to prefer an *envelope*, and the quinazolone ring a *twisted boat* conformation; while in naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones (**18a-f**) the oxazine ring prefers a *twisted chair* conformation and the quinazolone ring is almost planar (Fig. 2).



14



18c

Fig. 2. Global minimum-energy structures of **14** and **18c**

8. The anisotropic effect of the 15-aryl ring on H-1 was calculated for **18b-f**: the excellent agreement of the computational and experimental results proved the stereochemistry of the naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives (**18b-f**) deduced from the theoretical calculations. Fig. 3 illustrates the ring current effects of the phenyl ring in **18c** and the 1-naphthyl ring in **18e** on H-1.

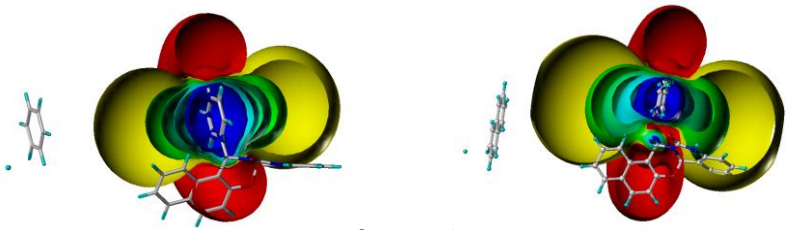
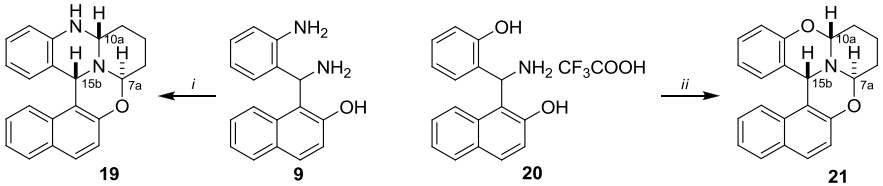


Fig. 3. Ring current effects of the phenyl ring in **18c** and the 1-naphthyl ring in **18e** on H-1

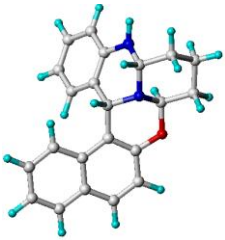
9. The reactions of 1-(amino(2-aminophenyl)methyl)-2-naphthol (**9**) and 1-(amino(2-hydroxyphenyl)methyl)-2-naphthol (**20**) with glutardialdehyde resulted in the formation of piperidine-fused quinazolinonaphthoxazine **19** and benzoxazinonaphthoxazine **21**, respectively, both in diastereopure form. The NOESY measurements on **19** and **21** revealed the following relative arrangements of H-7a–H-15b–H-10a: $H-7a \overset{trans}{\longleftrightarrow} H-15b$; $H-10a \overset{cis}{\longleftrightarrow} H-15b$; $H-7a \overset{trans}{\longleftrightarrow} H-10a$.



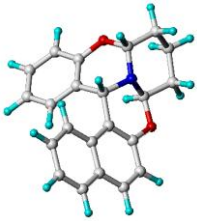
Reagents and conditions: (*i*) 25% aq. $OHC(CH_2)_3CHO$, EtOH, r.t., 3 h, 43%; (*ii*) Et_3N, 25% aq. $OHC(CH_2)_3CHO$, EtOH, r.t., 24 h, 81%.

Scheme 6

The experimental results were supported by theoretical calculations at the DFT level of theory. These calculations and the H,H coupling pattern of the protons in the flexible part of the piperidine ring moiety highlighted that the configuration with a *twisted chair* conformation is preferred for both **19** and **21** (Fig. 4).



19



21

Fig. 4. Global minimum-energy structures of **19** and **21**

C. METHODS

The reactions were accomplished on the milligrams or gram scale. The derivatives prepared were purified by recrystallization or column chromatography. The new derivatives were characterized by their physical constants (melting point), mass-spectrometric measurements and elemental analysis. The ^{1}H, ^{13}C, H-COSY, gs-HMQC, gs-1D-HMQC, gs-HMBC and NOESY spectra were recorded in DMSO or in CD_2Cl_2 solution, in 5 mm tubes, at r.t., on a Bruker Avance DRX400 spectrometer at 400.13 (^{1}H) and 100.61 (^{13}C) MHz and on a Bruker Avance III spectrometer at 600.13 (^{1}H) and 150.61 (^{13}C) MHz. The enantiomers of hydroxynaphthyl-substituted glycine derivatives were separated by chiral HPLC technique. The *ab initio* calculation were carried out at the B3LYP/6-31G** level of theory with the Gaussian 09 program package.

D. PUBLICATIONS

I. **Renáta Csütörtöki**, István Szatmári, Attila Mándi, Tibor Kurtán, Ferenc Fülöp
Synthesis of hydroxynaphthyl-substituted α-amino acid derivatives via a modified Mannich reaction
Synlett **2011**, 1940-1946. **IF: 2.447**

II. **Renáta Csütörtöki**, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of new naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives
Tetrahedron **2011**, *67*, 8564-8571. **IF: 3.011**

III. **Renáta Csütörtöki**, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Syntheses and conformational analyses of new naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones
Tetrahedron **2012**, *68*, 4600-4608. **IF: 3.011**

IV. **Renáta Csütörtöki**, István Szatmári, Matthias Heydenreich, Andreas Koch, Ines Starke, Ferenc Fülöp, Erich Kleinpeter
Novel piperidine-fused benzoxazino- and quinazolinonaphthoxazines – synthesis and conformational study
Tetrahedron **2012**, *68*, 6284-6288. **IF: 3.011**

V. **Renáta Csütörtöki**, István Szatmári, Ferenc Fülöp
Syntheses of amido-, carbamido- and carbamatoalkylnaphthols
Current Organic Synthesis, submitted.

E. CONFERENCE LECTURES

VI. **Csütörtöki Renáta**
Módosított Mannich-reakció alkalmazása új funkcionalizált aminonaftol-származékok szintézisére
XXXII. Kémiai Előadói Napok, Szeged, 2009. október 26-28., Absztr.: 105.

VII. **Csütörtöki Renáta**
Módosított Mannich-reakció alkalmazása α-aminosav-származékok szintézisére
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 10. tudományos előadóülése
Szeged, 2010. május 5.

VIII. István Szatmári, **Renáta Csütörtöki**, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of new naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives
XIVth Conference on Heterocycles in Bio-organic Chemistry, Brno, Czech Republic, September 4-8, 2011. Abstr.: P-30.

IX. Ines Starke, **Renáta Csütörtöki**, Andreas Koch, Erich Kleinpeter, István Szatmári, Ferenc Fülöp
Mass spectrometric behaviour of new naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones
Joint Conference of Polish Mass Spectrometry Society and German Mass Spectrometry Society Poznań, Poland, March 4-7, 2012. Abstr.: P-90.

X. **Renáta Csütörtöki**, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones
XIIth Eurasia Conference on Chemical Sciences, Corfu, Greece, April 16-21, 2012. Abstr.: S_3-PP5.

XI. **Csütörtöki Renáta**, Szatmári István, Fülöp Ferenc
Naftoxazinnal kondenzált kinazolin-származékok szintézise és konformáció-analízise
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2012. június 6-8.