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Synthesis and conformational analysis of novel naphthoxazine fused poliheterocycles

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A. INTRODUCTION AND AIMS

Mannich reaction is an important C-C bond formation one-pot multicomponent reaction that is widely used in the synthesis of many biologically active and natural compounds. Originally, the Mannich product is formed through a three-component reaction contains a C-H acid, formaldehyde and a secondary amine. Although nowadays one of its special variations called modified Mannich reaction gained ground in which C-H acid is replaced by electron-rich aromatic compounds such as 1- or 2-naphthol as an active hydrogen source. At the beginning of the 20th century, Mario Betti reported the synthesis of 1-aminobenzyl-2-naphthol starting from ammonia, benzaldehyde and 2-naphthol. This protocol is known as Betti reaction and the compound formed as Betti base. Several examples have been published to extend the reaction and synthesize variously substituted aminonaphthol derivatives. Their relatively easy accessibility and promising biological properties have led to the chemistry of these compounds again becoming in focus of pharmacological researches.

The formation of the aminonaphthol can be explained by two mechanisms known in the literature. According to one possibility, a Schiff base is formed at first by the reaction of the amine and the aldehyde and it reacts with 2-naphthol in the second nucleophilic addition step. Other theory assumes the formation of an ortho-quinone methide (*o*-QM) intermediate by the reaction of 2-naphthol and benzaldehyde. The driving force of the transformation is the urge of rearomatization which occurs in the second step by the nucleophilic addition of the amine component. As an extention of this modified Mannich reaction, 1- and 2-naphthol and their N-containing analogues were reacted with a wide range of cyclic amines to furnish various aminonaphthol derivatives. These processes followed by ring closure reactions led to the formation of naphth[1,2-*e*][1,3]oxazino[3,4-*c*][1,3]benzoxazines, naphth[1,2-*e*][1,3] oxazino[3,4-*c*]quinazolines, naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones and naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinoline derivatives.

Our first aim was to examine the scope and limitations of this latter reaction to achieve napthoxazino-benzazepines, -thienopyridines and –quinoxalinones. It has

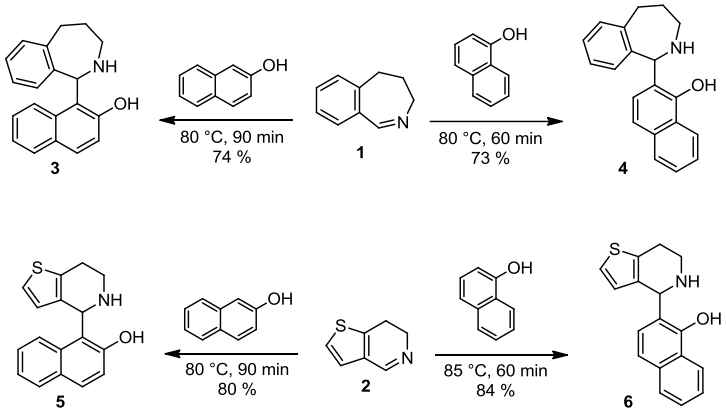
been planned by reacting cyclic imines with electron rich aromatic compounds such as 1- or 2-naphthol and in some cases, N-containing naphthol analogues such as 5-hydroxyisoquinoline or 6-hydroxyquinoline. The isolated secondary aminonaphthols, aminoquinolinols or aminoisoquinolinols then underwent a cyclization reaction using formaldehyde to isolate the desired naphthoxazine fused poliheterocycles.

The class of *o*-QMs is known as short-lived species that play important role as key intermediates in numerous synthetic pathways. One of the first examples of the [4+2] cycloaddition reaction between *o*-QMs formed by aminoalkylnaphthols and partially saturated cyclic imines is published by our group when a seredipitious reaction led to the formation of 9,10-dimethoxynaphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines by the reaction of 1-α-aminobenzyl-2-naphthol and 6,7-dimethoxy-3,4-dihydroisoquinoline.

The second aim of my PhD work was to investigate the applicability of various cyclic imines such as 4,5-dihydro-3H-benz[*c*]azepine, 6,7-dihydrothieno-[3,2-*c*]pyridine and enantiomeric (4a*S*,8a*S*)-4a,5,6,7,8,8a-hexahydro-2-quinoxalinone in this [4+2] cycloaddition reaction mentioned above and to extend the syntheses by the application of variously substituted 1-aminoalkyl-2-naphthols and 2-aminoalkyl-1-naphthols to isolate a wide range of novel naphthoxazine fused poliheterocycles.

B. RESULTS AND DISCUSSION

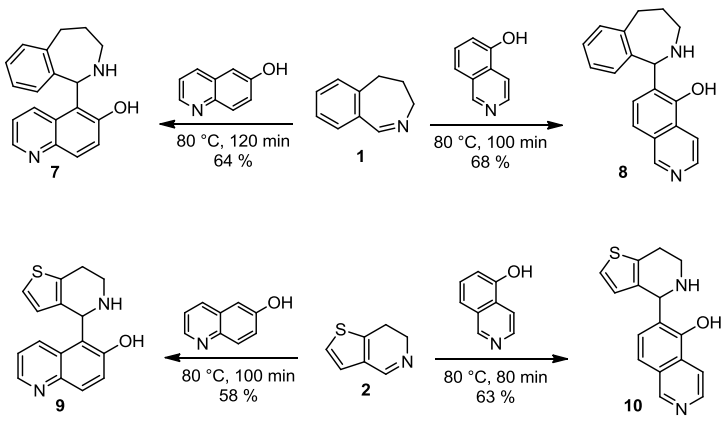
1. C1 couplings of 4,5-dihydro-3H-benz[*c*]azepine (**1**) and 6,7-dihydrothieno[3,2-*c*]pyridine (**2**) were achieved by reacting cyclic imines with 1- or 2-naphthol under neat conditions resulting in hydroxynaphthyl-benzazepines (**3**, **4**) and hydroxynaphthyl-thienopyridines (**5**, **6**; Scheme 1).



Scheme 1

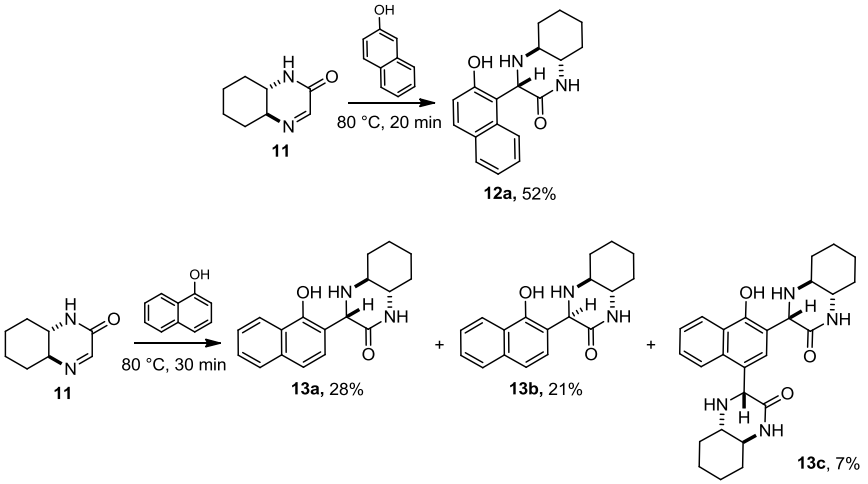
N-containing naphthol analogues such as 5-hydroxyisoquinoline and 6-hydroxyquinoline were also applied. Achieving the transformations under microwave irradiation at 80 °C, hydroxyisoquinolyl and hydroxyquinolyl derivatives (**7-10**) were isolated as novel bifunctional derivatives (Scheme 2)

Comparing the syntheses to naphthols, the desired products were isolated in lower yields however the transformations required longer reaction times.



Scheme 2

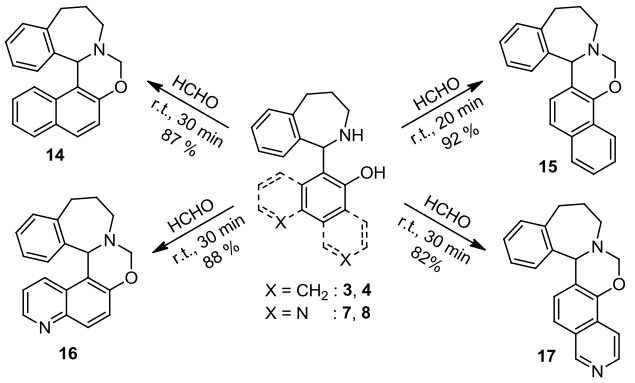
2. Syntheses were then extended by the application of (4a*S*,8a*S*)-4a,5,6,7,8,8a-hexahydro-2-quinoxalinone (**11**) as cyclic imine component in the C1 coupling reactions. While the syntheses required short reaction times (20 and 30 minutes), the application of conventional heating method was preferred. (Scheme 3).



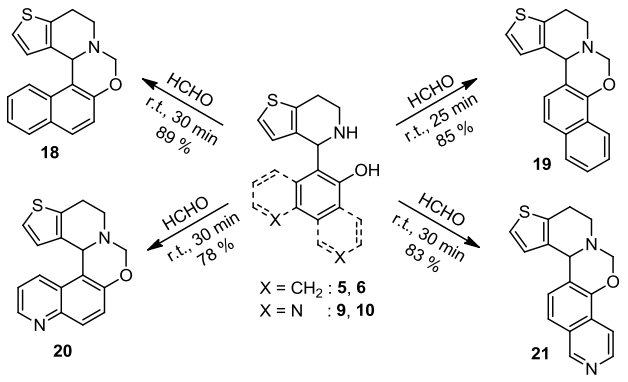
Scheme 3

The preparation of hydroxynaphthyl-quinoxalinones by the application of 2-naphthol found to be diastereoselective and **12a** was isolated as single product. In case of 1-naphthol, the formation of (3'*S*,3''*R*,4a'*S*,4a''*S*,8a'*S*,8a''*S*)-3',3''-(4-hydroxynaphthalene-1,3-diyl)bis (octahydro-quinoxalin-2'-one) **13c** was also detected in around 10% amongst the two possible diastereomers **12a** and **12b**.

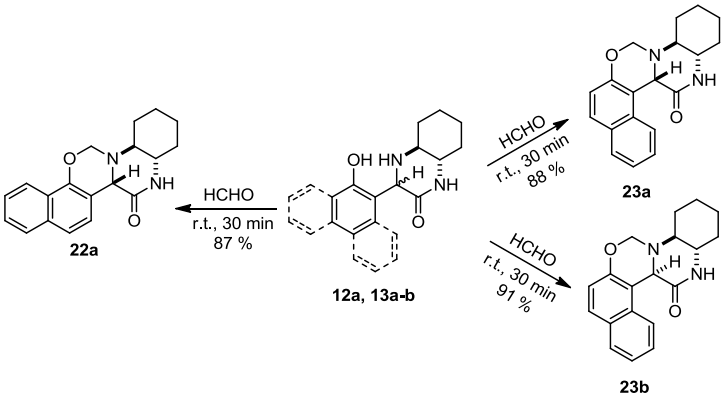
3. Isolated bifunctional compounds **3-10**, **12a**, **13a-c** then underwent cyclizating reactions using a 35% aqueous solution of formaldehyde as cyclizing agent. Achieving the reactions at room temperature in dichloromethane, desired naphthoxazine-, oxazino-isoquinoline- or oxazino-quinoline-fused poliheterocycles (**14-21**, **22a**, **23a-b**) were formed under short reaction times in excellent yields. (Scheme 4-6) By the application of **13c** as starting material, the addition of formaline led to decomposition and no product was isolated.



Scheme 4

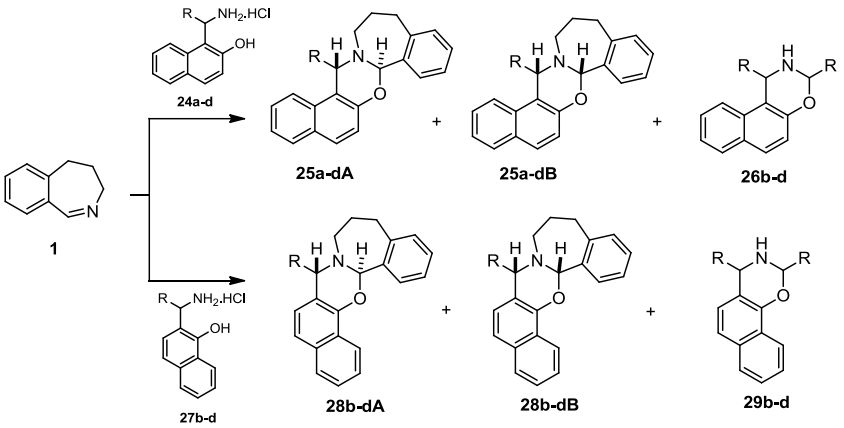


Scheme 5



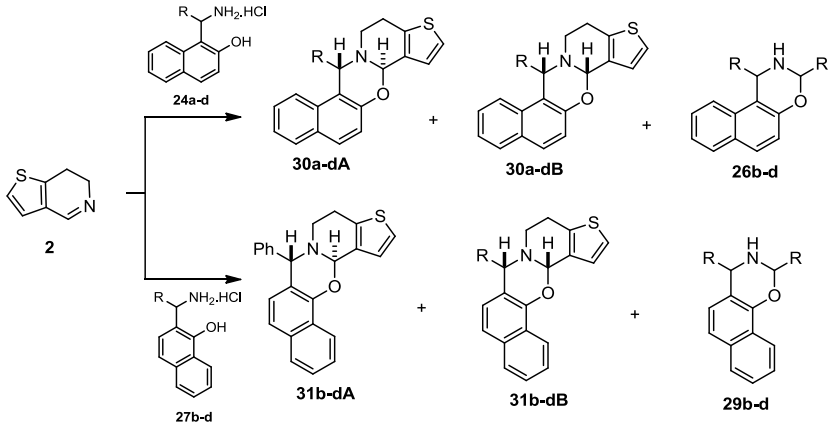
Scheme 6

4. A synthetic route to annelational analogue naphth[1,3]oxazino[2,3-*a*]benzazepines and –thienopyridines was developed. Starting from 4,5-dihydro-3*H*-benz[*c*]azepine or 6,7-dihydrothieno[3,2-*c*]pyridine and variously substituted primary aminonaphthols (**24a-d**, **27b-d**), the formation of desired poliheterocycles (**25a-d**, **28b-d**, **30a-d**, **31b-d**) was occurred amongst unexpected side products (**26b-d**, **29b-d**; Scheme 7-8).



Scheme 7

The formation of the possible diastereomers was also investigated by crude product NMR analysis which indicated that the presence of the minor diastereomers **28bB**, **28dB**, **31bB** and **31dB** could only be detected when the reaction was performed with aminonaphthols **27b** or **27d**.

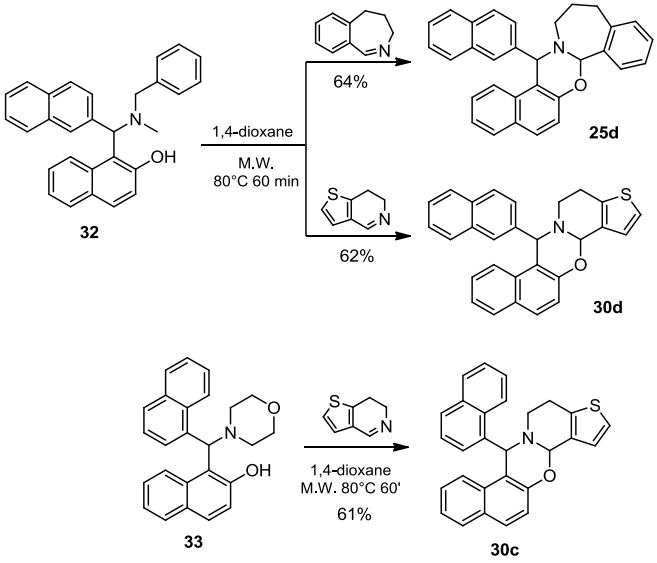


R: H (**a**), Ph (**b**), 1-Nph (**c**), 2-Nph (**d**)

Scheme 8

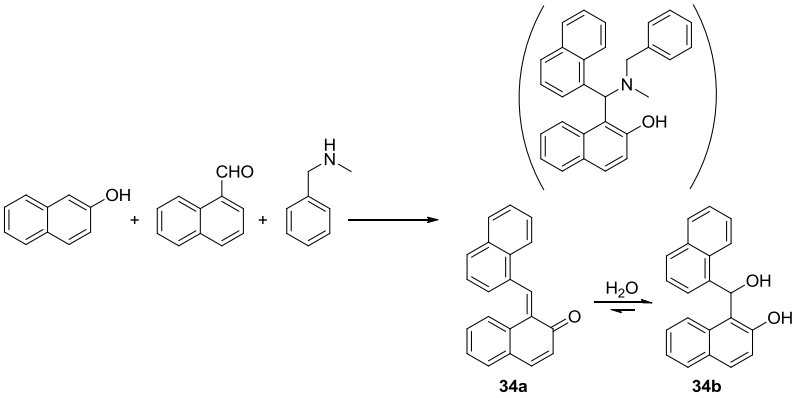
It was found that the diastereoselectivity of the reaction depends on the steric effect of the aromatic ring at position 14 or 16 and on the position of annulation of the naphthyl ring. In most cases, the separation of desired naphthoxazines from side products could succesfully be achieved however **25d**, **30c** and **30d** could not be isolated in pure form. Based on that, a new synthetic strategy was needed.

5. A systematic study was started to compare the reactivity and applicability of different order aminonaphthols in the [4+2] cycloaddition reaction. Based on that study, tertiary aminonaphthols proved to be the best therefore the synthesis of 16-naphth-2-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine (**25d**), 14-naphth-1-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (**30c**) and 14-naphth-2-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine (**30d**) was achieved starting from tertiary aminonaphthols **32** and **33** (Scheme 9).



Scheme 9

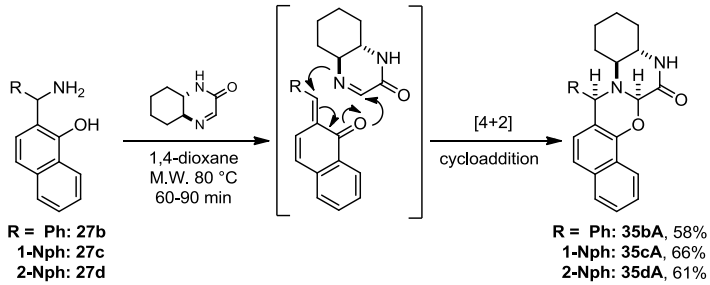
During the preparation of initial bifunctional compounds, an unexpected transformation led to **34** (Scheme 10). The scope and limitations of its formation was investigated from the point of view of both amine and aldehyde scope but no structure similar to **34** was isolated.



Scheme 10

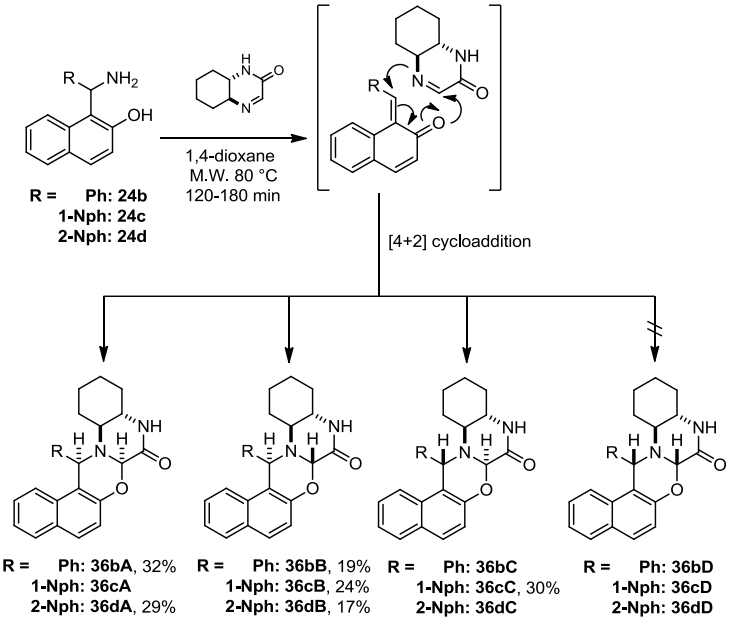
6. A simple synthesis of naphth[1,3]oxazino[3,2-*a*]quinoxalinones was developed. Starting from enantiomeric hexahydroquinoxalinone (**11**) and 1-aminoalkyl-2-naphthols (**24a-d**) or 2-aminoalkyl-1-naphthols (**27b-d**), the transformations were achieved at 80 °C under microwave irradiation.

The formation of the possible diastereomers was checked by crude product NMR spectra. In case of starting from **27b-d**, syntheses proved to be diastereoselective and **35bA-35dA** were isolated as single products (Scheme 11).



Scheme 11

By the application of aminonaphthols **24a-d**, the reactions achieved under microwave irradiation and desired products **36b-d** could be successfully synthesized. In all cases, two of four diastereomers formed were isolated, respectively. The stereocentre configurations of the stereoisomers are defined as follows: 7a*R*,9a*S*,13a*S*,14*R* as **A**, 7a*R*,9a*S*,13a*S*,14*S* as **B,** 7a*S*,9a*S*,13a*S*,14*R* as **C** and 7a*S*,9a*S*,13a*S*,14*S* as **D**. Sterically similar aromatic substituents like phenyl and 2-naphthyl were found to favour the formation of **A** and **B**, while **B** and **C** was preferably formed when initial aminonaphthol bears sterically hindered 1-naphthyl moiety. Note, that stereoisomer **D** has never been detected (Scheme 12).



Scheme 12

C. PUBLICATIONS

I. **Petra Barta**, István Szatmári, Ferenc Fülöp, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter

Synthesis and stereochemistry of new naphth[1,3]oxazino[3,2-*a*]benzazepine and naphth[1,3]oxazino[3,2-*e*]thienopyridine derivatives

Tetrahedron **2016**, *72*, 2402-2410. DOI: 10.1016/j.tet.2016.03.058 **IF: 2.651**

II. István Szatmári, **Petra Barta**, Antal Csámpai, Ferenc Fülöp

Synthesis and detailed conformational analysis of new naphthoxazino [2,3-*a*]benz[*c*]azepine and naphthoxazino[2,3-*a*]thieno[3,2-*c*]pyridine derivatives

Tetrahedron **2017**, *73*, 4790-4804. DOI: 10.1016/j.tet.2017.06.060 **IF: 2.651**

III. István Szatmári, **Petra Barta**, Gábor Tóth, Attila Balázs, Judit Halász, Ferenc Fülöp

Synthesis and conformational behaviour of novel enantiomeric naphthoxazino-quinoxalinone derivatives

Eur. J. Org. Chem. **2017**, 5537-5545. DOI: 10.1002/ejoc.201700699 **IF: 2.834**

IV. **Petra Barta**, Ferenc Fülöp, István Szatmári

Mannich base connected syntheses mediated by ortho-quinone methides

Beilstein J. Org. Chem. **2018**, *14*, 560-575. DOI:10.3762/bjoc.14.43 **IF: 2.3**

D. CONFERENCE LECTURES

I. Barta Petra
Új, benzazepinnel és tienopiridinnel kondenzált naftoxazin-származékok szintézise
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány előadóülése
Szeged, 2015. április 29.

II. Barta Petra, Szatmári István és Fülöp Ferenc
Új naftoxazino[2,3-*a*]benz[*c*]azepin-, valamint naftoxazino[2,3-*a*]tieno[3,2-*c*]piridin-származékok szintézise
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2015. május 27-29.

III. Barta Petra, Szatmári István és Fülöp Ferenc
Potenciális farmakológiai aktivitással rendelkező naftoxazinokinoxalinon-származékok szintézise
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '16
Herceghalom, 2016. szeptember 15-16.

IV. Barta Petra, Szatmári István, Csámpai Antal és Fülöp Ferenc
A 3-hidroxiizokinolin finomhangolt reaktivitása
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2017. május 15-17.

V. István Szatmári, Petra Barta and Ferenc Fülöp
Synthesis of new naphthoxazine-fused heterocycles via the modified Mannich reaction
15th Tetrahedron Symposium, Challenges in Bioorganic and Organic Medicinal Chemistry
24-27th June, 2014 London, UK, Abstr.: P2.33

VI. Petra Barta, István Szatmári and Ferenc Fülöp
Synthesis of new naphthoxazino-benzazepine and -thienopyridine derivatives
16th Blue Danube Symposium on Heterocyclic Chemistry
14-17th June, 2015 Balatonalmádi, Abstr.: P5

VII. Petra Barta, István Szatmári and Ferenc Fülöp
Synthesis and conformational analysis of enantiomeric naphthoxazino-quinoxalinone derivatives
25th International Symposium: Synthesis in Organic Chemistry
17-20th July, 2017 Oxford, UK, Abstr.: P55