BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL

Synthesis of new triazepine derivatives

PhD Thesis

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Egis Pharmaceuticals Plc.

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1. Introduction

2,3-Benzodiazepines are very important, biologically active compounds. The first representative was tofisopam, which was distributed with the name Grandaxin by Egis Pharmaceuticals in 1974. Tofisopam proved to be a good anxiolytic drug. It is a big advantage that tofisopam has no sedative, tranquilizer and nerve system dampening effects, besides this, no addiction is developed even by for a long-term usage. Research of the 2,3-benzodiazepines was continued, as a result of this, several derivatives of this compound family were pharmacologically tested. Among the synthesized derivatives, only nerisopam reached the clinical stage.[1] The compound with number GYKI-52466 shows α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist activity, which feature could be useful to prevent the nervous system against damage caused by cerebral vascular occlusion.[2] In this field, talampanel reached the clinical stage (Fig. 1.).[3]

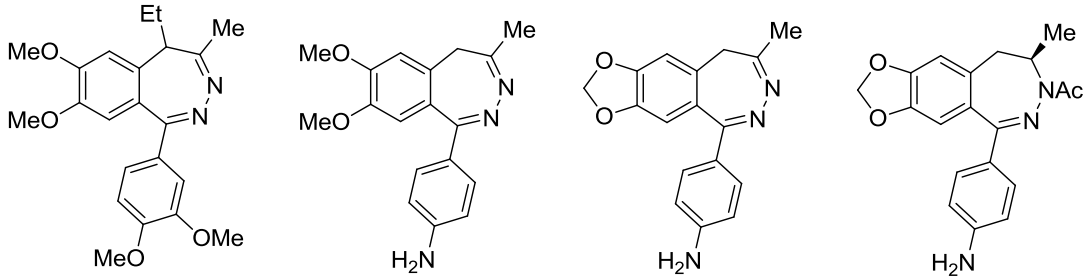

Figure 1. Biologically active benzodiazepines

Later, several fused tricyclic benzodiazepine derivatives were synthesized and examined. The imidazole-fused derivative GYKI-47261 showed antiparkinson effect beside the AMPA antangonist activity.[4] Triazolone- (**1**), triazole- (**2**) and tetrazole-containing compounds (**3**) bear also improved anticonvulsant activities (Fig. 2.).[2,5]

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[1] Palkovits, M.; Baffi, J. S.; Berzsenyi, P.; Horváth, E. J. *Eur. J. Pharmacol*. **1997**, *331*, 53−63.
[2] Sólyom, S.; Tarnawa, I.; *Curr. Pharm. Design.*, **2002**, *8*, 913–939.
[3] Tarnawa, I.; Berzsenyi, P.; Andrási, F.; Botka, P.; Hámori, T.; Ling, I.; Kőrösi, J.; *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 99–104.
[4] Ábrahám, G; Sólyom, S.; Csuzdi, E.; Berzsenyi, P.; Ling, I.; Tarnawa, I.; Hámori, T.; Pallagi, I.; Horváth, K.; Andrási, F.; Kapus, G.; Hársing Jr., L. G.; Király, I.; Patthy, M.; Horváth, G.; *Bioorg. Med. Chem*., **2000**, *8*, 2127–2143.
[5] (a) Zappala, M.; Gitto, R.; Bevacqua, F.; Quartarone, S.; Chimirri, A.; Rizzo, M.; De Sarro, G.; De Sarro, A.; *J. Med. Chem*., **2000**, *43*, 4834–4839. (b) Gitto, R.; Zappala, M.; De Sarro, G.; Chimirri, A.; *Il Farmaco*, **2002**, *57*, 129–134. (c) Csuzdi, E.; Hámori, T.; Ábrahám, G.; Sólyom, S.; Tarnawa, I.; Berzsenyi, P.; Andrási, F.; Ling, I.; Simay, A.; Gál, M.; Horváth, K.; Szentkuti, E.; Szöllösy, M.; Pallagi, I.; PCT Intern. Pat. Appl. WO 9728163; *Chem. Abstr*. **1997**, *127*, 205597.

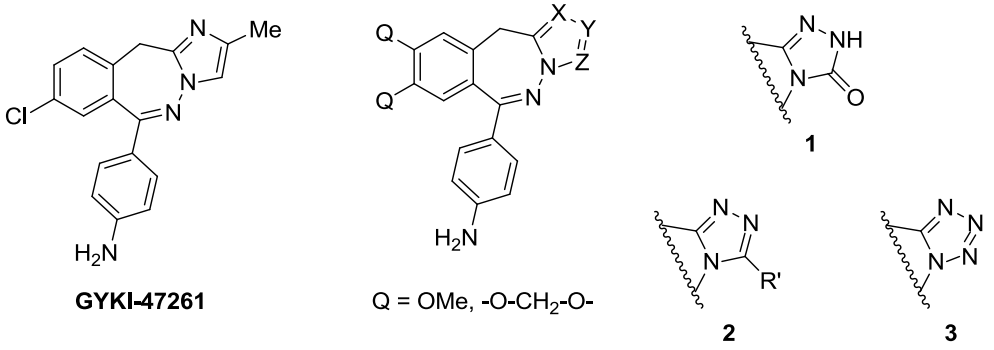


Figure 2. Biologically active tricyclic benzodiazepine derivatives

The benzene ring and the five-membered heterocycles containing one heteroatom, e.g. thiophene, furane and pyrrole are bioisosteres to each other.[6] Consequently, replacing the benzene ring with heterocycles and synthesizing new ring systems is an interesting and important field of medicinal chemistry.

During my PhD research our aim was the synthesis of three new pyrrolotriazepine derivatives condensed with an imidazole (**5**), a triazole (**6**), tetrazole (**7**), triazolone (**8**) and quinazolinone (**9**) ring, using the previously described and synthesized pyrrolotriazepinones[7] **4** (Fig. 3.).

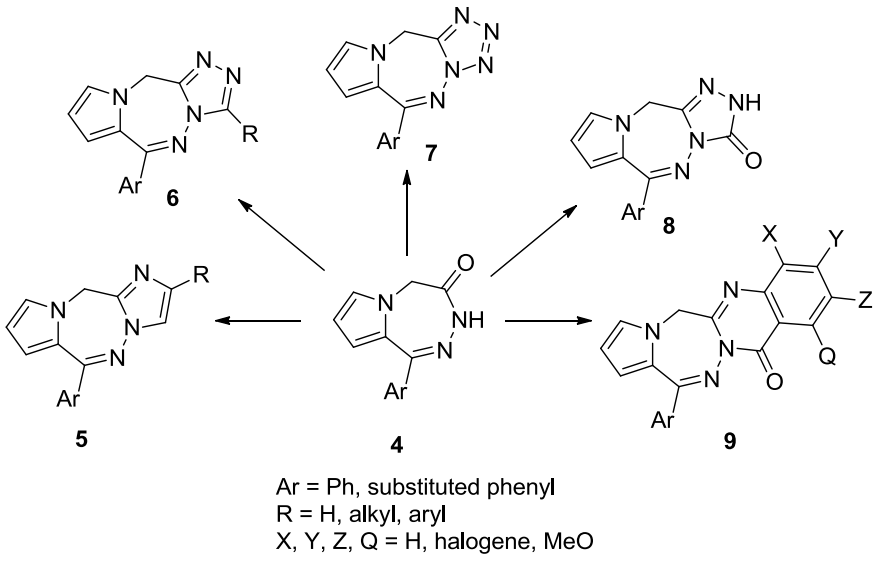


Figure 3. Our first objecitve.

[6] (a) Russell, R. K.; Press, J. B.; In *Progress in Heterocyclic Chemistry*; Suschitzky, H.; Scriven, E. F. V., Eds.; Pergamon: 1995; Vol. 7, p 82. (b) Hernandez, M. A.; Rathinavelu, A. In *Basic Pharmacology*; Taylor & Francis: **2006**, p 69–70.

[7] Milen, M.; Ábrányi-Balogh, P.; Dancsó, A.; Simig, G.; Volk, B.; *Tetrahedron*, **2014**, *70*, 465–476.

Our further objective was the synthesis of 1,4-diaryl-pyrrolotriazepines (**10**) (Fig. 4.), which can also be biologically active compounds.

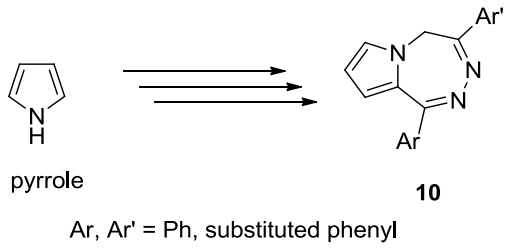


Figure 4. Our second objective.

Moreover, we also aimed at the synthesis of a new imidazoletriazepinone compound family (**11**) (Fig. 5.), which can be used for synthesis of new tricyclic ring systems with expected biological activities.

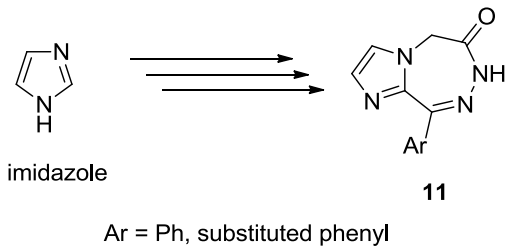


Figure 5. Our third objective.

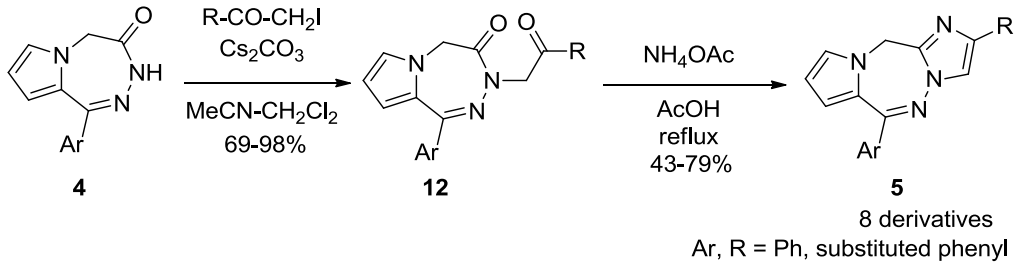
2. Experimental methods

The reaction mixtures were analysed by thin layer chromatography (TLC) and HPLC-MS. Purification of the crude products was carried out by flash chromatography (Isco CombiFlash Rf) and recrystallization. The products were identified and characterized by melting point, ^{1}H and ^{13}C NMR, high-resolution mass spectrometry or elemental analysis. The structures of the new compounds were confirmed by single crystal diffractometric measurements.

3. New scientific results

3.1. Forming an imidazole ring onto the pyrrolotriazepine core

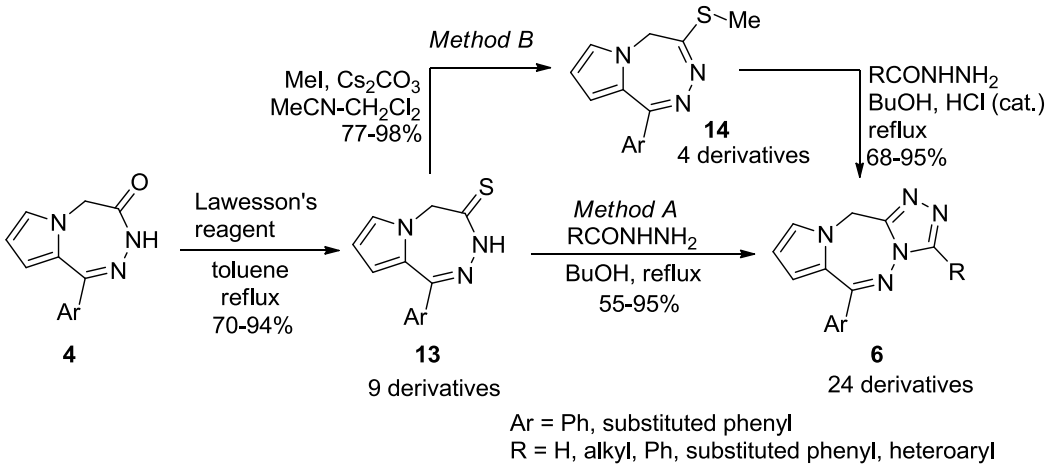
Imidazo-pyrrolotriazepines **5** were synthesized by a two-step synthesis from starting materials **4** [1]. At the first step, the amide nitrogen atoms of **4** were alkylated with appropriate iodo-acetophenone derivatives in the presence of cesium carbonate base. The obtained dioxo compounds **12** were cyclized with ammonium acetate in boiling acetic acid (Scheme 6).



Scheme 6. Synthesis of imidazo-pyrrolotriazepines

3.2. Forming a triazole ring onto the pyrrolotriazepine core

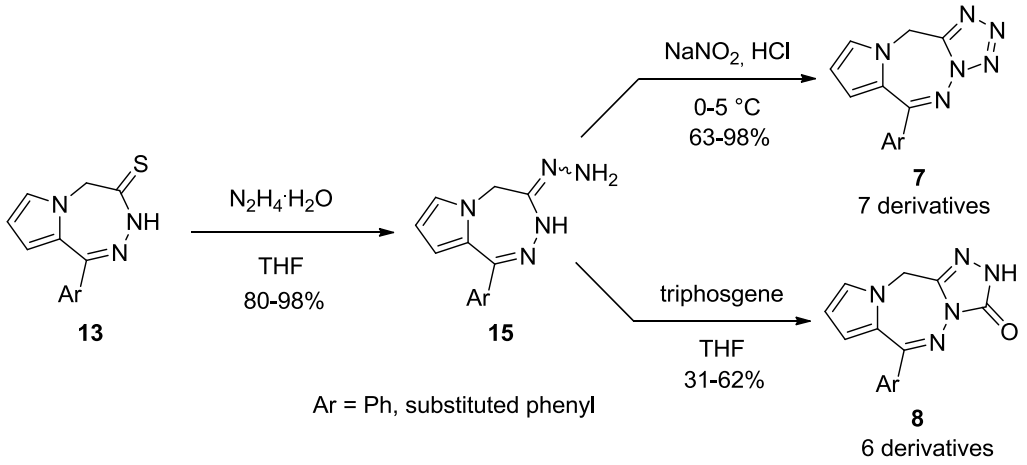
Triazole derivatives **6** were also synthesized from **4** [1]. At first, an oxigen-sulfur exchange was carried out with Lawesson's reagent in refluxing toluene, which procedure gave thio compounds **13**. In the second step, thiones **13** were treated with various acyl hydrazides in boiling butanol to obtain the desired triazole derivatives (Scheme 7., Method A). Nevertheless, in a few cases the expected triazole compounds were not formed. In these cases we took a bypass: methylation of compounds **13** provided *S*-methyl derivatives **14**, which could be transformed easily to the triazole derivatives in the presence of a catalitic amount of hydrochloric acid (Scheme 7., Method B).



Scheme 7. Synthesis of triazolo-pyrrolotriazepines

3.3. Synthesis of tetrazole and triazolone compounds

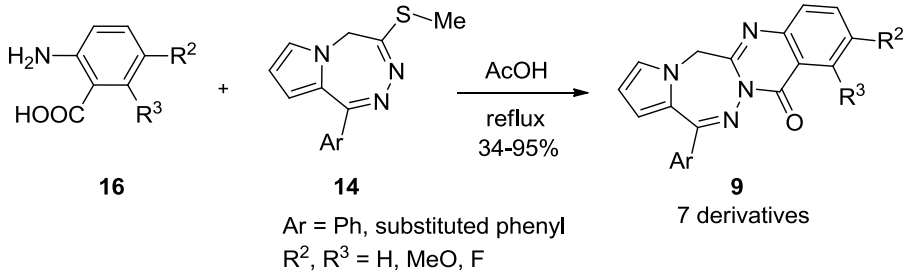
Tetrazole-bearing compounds **7** could be reached from thio derivatives **13** in a two-step synthesis [1]. At first, thiones **13** were treated with hydrazine hydrate in tetrahydrofurane, when hydrazones **15** were formed. Compounds **7** were preapred by treatment of **15** with sodium nitrite and hydrochloric acid (Scheme 8.). Triazolone derivtives 8 were obtained the reaction of hydrazones **15** and triphosgene (Scheme 8.) [2].



Scheme 8. Synthesis of tetrazole and triazolone compounds

3.4. Synthesis of a quinazolinone-condensed new ring system

Seven members of a new tetracyclic ring system were preapred from *S*-methyl derivatives **14** and anthranilic acids under conditions of a modified Niementowski-condensation [3] (Scheme 9.). Single-crystal X-ray measurement was performed on one representative from this new compound family. The single crystal was growed from $CDCl_3$ (Scheme 10.). On the perspective view, an interesting phenomenon could be observed: a molecule of $CDCl_3$ takes a typical hydrogen-bond position. The measured geometrical data (a) and calculated charge distribution (b) can be seen on Scheme 10. This type of hdyrogen-bond is already known, but a rare phenomenon,[8] therefore this experience is definitely worth mentioning.



Scheme 9. Synthesis of quinazolinone-pyrrolotriazepines

[8] Khare, B. N.; Mitra, S. S.; Lengyel, G. *J. Chem. Phys*. **1967**, *47*, 5173–5179.

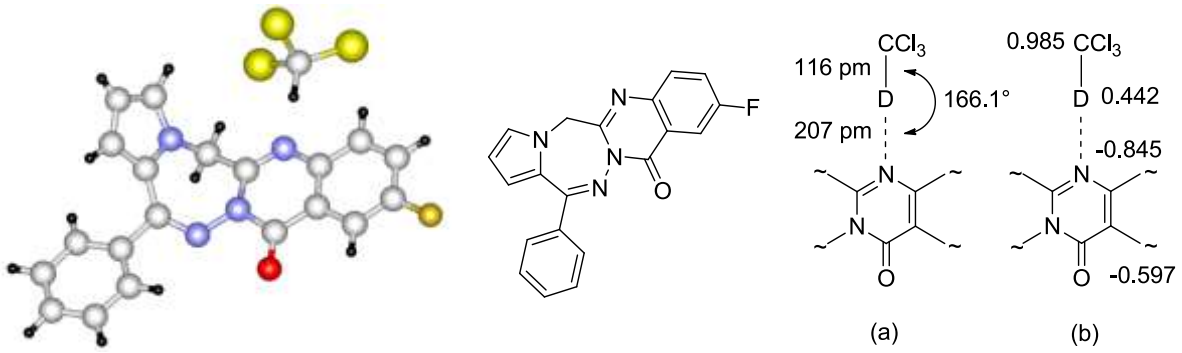
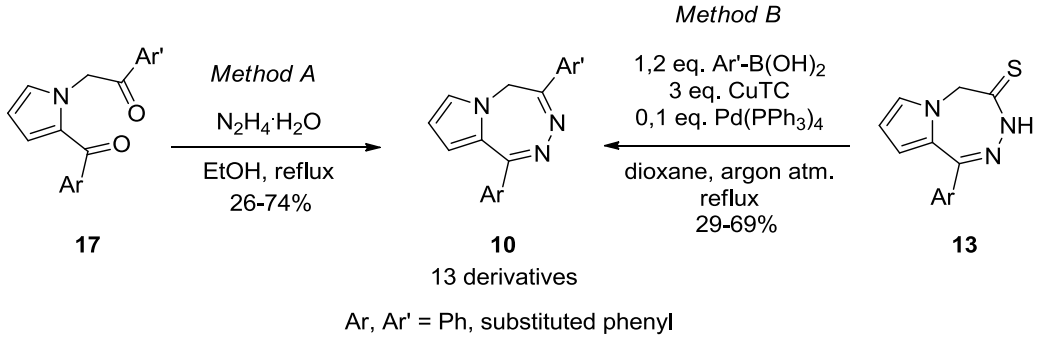


Fig. 10. Pyrrolotriazepine derivative condensed with a quinazolinone ring complexed with $CDCl_3$ – structure

3.5. Synthesis of 1,4-diaryl-pyrrolotriazepines

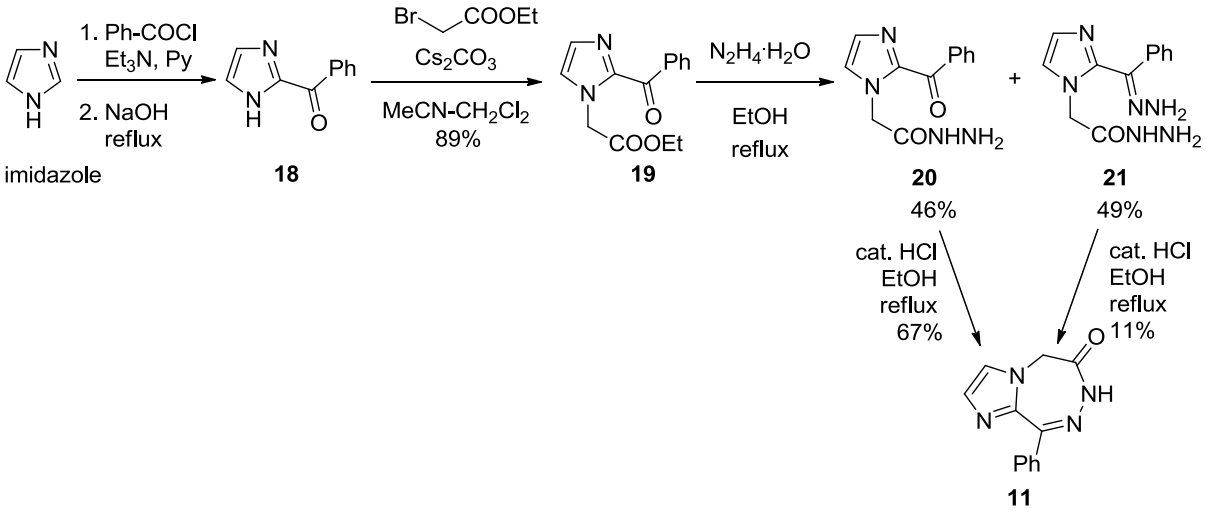
Altogether 13 representatives of a new compound family, 1,4-diaryl-pyrrolotriazepines (**10**) were prepared by two diverse synthetic pathways [4]. At first, diketones (**17**) obtained from alkylating of 2-aroylpyrroles were treated with hydrazine hydrate to form the triazepine ring. Liebeskind-Srogl coupling reaction of thiones **13** and boronic acids also served triazepines **10** (Scheme 11.).



Scheme 11. Synthesis of diaryl-pyrrolotriazepines

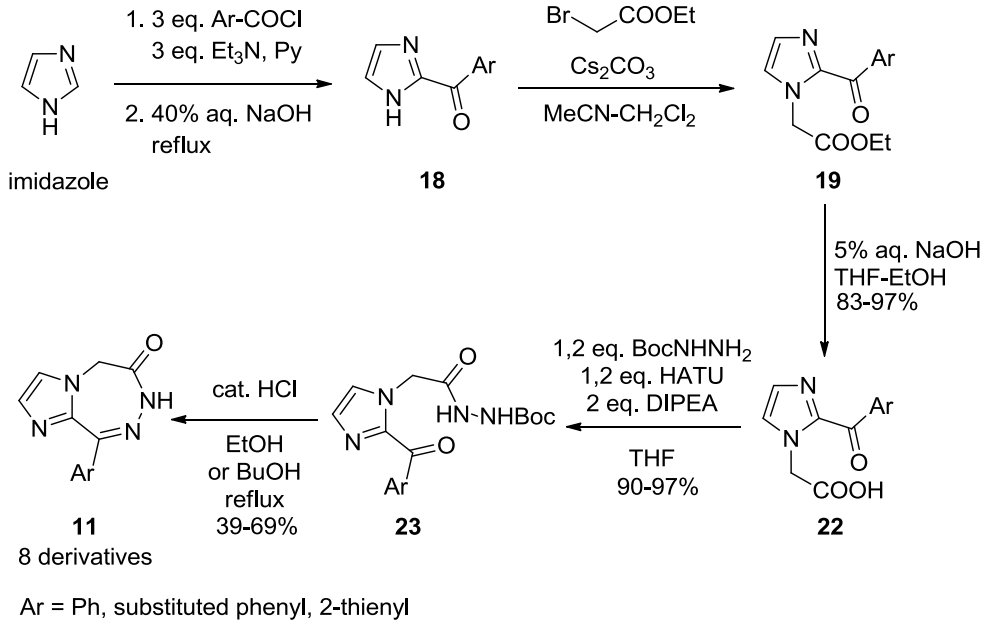
3.6. Synthesis of new imidazotriazepinone compound family

We planned to prepare the new series of triazepinones from imidazole in analogy to the previously described pyrrole-condensed derivatives, in four steps. At first, imidazole was acylated by appropriate acyl halides, then these compounds (**18**) were alkylated with ethyl bromoacetate. However, the reaction of ester **19** with hydrazine hydrate lead to formation of a non-desired product (**21**), reduction of formation of this compound could not be reached [5] (Scheme 12.).



Scheme 12. Synthesis of imidazotriazepinone compounds – original approach

Because of this finding, compounds **11** have been prepared in a different synthetic route. Alkaline hydrolysis of esters **19** gave carboxylic acids **22**, which were coupled with tert-butyl carbazate using HATU coupling agent, and acid-catalized reaction of protected acyl hydrazides **23** afforded the desired products [5] (Scheme 13.).



Scheme 13. Synthesis of imidazotriazepinone compounds

4. Theses

I. I have synthesized novel imidazolo[1,2-*b*]pyrrolo[1,2-*e*][1,2,5]triazepines from 3*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-4(5*H*)-ones in two steps. 8 derivatives were prepared with this method [1].

II. I have prepared new 6-aryl-pyrrolo[1,2-*e*][1,2,4]triazolo[4,3-*b*][1,2,5]triazepines from 1-aryl-3*H*-pyrrolo[2,1-d][1,2,5]triazepin-4(5*H*)-ones. 24 derivatives were prepared. [1].

III. I have synthesized new new ring systems, 6-aryl-11*H*-pyrrolo[1,2-*e*]tetrazolo[1,5-*b*][1,2,5]triazepines and 6-aryl-2,11-dihydro-3*H*-pyrrolo[1,2-*e*][1,2,4]triazolo-[4,3-*b*][1,2,5]triazepin-3-ones from 1-aryl-3*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-4(5*H*)-thiones. With these methods 7 and 6 representatives were prepared [1,2].

IV. I have synthesized 7 representatives of the new tetracyclic 14-aryl-[20,10:4,5][1,2,5]triazepino[7,1-*b*]quinazolin-11(5*H*)-ones by the reactions of anthranilic acids and 1-aryl-4-(methylsulfanyl)-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepines [3].

V. I have prepared 13 representatives of the novel 1,4-diaryl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepines by two diverse strategies. Target compounds were reached either by cyclizing the corresponding diketones or by Liebeskind-Srogl cross-coupling reaction [4].

VI. I have elaborated a five-step total synthesis of the new 9-aryl-5*H*-imidazo[2,1-*d*][1,2,5]triazepin-6(7*H*)-ones from imidazole [5].

5. Application possibilities

During my PhD research seven new ring systems were synthesized and characterised. In these compounds the condensation of frequently biologically active rings may result in pharmacologically significant molecules, if it possess one or both constituent's appropriate properties.

6. Publications

6.1. Full scientific publications related to the PhD Thesis

[1] Mátyás Milen, **Tamás Földesi**, András Dancsó, Gyula Simig, Balázs Volk; Synthesis of three new tricyclic ring systems: pyrrolotriazepines condensed with an imidazole, a triazole, or a tetrazole ring. *Synlett*, **2015**, *26*, 2418–2424 [IF = 2,323 (2015)].

[2] **Tamás Földesi**, Mátyás Milen, András Dancsó, Balázs Volk; Synthesis of 6-aryl-2,11-dihydro-3*H*-pyrrolo[1,2-*e*][1,2,4]triazolo[4,3-*b*][1,2,5]triazepin-3-ones. *Lett. Org. Chem*., **2016**, 13, 531–535 [IF = 0,756 (2015)].

[3] **Tamás Földesi**, András Dancsó, Gyula Simig, Balázs Volk, Mátyás Milen; Synthesis of a new tetracyclic ring system: pyrrolotriazepinoquinazolinone derivatives. *Tetrahedron*, **2015**, *71*, 6759–6763 [IF = 2,645 (2015)].

[4] **Tamás Földesi**, András Dancsó, Gyula Simig, Balázs Volk, Mátyás Milen; Synthesis of 1,4-diarylpyrrolotriazepine derivatives by two diverse strategies. *Monatsh Chem*., **2016**, *147*, 1975–1983 [IF = 1,131 (2015)].

[5] **Tamás Földesi**, András Dancsó, Gyula Simig, Balázs Volk, Mátyás Milen; Efficient synthesis of a new compound family, 9-aryl-5*H*-imidazo[2,1-*d*][1,2,5]triazepin-6(7*H*)-ones. *Tetrahedron*, **2016**, *72*, 5427–5432. [IF = 2,645 (2015)]

6.2. Other publications not related to the PhD Thesis

[6] Alajos Grün, Mátyás Milen, **Tamás Földesi**, Péter Ábrányi-Balogh, László Drahos, György Keglevich: Microwave-assisted amidation of arylacetic acids by reaction with 2-aryl-ethylamines. *Synth. Commun*., **2013**, *43*, 1491–1498 [IF = 0,984 (2013)]

[7] Péter Ábrányi-Balogh, **Tamás Földesi**, Mátyás Milen; Total synthesis of racemic 1-aryl-tetrahydroisoquinoline alkaloids. *Monatsh Chem*., **2015**, *146*, 1907–1912 [IF = 1,131 (2015)]

[8] Péter Ábrányi-Balogh, **Tamás Földesi**, Alajos Grün, Balázs Volk, György Keglevich, Mátyás Milen; Synthetic study on the T3P-promoted one-pot preparation of 1-substituted-3,4-dihydro-β-carbolines by the reaction of tryptamine with carboxylic acids. *Tetrahedron Lett*., **2016**, *57*, 1953–1957 [IF = 2.347 (2015)]

[9] Mátyás Milen, András Dancsó, **Tamás Földesi**, Péter Slégel, Balázs Volk; Propylphosphonic anhydride (T3P) mediated one-pot three-component synthesis of racemic dialkyl (2-substituted-3-oxo-2,3-dihydro-1H-isoindol-1-yl)phosphonates. *Tetrahedron*, **2016**, *72*, 5091–5099 [IF = 2,645 (2015)]

6.3. Oral presentations

[1] **Földesi Tamás**, Dancsó András, Simig Gyula, Volk Balázs, Milen Mátyás; **Új triazepinszármazékok előállítása**; Heterociklusos és Elemorganikus Munkabizottsági Ülés, Balatonszemes, 2015.05.27–29.

[2] **Földesi Tamás**, Dancsó András, Simig Gyula, Volk Balázs, Milen Mátyás; **Új tri- és tetraciklusos pirrolotriazepin-származékok előállítása**; XXXVIII. Kémiai Előadói Napok, Szeged, 2015.10.26–28.

[3] **Földesi Tamás**, Dancsó András, Simig Gyula, Volk Balázs, Milen Mátyás; **Új tri- és tetraciklusos pirrolotriazepin-származékok előállítása**; Oláh György Doktori Iskola XIII. konferenciája, Budapest, 2016.02.11.

[4] **Földesi Tamás**, Dancsó András, Simig Gyula, Volk Balázs, Milen Mátyás; **Új tri- és tetraciklusos pirrolotriazepin-származékok előállítása**; 22nd International conference on chemistry, Timisoara, 3–6.11.2016.