Summary of professional accomplishements

Title of the scientific achievement:

„Expansion of hetero-Diels−Alder cycloaddition reaction scope of 1-oxa-1,3-butadienes and alkenes – in search of new heterodienes and dienophiles as well as reactions with potential application in bioorthogonal chemistry”

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enclosure 2

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Contents

I. Description of scientific achievement

1. Indication of scientific achievement

1.1. Title of scientific achievement

Title of scientific achievement, determined in: „art. 16 ust. 2 ustawy z dnia 14 marca 2003 r. o stopniach naukowych i tytule naukowym oraz o stopniach i tytule w zakresie sztuki (Dz. U. nr 65, poz. 595 z późniejszymi zmianami)":

„Expansion of hetero-Diels−Alder cycloaddition reaction scope of 1-oxa-1,3-butadienes and alkenes – in search of new heterodienes and dienophiles as well as reactions with potential application in bioorthogonal chemistry"

The monothematic series of publications is my scientific achievement.

1.2. The monothematic series of publications from Journal Citation Reports date base with commentary

* Corresponding author

H1. A. Pałasz* *Top. Curr. Chem.*, **2016**, *374 (3)*, 1-37: „Recent advances in inverse-electron-demand hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes". DOI: 10.1007/s41061-016-0026-2, First online: 20 April 2016 as Open Access Article

5-Year IF (2014): **5.325**, the number of citations **0**

Unassisted work

My own idea to take up this topic in review. I did overview of scientific literature. I wrote article and I corresponded with editor and reviewers.

H2. K. Bogdanowicz-Szwed*, **A. Pałasz**, *Monatsh.Chem.*, **1999**, *130*, 795-807: „Intramolecular hetero-Diels–Alder reactions of functionalized α,β-unsaturated carbonyl compounds: Polycyclic 2*H*-pyran derivatives".

5-Year IF (2014): **1.326**, the number of citations **15**

Approximate own contribution 50%

I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared date to the experimental part of the article.

H3. K. Bogdanowicz-Szwed*, **A. Pałasz**, *Monatsh.Chem*., **2001**, *132*, 393-401:„ Polycyclic 2*H*-pyran derivatives by intramolecular hetero-Diels–Alder reactions of α-sulfur-substituted – α,β-unsaturated carbonyl compounds".
5-Year IF (2014): **1.326**, the number of citations **8**
Approximate own contribution 50%.
I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared date to the experimental part of the article.

H4. K. Bogdanowicz-Szwed*, **A. Pałasz**, *Z. Naturforsch. B*., **2001**, *56*, 416-422: "Synthesis of 3,4-dihydro-2*H*-pyrans by hetero-Diels–Alder reactions of functionalized α,β-unsaturated carbonyl compounds with styrenes".
5-Year IF (2014): **0.690**, the number of citations **10**
Approximate own contribution 50%
I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared date to the experimental part of the article.

H5. A. Pałasz*, K. Bogdanowicz-Szwed, *Monatsh.Chem*., **2008**, *139*, 647-655:„Hetero-Diels–Alder reaction of propenenitriles with enol ethers: a convenient approach to functionalized 3,4-dihydro-2*H*-pyrans".
5-Year IF (2014): **1.326**, the number of citations **5**
Approximate own contribution 70%.
I synthesized all products. I did a spectroscopic analysis of the synthesized compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H6. A. Pałasz*, *Org.Biomol.Chem*., **2005**, *3*, 3207-3212: „Synthesis of 3,4-dihydro-2*H*-pyrans by hetero-Diels–Alder reactions of functionalized unsaturated carbonyl compounds with *N*-vinyl 2-oxazolidinone".
5-Year IF (2014): **3.382**, the number of citations **24**
Unassisted work
My own idea to take up this topic in my research. I made plans of the synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole

manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H7. A. Pałasz*, K. Jelska, M. Ożóg, P. Serda, *Monatsh.Chem*., **2007**, *138*, 481-488:
„5-Arylidene derivatives of Meldrum's acid as synthons in pyrano[4,3-*b*]pyran synthesis".
5-Year IF (2014): **1.326**, the number of citations **8**
Approximate own contribution 60%.
My own idea to take up this topic in research. I made plans of the synthesis. I synthesized the majority of the products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H8. A. Pałasz*, *Monatsh.Chem*., **2008**, *139*, 1397-1404: „Three-component one-pot synthesis of fused uracils – pyrano[2,3-*d*]pyrimidine-2,4-diones".
5-Year IF (2014): **1.326**, the number of citations **10**
Unassisted work
My own idea to take up this topic in my research. I made plans of synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H9. A. Pałasz*, T. Pałasz, *Tetrahedron*, **2011**, *67*, 1422-1431: "Knoevenagel condensation of cyclic ketones with benzoylacetonitrile and *N,N'* – dimethylbarbituric acid. Application of sterically hindered condensation products in the synthesis of spiro and dispiropyrans by hetero-Diels–Alder reactions".
5-Year IF (2014): **2.675**, the number of citations **9**
Approximate own contribution 80%.
My own idea to take up this topic in research. I made plans of the synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H10. A. Pałasz*, *Synthesis*, **2010**, 4021-4032: ”A green approach to the synthesis of fused uracils: Pyrano[2,3-*d*]pyrimidines. On - water one-pot synthesis by domino Knoevenagel/Diels–Alder reactions”.

5-Year IF (2014): **2.389**, the number of citations **12**

Unassisted work

My own idea to take up this topic in my research. I made plans of synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H11. A. Pałasz*, *Monatsh.Chem*., **2012**, *143*, 1175-1185:„Synthesis of fused uracils: pyrano[2,3-*d*]pyrimidines and 1,4-bis(pyrano[2,3-*d*]pyrimidinyl)benzenes by domino Knoevenagel/Diels–Alder reactions”.

5-Year IF (2014): **1.326**, the number of citations **3**

Unassisted work

My own idea to take up this topic in my research. I made plans of synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H12. A. Pałasz*, D. Cież, *Eur. J. Med. Chem*., **2015**, *97*, 582-611: “In search of uracil derivatives as bioactive agents. Uracils and fused uracils: Synthesis, biological activity and applications”.

5-Year IF (2014): **3.946**, the number of citations **4**

Approximate own contribution 85%.

My own idea to take up this topic in review. I did overview of scientific literature. I wrote article. I prepared the majority of schemes. I corresponded with editor and reviewers.

H13. A. Pałasz*, J. Kalinowska-Tłuścik, M. Jabłoński, *Tetrahedron*, **2013**, *69*, 8216-8227: „Application of 2,4,6-trioxo-pyrimidin-5-ylidene alditols in the synthesis of pyrano[2,3-*d*]pyrimidines containing a sugar moiety by hetero-Diels–Alder reactions and by conjugate Michael addition-cyclizations”.

5-Year IF (2014): **2.675**, the number of citations **6**

Approximate own contribution 80%.

My own idea to take up this topic in research. I made plans of the synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

H14. A. Pałasz*, D. Cież, B. Musielak, J. Kalinowska-Tłuścik, *Tetrahedron* **2015**, *71*, 8911-8924: "Application of dimedone enamines as dienophiles: Stereoselective synthesis of amino enols of fused uracils containing a sugar moiety by hetero-Diels–Alder reactions of barbituric acid 5-ylidene alditols with dimedone enamines".
5-Year IF (2014): **2.675**, the number of citations **1**
Approximate own contribution 65%.
My own idea to take up this topic in research. I made plans of the synthesis. I synthesized the majority of the products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

2. Introduction and the aims of the work

My scientific achievement is connected with my research concerning hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes and alkenes. The monothematic series of publications **H1-H14**, consisting of 14 articles is my scientific achievement.

The Diels–Alder reaction is one of the most important synthetic procedures since its first description in 1928 by Diels and Alder. This reaction meets the requirements of a modern synthetic methods by showing an excellent chemo- and regioselectivity as well as a high diastereoselectivity and enantioselectivity in many cases. Most importantly, the scope of the Diels-Alder reaction is very high allowing the synthesis of cyclohexenes and different heterocycles. The use of hetero-substituted diene and dienophiles is important for the application of Diels−Alder cycloadditions towards natural and biologically active product synthesis. There are two types of Diels−Alder reactions (Fig. 1.). The first one is cycloaddition of dienes possessing electron-donating groups with dienophiles equipped with electron-withdrawing groups. The second route, named as inverse-electron-demand, is the Diels−Alder reactions of electron deficient dienes with electron rich alkenes. The cycloaddition reactions appear to be under frontier molecular orbital control. In inverse-electron-demand Diels−Alder reactions, the HOMO orbital of the dienophile overlaps with the LUMO orbital of the diene. For an inverse-electron-demand Diels−Alder cycloaddition

the presence of an electron-withdrawing group in the diene and an electron-releasing substituent in the dienophile contracts the LUMO(diene)−HOMO(dienophile) energy separation through raising the energy of the HOMO(dienophile) and lowering the energy of the LUMO(diene) and hence increases the reactivity (Fig.1).

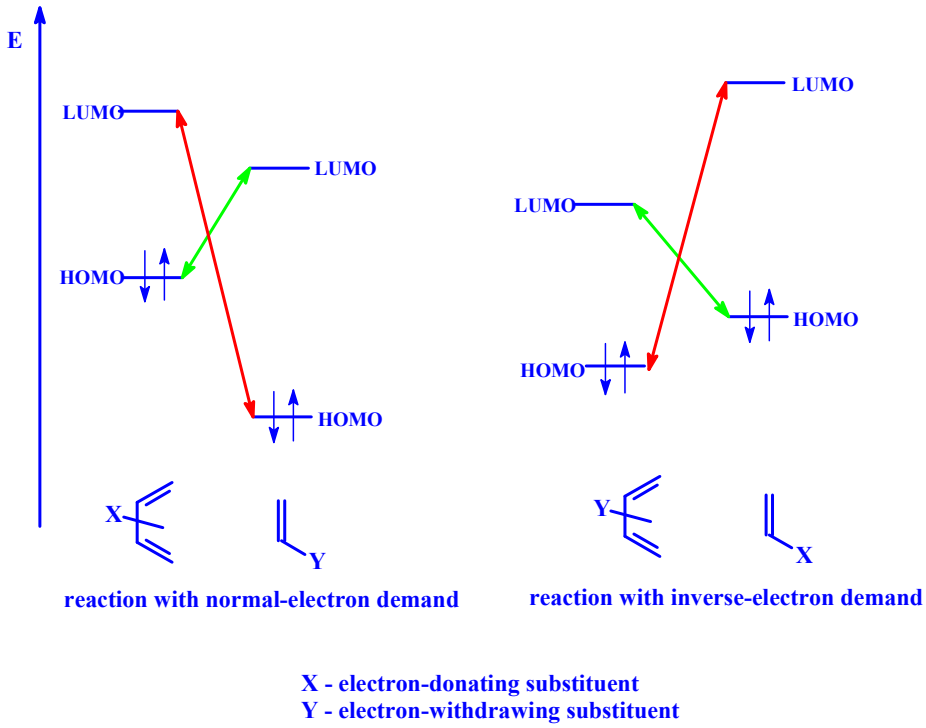


Fig. 1. Types of Diels–Alder reactions.

Hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes with alkenes lead to dihydropyran derivatives which are valuable precursors for the synthesis of many natural products such as carbohydrates, alkaloids, iridoids and antibiotics. These reactions have been classified as cycloadditions with inverse-electron-demand. The reviews on this topic have already been published but they cover the literature until 1997. The most comprehensive one was written by Tietze and Kettschau in Topics in Current Chemistry in 1997 [A1]. Recently, in April 2016 I published online the review (Open Access Article) which is an endeavor to highlight the progress in the hetero-Diels−Alder reactions with inverse-electron-demand of 1-oxa-1,3-butadienes after the year 1999 [**H1**]. Two different modes of inverse-electron-demand hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes are discussed in this paper: inter- and intramolecular mode. The geometry of the transition structures of hetero-Diels−Alder reactions influence on the diastereoselectivity of cycloadditions. There are four different transition states for hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes, according to an *endo*- or *exo*-orientation of the dienophile and an (*E*)- or (*Z*)-configuration of the 1-oxa-1,3-butadiene. The four transition structures for inter- and intramolecular hetero-Diels−Alder

reactions providing the two diastereomers *cis* and *trans* are showed in Figure 2 and 3. The orientation of the dienophile – vinyl ether, with the alkoxy group being close to the oxygen atom in the heterodiene is called *endo* (Fig. 2). The opposite is called *exo*. For intramolecular hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes, the orientation with the chain connecting the heterodiene and dienophile lying close to the heterodiene is called *endo*.(Fig. 3). The *cis*-adduct can be formed by an *endo-E* or *exo-Z* orientation. The *trans*-adduct is obtained by either an *exo-E* or *endo-Z* transition state (Fig. 2, 3).

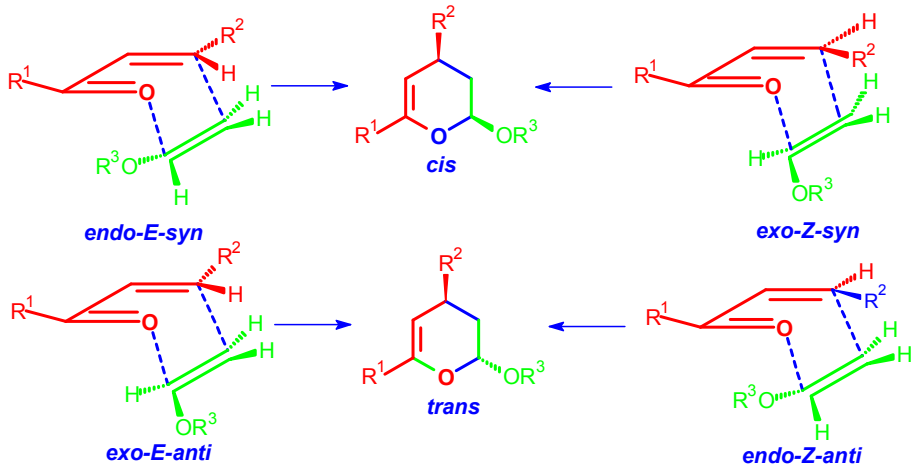


Fig. **2**. Four different transition structures for the intermolecular hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes and vinyl ether.

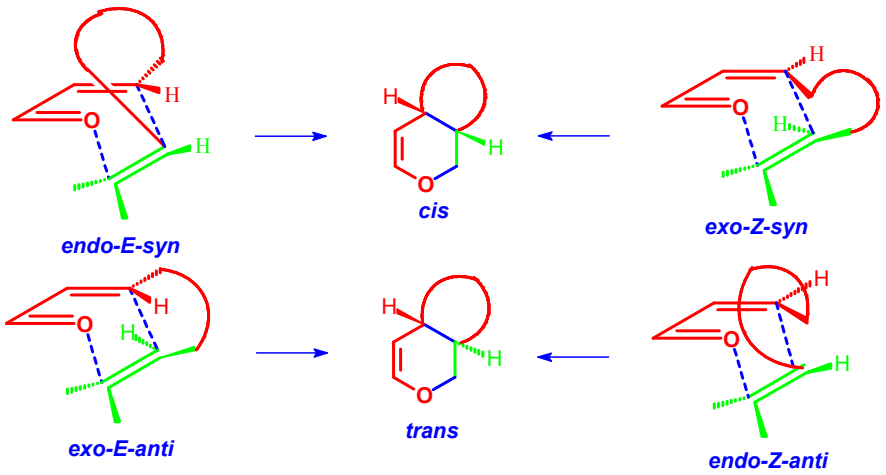


Fig. **3**. Four different transition structures for the intramolecular hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes and alkenes.

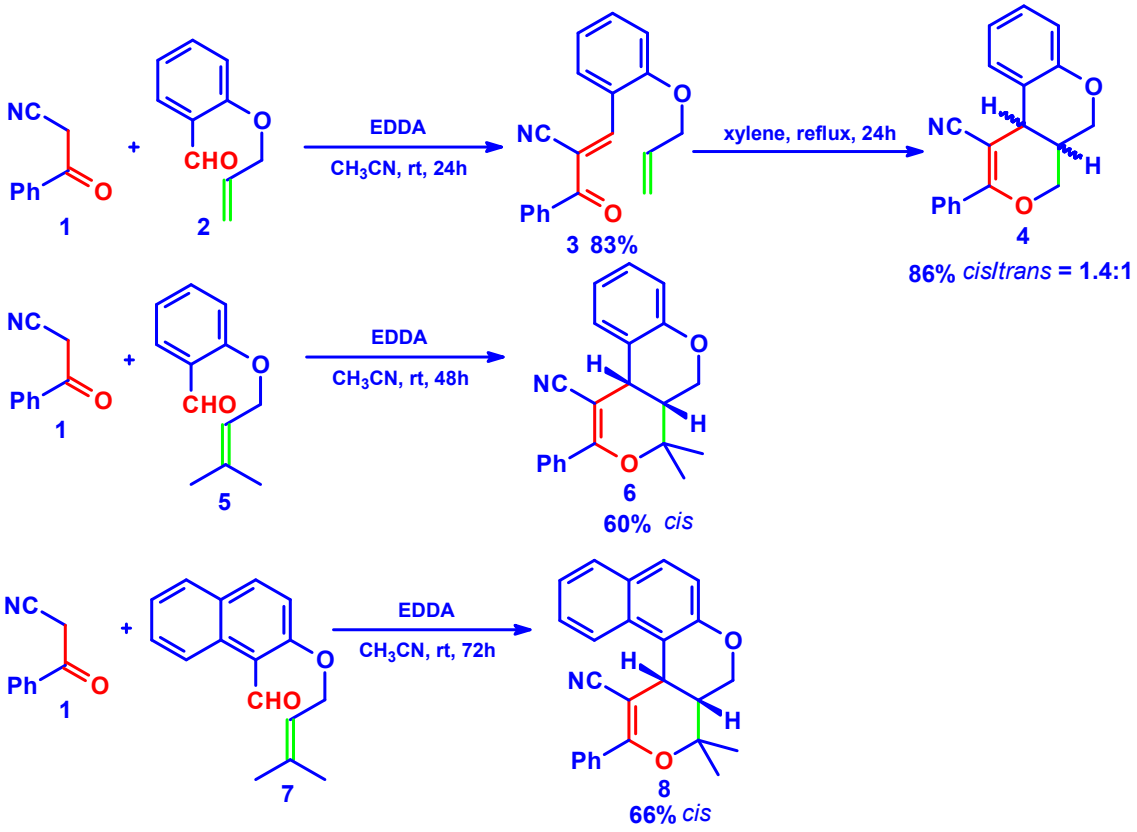
The aims of my work were:

- Determination of the influence of electron-withdrawing and electron-donating groups located in 1-oxa-1,3-butadiene and alkene systems on the reactivity in hetero-Diels–Alder reactions with inverse-electron-demand
- Determination of the influence of the substituents located in heterodiene and dienophile on the diastereoselectivity of examined reactions
- Research of hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes and alkenes in water at room temperature in order to apply these reactions in bioorthogonal chemistry
- Determination of the configuration and the conformation of prepared cycloadducts
- Synthesis of new compounds of potential pharmacological activity, especially uracil derivatives

3. Research of two component domino Knoevenagel hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes with an intramolecular cycloaddition

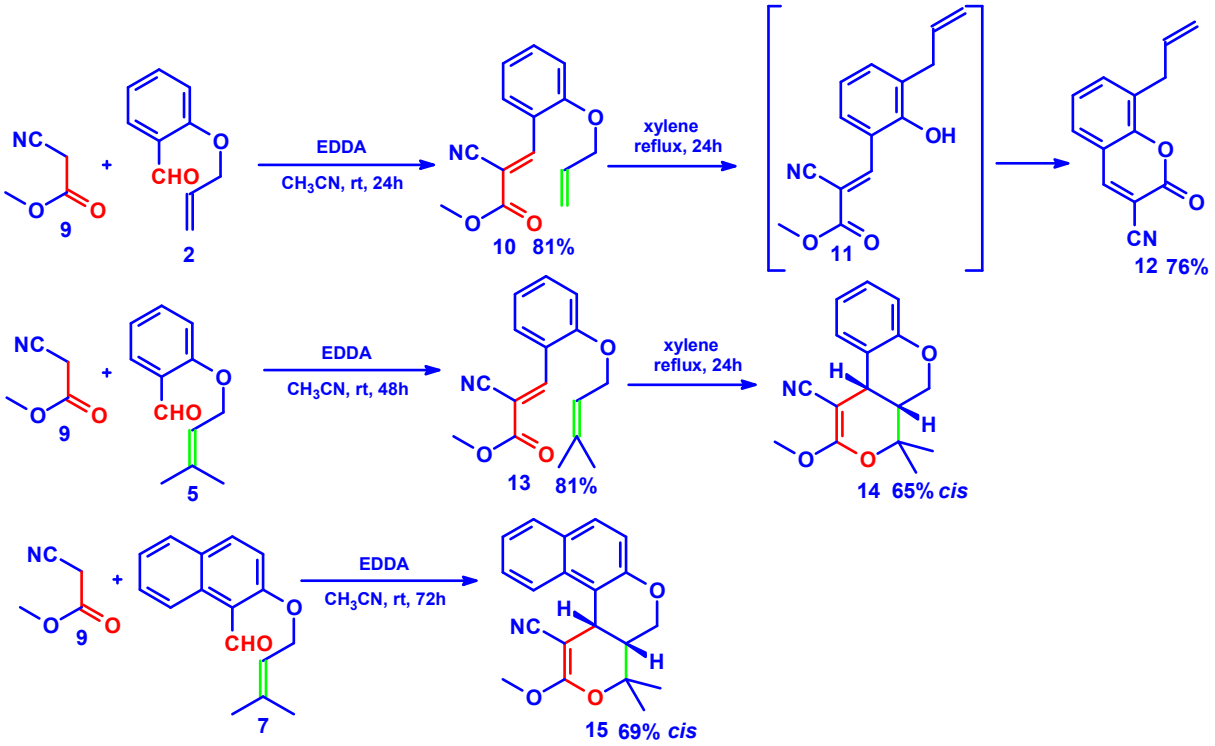
The development of new heterodienes and dienophiles is a continuous challenge in the field of cycloaddition reactions. At the beginning, I investigated the intramolecular hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes and alkenes. In my investigations of domino Knoevenagel/intramolecular hetero-Diels−Alder reactions, I applied for the first time, different active methylene compounds and aromatic aldehydes contained alkenyloxy groups, in *ortho* position to the aldehyde group. I studied these reactions taking into account the character of the substituents in the heterodiene and in dienophile moieties.

I started my work from investigation of influence of nitryle group at C(3) position on intramolecular cycloaddition of 1-oxa-1,3-butadienes [**H2**]. Knoevenagel condensations of benzoylacetonitrile **1** with 2-alkenyloxy aromatic aldehydes **2**, **5** and **7** were carried out in acetonitrile solution in the presence of catalytic amounts of ethylene diammonium diacetate EDDA, at room temperature (Scheme 1). Next, intramolecular hetero-Diels−Alder reactions afforded exclusively the *cis*-annulated cycloadducts **6** and **8** or a mixture of *cis* and *trans* polycyclic 2*H*-pyran derivatives **4** was obtained.



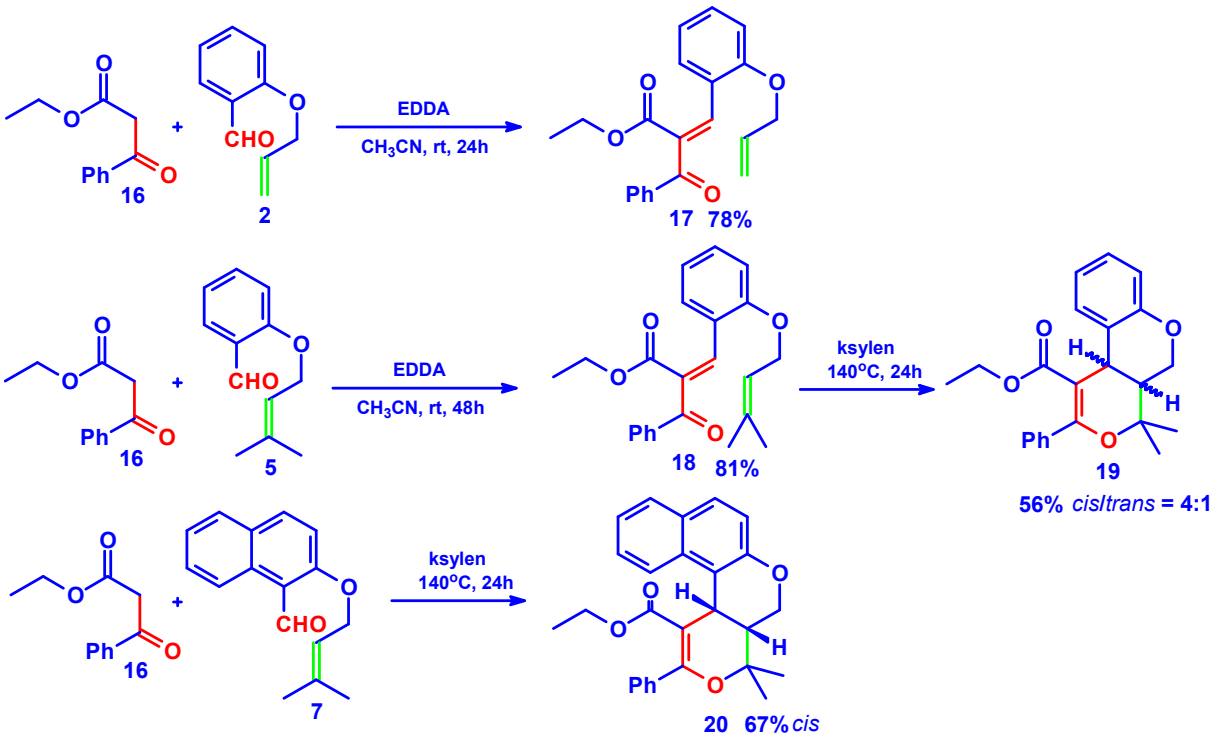
Scheme 1. Synthesis of polycyclic 2*H*-pyran derivatives **4**, **6** and **8** by domino Knoevenagel/ intramolecular hetero-Diels−Alder reactions of benzoylacetonitrile **1** with 2-alkenyloxy aromatic aldehydes **2**, **5** and **7** [**H2**].

Next, in my investigations, I applied metyl cyanoacetate **9** as active methylene compound (Scheme 2) [**H2**]. In this case I wanted also to determinate the influence of nitryle group at C(3) position on intramolecular cycloaddition of 1-oxa-1,3-butadienes. Moreover, the influence of electron-donating methoxy group at C(2) position could be observed. The condensation of **9** with aldehyde **2** in acetonitrile in the presence of EDDA furnished the condensation product **10** that was thermally stable at room temperature (Scheme 2). However, heating of **10** in boiling xylene resulted in the formation of lactone **12**. The formation of **12** consisted in a 3,3-sigmatropic shift of the allyl group and formation of *o*-phenol derivative **11** which subsequently underwent ring closure with elimination of metanol to give **12**. The reaction of **9** with **5**, performed at room temperature, yielded the condensation product **13** exclusively. Its cycloaddition was accomplished in boiling xylene giving the *cis*-annulated cycloadduct **14** as the sole product (Scheme 2). In contrast, the reaction of **9** with dimethyl-substituted aldehyde **7** occurred at room temperature, leading directly to the *cis*-fused compound **15**.



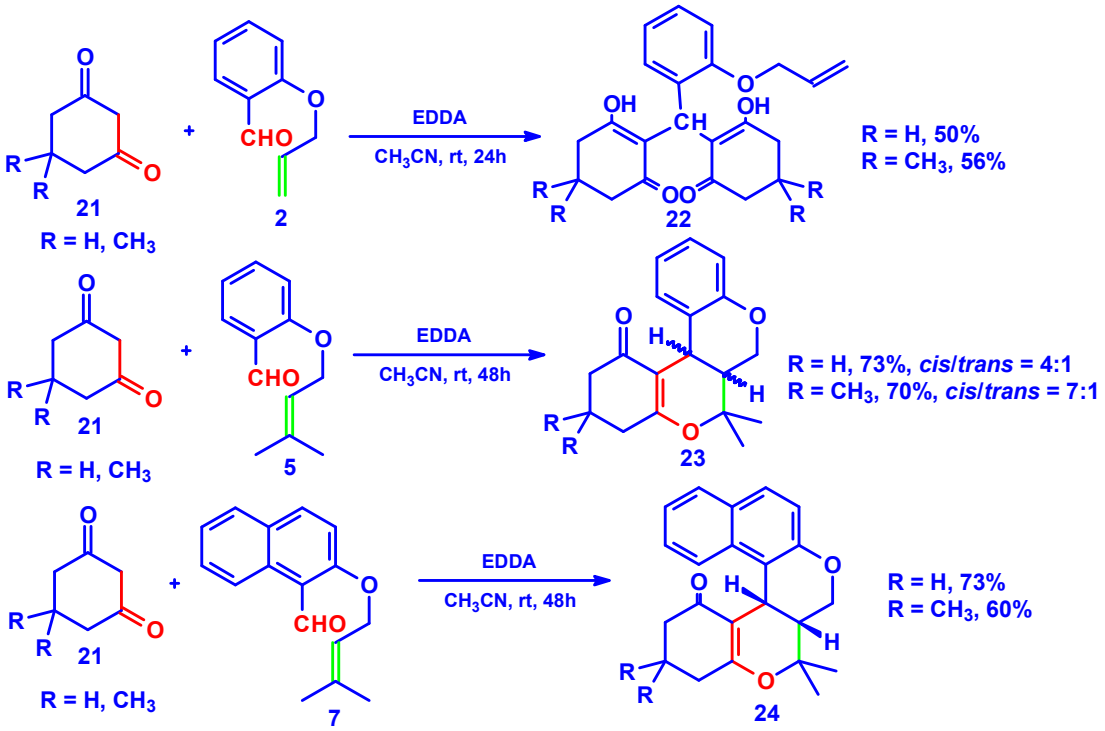
Scheme 2. Synthesis of polycyclic 2*H*-pyran derivatives **14** and **15** by domino Knoevenagel/ intramolecular hetero-Diels–Alder reactions of metyl cyanoacetate **9** and 2-alkenyloxy aromatic aldehydes **2**, **5** and **7** [**H2**].

In further experiments I studied the reactions of ethyl benzoylacetate **16** with 2-alkenyloxy aromatic aldehydes **2**, **5** and **7** (Scheme 3) [**H2**]. In these reactions I expected to observe the influence of the 3-ethoxycarbonyl group in the 1-oxa-1,3-butadiene intermediates on the intramolecular cycloaddition. Knoevenagel condensation of **16** with **2** or **5**, carried out at room temperature, led to products **17** and **18**, respectively (Scheme 3). Prolonged heating of **17** in xylene did not afford the expected cycloadduct, whereas compound **18** underwent cycloaddition yielding a mixture of the *cis*/*trans*-annulated cycloadducts **19** in a ratio of 4:1 under these conditions. The reaction of **16** with aldehyde **7** at room temperature gave rise to the formation of a mixture of the Knoevenagel condensation product and the Diels-Alder cycloadduct. To complete the cycloaddition, the reaction mixture was heated in xylene, and the *cis* cycloadduct **20** was obtained as the sole product (Scheme 3).



Scheme 3. Synthesis of polycyclic 2*H*-pyran derivatives **19** and **20** by domino Knoevenagel/ intramolecular hetero-Diels−Alder reactions of ethyl benzoylacetate **16** and 2-alkenyloxy aromatic aldehydes **2**, **5** and **7** [**H2**].

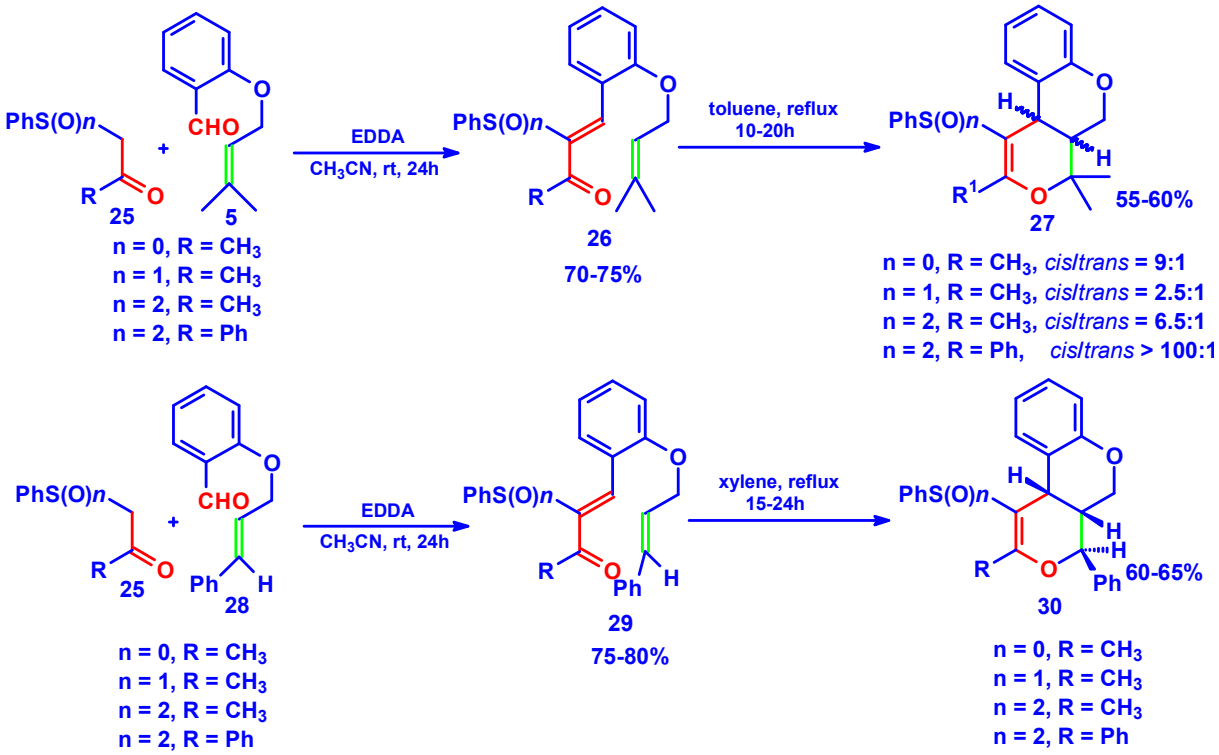
Next I investigated the reactions of cyclic 1,3-dicarbonyl compounds such as cyclohexane-1,3-dione and dimedone with aldehydes **2**, **5** and **7** (Scheme 4) [**H2**]. In these studies I have examined the influence of carbonyl group at C(3) in 1-oxa-1,3-butadienes on the intramolecular hetero-Diels-Alder reaction. The reactions of **21** with **2**, carried out at room temperature in acetonitrile in the presence of EDDA, involved the formation of condensation products **22**. They were formed by condensation of two molecules of 1,3-dicarbonyl compounds **21** with one molecule of **2**. Changing of the reaction condition, *e.g.* the sequence of addition of the reagents or lowering of the temperature, did not influence the course of these reactions. In contrast to **2**, aldehyde **5** reacted with **21** to afford the Diels-Alder cycloadducts **23** in one-pot reactions. The ^{1}H NMR analysis of the crude products showed that they consisted of a mixture of *cis*/*trans*-annulated cycloadducts. In both reactions the *cis*-cycloadducts were the major products. The reaction of aldehyde **7** with **21**, carried out at room temperature, led exclusively to formation of *cis*-fused cycloadducts 24 (Scheme 4).



Scheme 4. Synthesis of polycyclic 2*H*-pyran derivatives **23** and **24** by domino Knoevenagel/ intramolecular hetero-Diels−Alder reactions of cyklohexane-1,3-dione and dimedone **21** with 2-alkenyloxy aromatic aldehydes **2**, **5** and **7** [**H2**].

Next I demonstrated that sulfur containing substituents incorporated into 1-oxa-1,3-butadienes positively influence the results of the cycloaddition. I investigated the intramolecular hetero-Diels-Alder reactions of α-sulfur-substituted α,β-unsaturated carbonyl compounds containing *o*-alkenyloxyaryl groups in position β. I wanted to compare the influence of the electron-withdrawing groups: phenylsulfenyl, phenylsulfinyl, and phenylsulfonyl at C(3) position of 1-oxa-1,3-butadiene, on diastereoselectivity and yields. The influence of alkyl and aryl groups in the dienophile moieties was also taken into account. I applied as substrates sulfide, sulfoxide and sulfone derivatives **25** as the active methylene compounds (Scheme 5) [**H3**]. Compounds **25** were condensed with aldehydes **5** or **28** at room temperature in acetonitrile in the presence of EDDA yielding the Knoevenagel condensation products **26** and **29** which in turn underwent intramolecular hetero-Diels-Alder reactions upon heating (Scheme 5). Generally, the *cis*-diastereoisomer or a mixture of *cis*- and *trans*-products **27** and **30** in which the *cis*-product predominates were obtained. A decrease of the diastereoselectivity of the reactions of the intermediate products **26** and **29** possessing the PhS, $PhSO_2$, and PhSO groups was observed in this order, whereas the reactivity increased (Scheme 5). No significant difference comparing the reactivity of compounds **26** possessing methyl groups attached to the terminal dienophile with that of the analogous compound **29**

containing phenyl groups at the same position was observed. In contrast, I noticed a large difference in diastereoselectivity of compounds **29** to compounds **26**. The reactions of **29** led exclusively to the *cis*-cycloadducts.



Scheme 5. Synthesis of polycyclic 2*H*-pyran derivatives **27** and **30** by domino Knoevenagel/ intramolecular hetero-Diels−Alder reactions of α-sulfur-substituted α,β-unsaturated carbonyl compounds **25** and 2-alkenyloxy aromatic aldehydes **5** and **28** [**H3**].

In conclusion, I have shown, that the reactions of the activated methylene compounds with aromatic 2-alkenyloxy aldehydes involved, in the first step, formation of α,β-unsaturated carbonyl compounds that were prone to undergo intramolecular hetero-Diels-Alder cycloadditions. It is worth to note that all one-pot reactions occurring at room temperature led to the exclusive formation of *cis*-annulated cycloadducts. In contrast, the cycloaddition of isolated Knoevenagel intermediates required heating and furnished *cis*-cycloadduct or a mixture of *cis*/*trans*-cycloadducts with predominant formation of *cis*-products. The cyclic 1,3-dicarbonyl compounds underwent the tandem Knoevenagel-hetero-Diels−Alder reactions easier than the activated acyclic carbonyl compounds. I did not notice a striking difference between the reactivity of acyclic carbonyl compounds possessing cyano or ethoxycarbonyl groups. I can assume that the highest diastereoselectivity was observed for reactions of aldehydes **5** and **7** possessing methyl groups attached to the terminal dienophile (Fig. 4). The reactions with aldehydes **5** and **7** were more effective than with **2** and led almost exclusively to the *cis*-cycloadducts. So, the methyl groups attached to the terminal dienophile

systems influence their reactivity. High diastereoselectivity was also observed for reactions of 2-((*E*)-3-phenyl-prop-2-enyloxy)-benzaldehyde **28** containing phenyl group at terminal alkene, because in its reactions only *cis*-cycloadducts were formed (Fig.4).

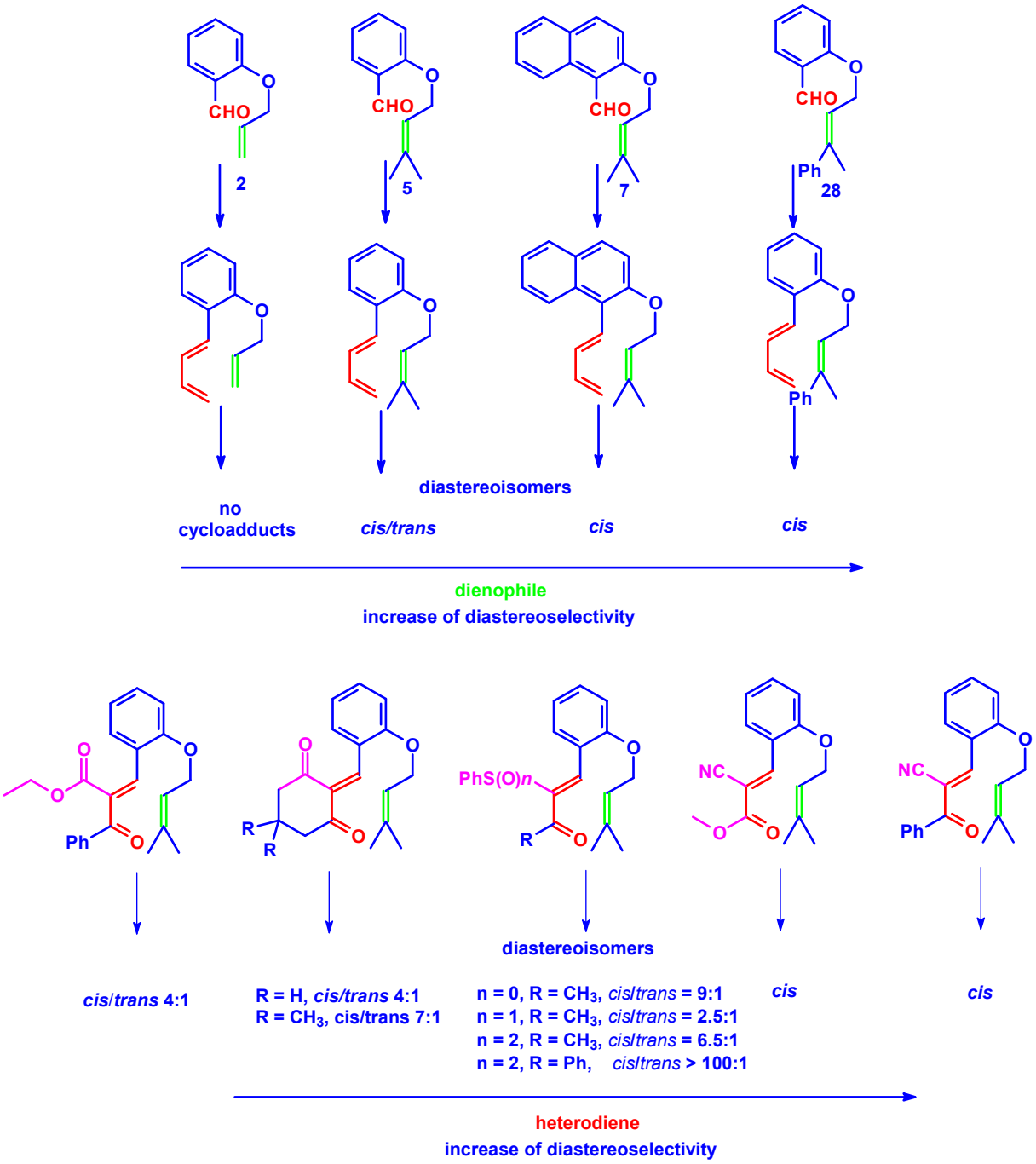


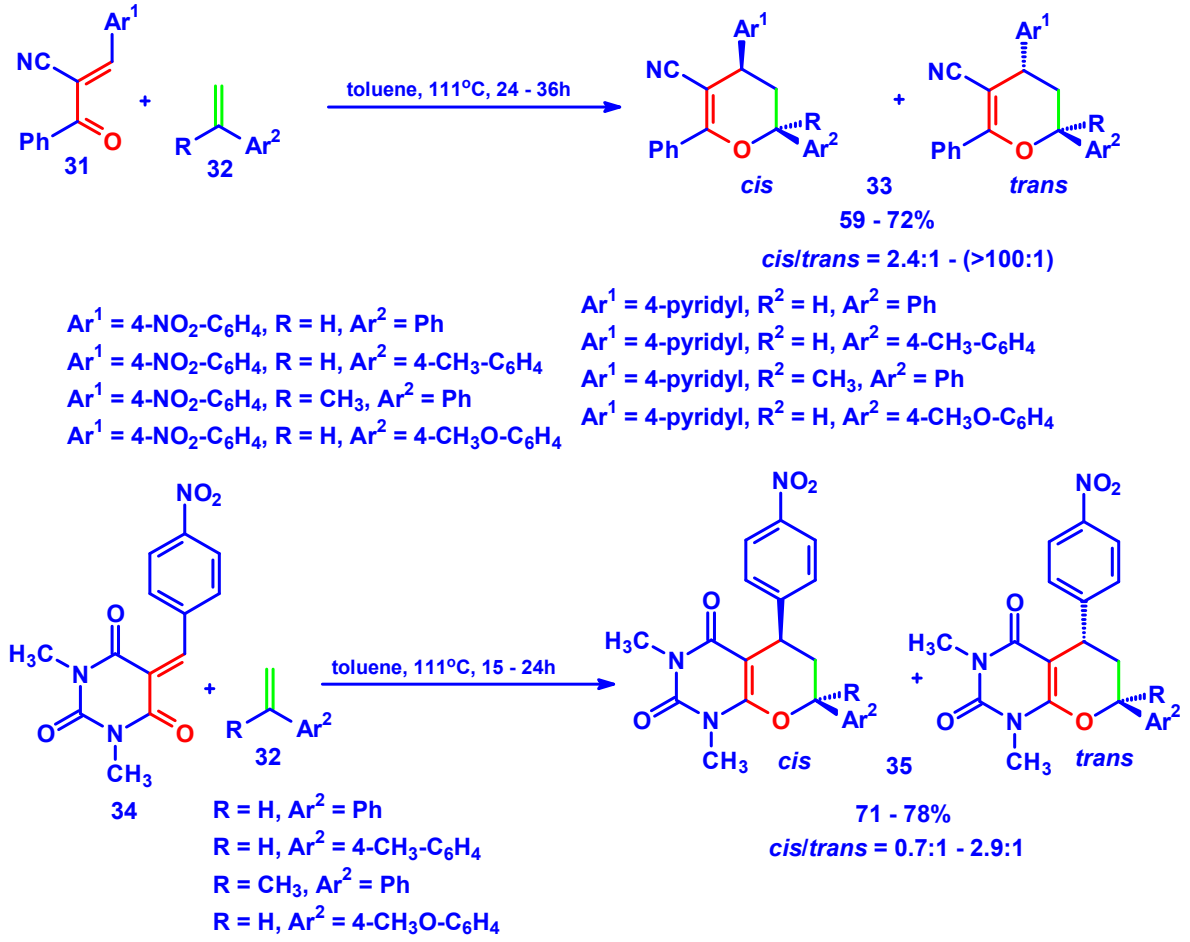
Fig. **4**. Summary of the research results of intramolecular hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes and alkenes.

4. Research of intermolecular hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes and alkenes

1-Oxa-1,3-butadienes containing electron-withdrawing cyano group at C(3) position were found to have high reactivity in intramolecular hetero-Diels–Alder reactions [**H2**]. Taking into account these results, I examined the intermolecular hetero-Diels–Alder reactions of 3-cyano-1-oxa-1,3-butadienes [**H4**]. In experiments were used *p*-substituted 2-benzoylcinnamonitriles **31** as starting materials (Scheme 6). They were obtained by condensation of benzoylacetonitrile with an appropriate aromatic or heteroaromatic aldehydes. Styrene and its 4-methyl-phenyl-, α-methyl-, 4-methoxyphenyl-substituted derivatives **32** were used as dienophile components. Styrenes are alkenes without electron-donating groups and therefore the reactions of 1-oxa-1,3-butadienes **31** with styrenes **32** were performed in boiling toluene. Most of these reactions go to completion within 36 h producing mixtures of the *cis* and *trans* diastereoisomers of 2,4,6-triaryl-3,4-dihydro-2*H*-pyran-5-carbonitriles **33** with the *cis*-**33** diastereoisomers as the main products (Scheme 6). However, the presence of electron-withdrawing substituent in *para* position of aromatic ring Ar^1 of heterodienes **31** was necessary to accomplish the cycloaddition with styrenes **32**.

In the next experiments I studied the reactions of 5-arylidene-1,3-dimethylbarbituric acid **34** with styrenes **32** (Scheme 6) [**H4**]. Only 5-(4-nitrobenzylidene)-1,3-dimethylbarbituric acid was active as heterodiene in these reactions. The cycloadditions were conducted in boiling toluene and most of them were completed within 24 h providing diastereoisomeric mixtures of 2*H*-pyrano[2,3-*d*]pyrimidine-2,4-diones **35**.

The presence of electron-donating metyl and methoxy groups in the dienophile increased the rate and the yield of these reactions (Fig. 5). 4-Methoxystyrene was the most reactive dienophile. So, the styrenes are known as efficient dienophiles in conventional Diels−Alder cycloadditions, however in cycloadditions with inverse-electron-demand they react reluctantly.



Scheme 6. Synthesis of 3,4-dihydro-2*H*-pyrans **33** and **35** by hetero-Diels–Alder reactions of functionalized α,β-unsaturated carbonyl compounds **31** and **34** with styrenes **32** [**H4**].

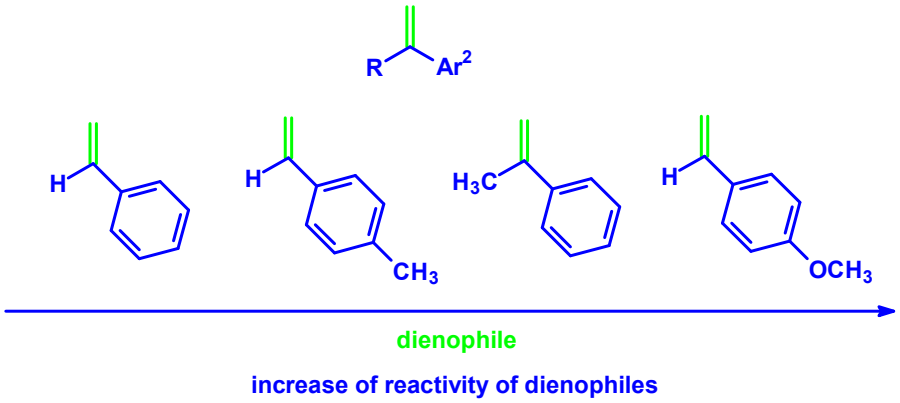
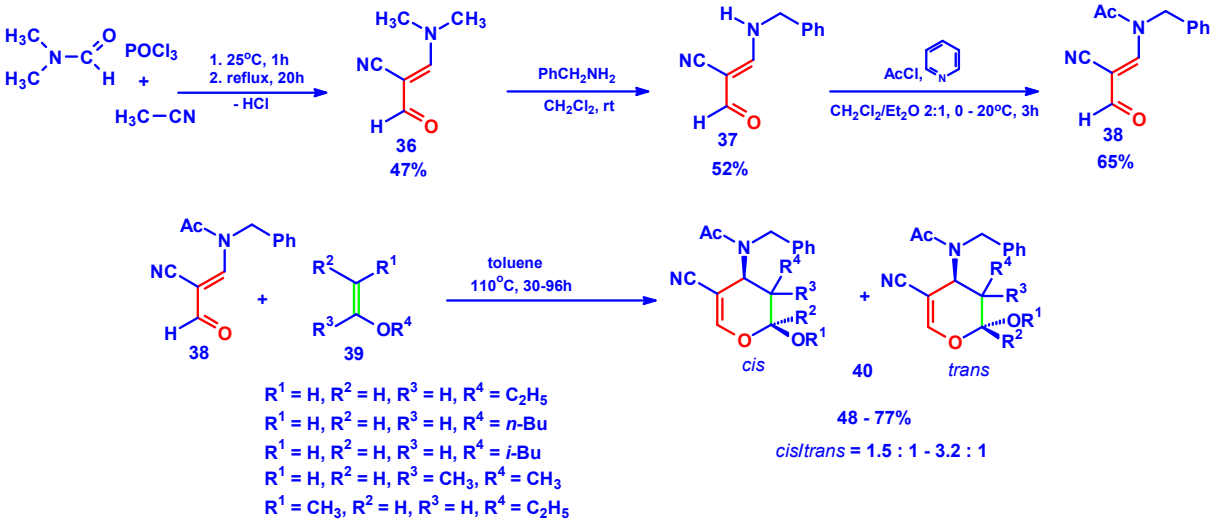


Fig. **5**. Reactivity comparison of styrenes in hetero-Diels–Alder reactions [**H4**].

Next I investigated reactions of enaminocarbaldehyde - 3-(*N*-acetyl-*N*-benzyloamino)-2-formylprop-2-enenitrile **38**, that acted as heterodiene in hetero-Diels–Alder reaction, with different enol ethers **39** (Scheme 7) [**H5**]. The object was to show that this enaminocarbaldehyde is a valuable precursor in the synthesis of 4-amino-3,4-dihydro-2*H*-pyrans with the skeleton of branched amino sugars. The synthesis of enaminocarbaldehyde **38**

was accomplished in a three-step reaction. Starting 3-*N*,*N*-dimethylamino-2-formylprop-2-enenitrile **36** was obtained in a Vilsmayer-Haack formylation reaction. Compound **36** did not give any cycloadducts with enol ethers. This is due to the electron-donating amino-function at C(3), which raises the LUMO energy of the heterodiene. Only *N*-acetyl derivative of enaminocarbaldehyde **38** was capable to undergo hetero-Diels–Alder reaction (Scheme 7). The reactions of heterodiene **38** with enol ethers **39** were performed in toluene solution at 111°C. They afforded two diastereoisomers of 4-amino-3,4-dihydro-2*H*-pyran-5-carbonitriles **40** (Scheme 7). The *cis* diastereoisomers **40** were always the main products.



Scheme 7. Synthesis of 4-amino-3,4-dihydro-2*H*-pyrans **40** as precursors of 3-amino sugars by hetero-Diels–Alder reactions of enaminecarbaldehyde **38** with enol ethers **39** [**H5**].

The highest diastereoselectivity and the lowest reactivity of the reactions was observed for disubstituted enol ethers. The reactions of *n*-butyl-vinyl ether characterized the lowest diastereoselectivity and the highest reactivity (Fig. 6).

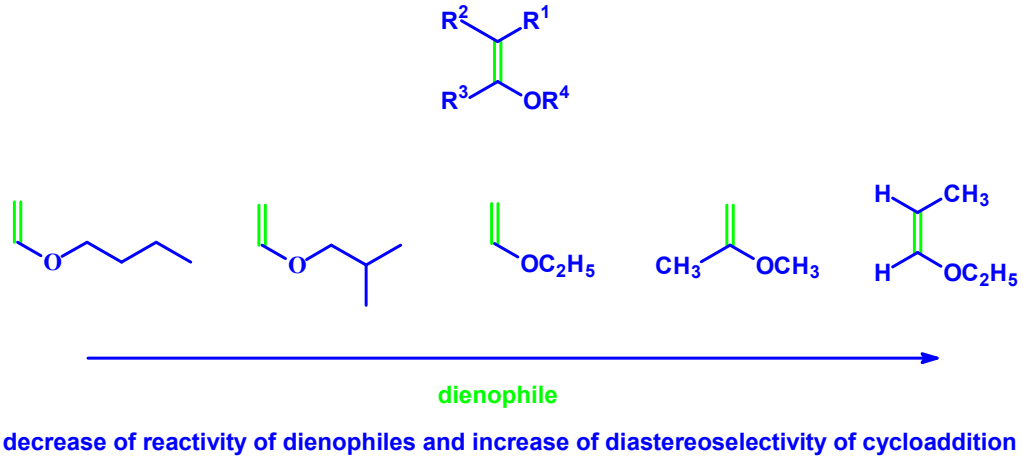
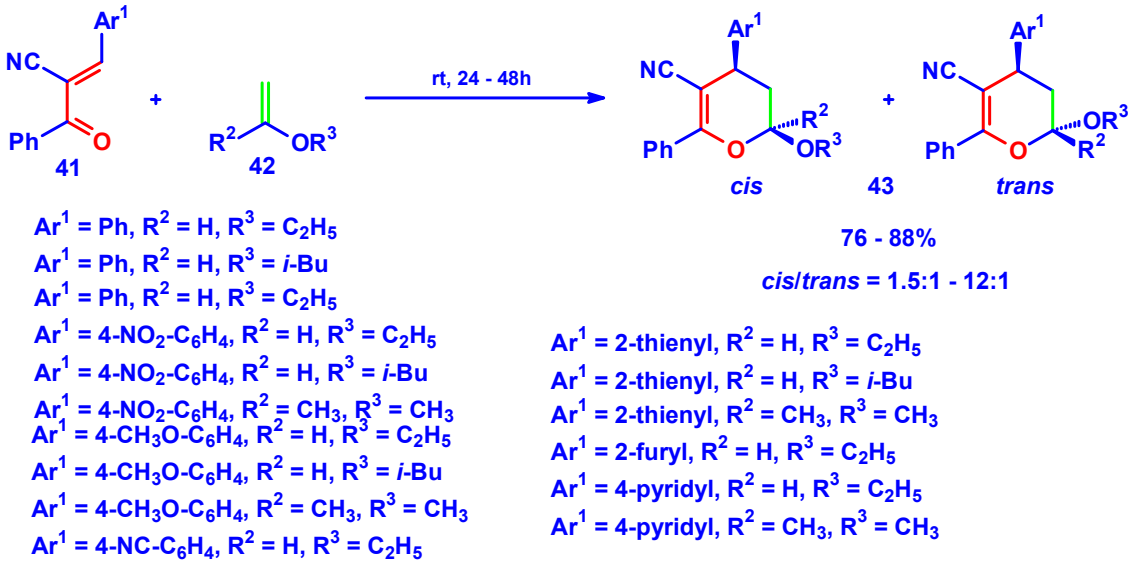


Fig. **6**. Reactivity comparison of enol ethers in hetero-Diels–Alder reactions with enaminecarbaldehyde **38**. Diastereoselectivity comparison in cycloaddition reactions [**H5**].

Among the electron-withdrawing substituents, the cyano group was found to have the most pronounced influence on facilitating the reaction of 1-oxadienes with enol ethers. In my next studies I determined the influence of the type of aryl substituent at C(4) in α,β-unsaturated ketones containing a cyano group at C(3) on their reactivity in hetero-Diels-Alder reactions with enol ethers. The cycloaddition reactions of 3-aryl-2-benzoylprop-2-enenitriles **41** and enol ethers **42** were investigated (Scheme 8) [**H5**]. Heterodienes **41** were obtained by Knoevenagel condensation of benzoylacetonitrile with different heteroaromatic aldehydes. The reactions of compounds **41** with enol ethers **42** were performed in methylene chloride solution at ambient temperature and *cis*/*trans* diastereoisomers of dihydropyrans **43** were obtained [**H5**]. Also cycloaddition reactions of 3-aryl-2-benzoyloprop-2-enenitriles **41**, prepared by condensation of benzoylacetonitrile with different derivatives of benzoic acid, with enol ethers are presented on Scheme 8 [A2]. Cycloadditions of such derivatives **41** and enol ethers **42** were conducted in toluene solution at room temperature [A2].

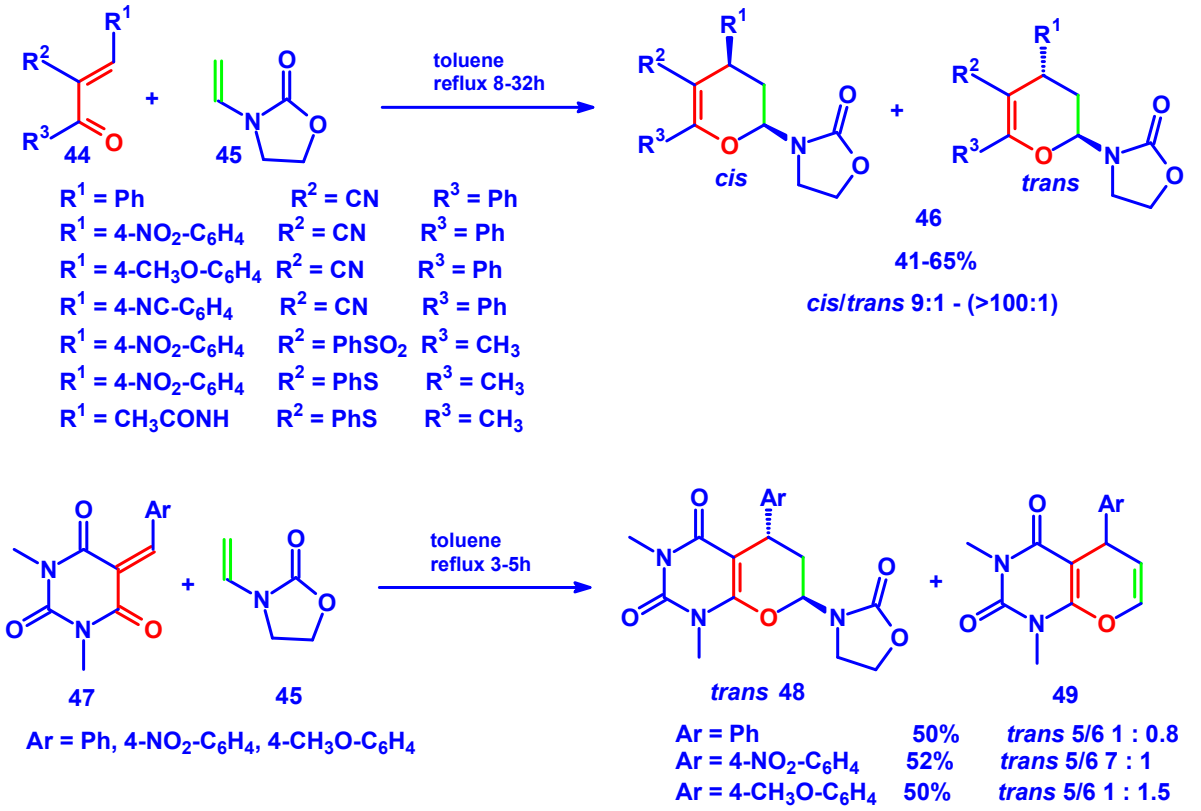


Scheme 8. Hetero-Diels−Alder reactions of 3-aryl-2-benzoylprop-2-enenitriles **41** with enol ethers **42** [**H5** and A2].

On the basis of the experimental findings concerning the yields of products and the required reaction times, one can conclude that the reactivity of heterodienes **41** towards ethyl-vinyl ether increases in the sequence 4-CH_3O-C_6H_4, C_6H_5, 4-pyridyl, 4-NO_2-C_6H_4 concerning Ar^1 substituent in 1-oxa-1,3-butadiene system. I observed the highest diastereoselectivity for cycloaddition reaction of **41** derivative possessing in *para* position electron-donating methoxy group or for reaction of 2-thienyl and 2-furyl derivatives.

In the next step of my experiments I studied if *N*-vinyl-2-oxazolidin-2-one as enecarbamate can act as a valuable dienophile in inverse-electron-demand cycloaddition.

Cycloadditions of 3-aryl-2-benzoyl-2-propenenitriles and 3-phenylsulfonyl-3-buten-2-one **44** to *N*-vinyl-2-oxazolidin-2-one **45** proceeded regio- and diastereoselectively yielding *cis* and *trans* diastereoisomers of dihydropyrans **46**. Cycloadducts *cis*-**46** were the major products. Reaction of 5-arylidene-1,3-dimethylbarbituric acids **47** with dienophile **45** afforded mixtures of pyrano[2,3-*d*]pyrimidine-2,4-diones *trans* **48** and products **49** resulted from an elimination of 2-oxazolidin-2-one (Scheme 9) [**H6**].

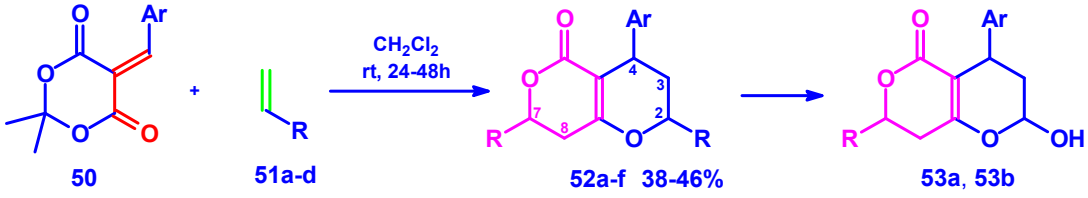


Scheme 9. Synthesis of 3,4-dihydro-2*H*-pyrans **46** and **48** by hetero-Diels–Alder reactions of functionalized α,β-unsaturated carbonyl compounds **44** and **47** with *N*-vinyloxazolidin-2-one **45** [**H6**].

N-Vinyloxazolidin-2-one **45** can act as a valuable dienophile in inverse-electron-demand hetero-Diels–Alder reaction. This compound was found to be less reactive than enol ethers because similar reactions of 3-aryl-2-benzoylprop-2-enenitriles **41** and enol ethers **42** (Scheme 8) occurred at room temperature whereas reactions with **45** required heating in boiling toluene. The presence of electron-withdrawing groups (4-cyanophenyl, 4-nitrophenyl) in the heterodiene **44** increases the rate and the yield of these reactions. *N*-Vinyloxazolidin-2-one **45** as enecarbamate is weaker dienophile than electron-rich enol ethers. Cycloaddition reactions of the dienophile **45** characterized higher diastereoselectivity than reactions of enol ethers. For example, diastereoselectivity of the reactions of 3-aryl-2-benzoylprop-2-enonitriles **41** and enol ethers **42** (Scheme 8) changed in the range *cis*/*trans*

1.5:1 – 12:1 whereas for reactions of compounds **44** and **45** (Scheme 9) observed diastereoselectivity was equal *cis*/*trans* 9:1 – (>100:1). This means that *N*-vinyloxazolidin-2-one is *endo*-selective in these reactions.

Next I investigated if 5-arylidene Meldrum's acids can act as a valuable heterodienes in inverse-electron-demand cycloaddition. I wanted to examine the influence of the electron-withdrawing alkoxycarbonyl group at C(3) position and the electron-donating alkoxy group at C(2) position on diastereoselectivity and yields. Reactions of 5-arylidene Meldrum's **50** with ethyl-vinyl ether and *N*-vinyloxazolidyn-2-one **51** led to pyrano[4,3-*b*]pyrans **52** or **53**, as the results of reactions: a Michael addition, a cyclization, a Michael addition, an elimination of acetone, and finally ring closure by addition (Scheme 10) [**H7**].



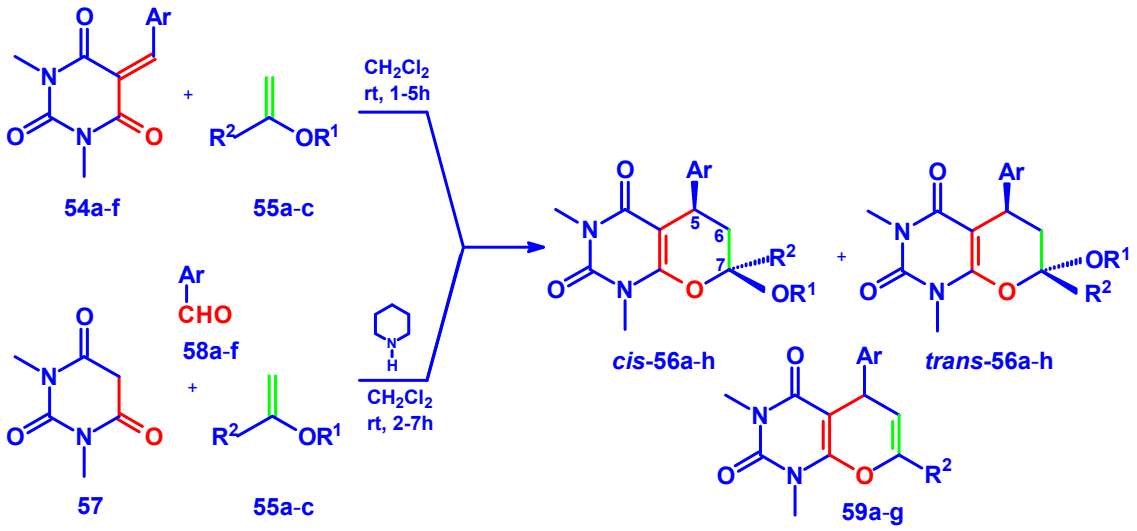
50	51	52 or 53	Ar	R
50a	2a	53a	4-CH_3O-C_6H_4	OC_2H_5
50b	2a	53b	4-NO_2-C_6H_4	OC_2H_5
50c	2a	52c		OC_2H_5
50d	2a	52d		OC_2H_5
50a	2b	52e	4-CH_3O-C_6H_4	
50b	2b	52f	4-NO_2-C_6H_4	
50b	2c	-	4-NO_2-C_6H_4	4-CH_3O-C_6H_4
50b	2d	-	4-NO_2-C_6H_4	4-CH_3-C_6H_4

Scheme 10. 5-Arylidene derivatives of Meldrum's acid **50** as synthons in pyrano[4,3-*b*]pyran **52** and **53** synthesis [**H7**].

Presented results indicate that 5-arylidene derivatives of Meldrum's acid can act as valuable reagents in pyran synthesis. Styrenes are not suitable reagents on account of their inertness towards 5-arylidene Meldrum's acids [**H7**].

Looking for new 1-oxa-1,3-butadiene derivatives which can act as active heterodiene in hetero-Diels–Alder reaction I directed my research to 5-ylidene derivatives of barbituric acids. Cycloadditions of these derivatives afford uracil derivatives which are known as valuable pharmaceuticals. 5-Arylidene-*N*,*N*-dimethylbarbituric acids **54** underwent smooth hetero-Diels–Alder reactions with enol ethers **55** to produce *cis* and *trans* distereoisomers of pyrano[2,3-*d*]pyrimidine-2,4-diones – fused uracils **56** in excellent yields (Scheme 11) [**H8**]. Cycloadducts **56** with *cis*-configuration were the major products. Three-component one-pot reactions of *N*,*N*-dimethyl barbituric acid **57**, aromatic and heteroaromatic aldehydes

58, and enol ethers **55** in the presence of piperidine gave uracils **56** also in very good yields. It is worth to note that trace amounts of compounds **59** created by *trans*-diaxial-elimination of the appropriate alcohol were obtained in these reactions.



					Ar	R^1	R^2
54a	55a	56a	58a	59a	4-CH_3O-C_6H_4	C_2H_5	H
54a	55b	56b	58a	59a	4-CH_3O-C_6H_4	*i*-Bu	H
54a	55c	56c	58a	59b	4-CH_3O-C_6H_4	CH_3	CH_3
54b	55a	56d	58b	59c	Ph	C_2H_5	H
54c	55a	56e	58c	59d	4-NO_2-C_6H_4	C_2H_5	H
54d	55a	56f	58d	59e	2-thienyl	C_2H_5	H
54e	55a	56g	58e	59f	2-furyl	C_2H_5	H
54f	55a	56h	58f	59g	4-pyridinyl	C_2H_5	H

two-component reaction
yield 84 - 94%
cis-56/*trans*-56 1.25:1 - 3.6:1

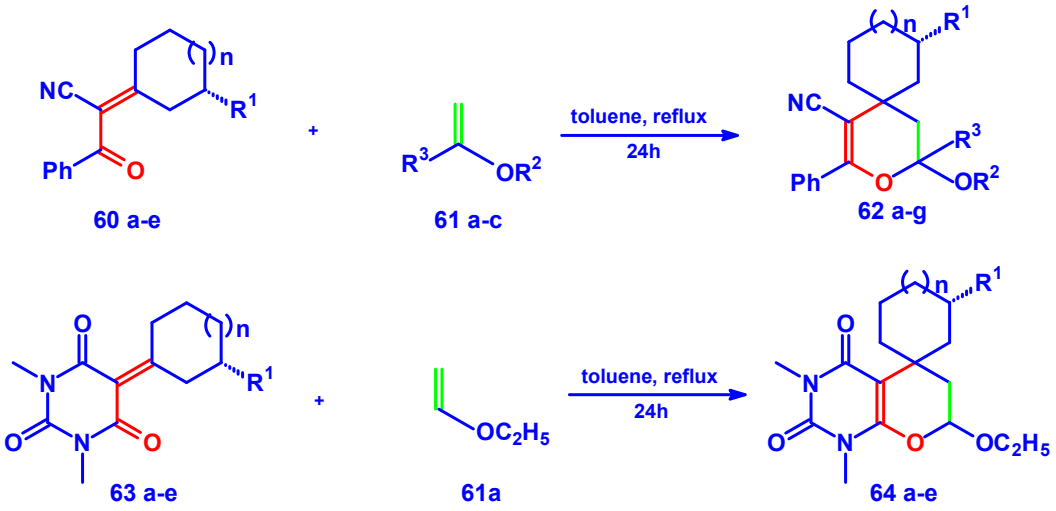
three-component reaction
yield 87 - 95%
cis-57/*trans*-57 1.1:1 - 2.9:1

Scheme 11. Synthesis of uracil derivatives - pyrano[2,3-*d*]pyrimidine-2,4-diones **56** by hetero-Diels−Alder reactions of 5-arylidene 1,3-dimethylbarbituric acids **54** with enol ethers **55** [**H8**].

The advantages of the presented reactions are: the excellent yields, short reaction times, and the fact that cycloadditions do not require drastic conditions, but can be carried out at room temperature. I noticed the highest reactivity for 5-arylidene derivative of *N*,*N*-dimethylbarbituric acid **54** possessing electron-withdrawing group in *para* position in aromatic ring Ar. Cycloadditions of heterodienes **54** with electron-donating methoxy group in *para* position characterized the highest diastereoselectivity. I did not notice a striking difference between the reactivity and diastereoselectivity of ethyl-vinyl ether or isobutyl-vinyl ether or isopropenyl-methyl ether.

The development of new cycloreactants is a continuous challenge in the field of pericyclic reactions. The aim of my next studies was to investigate if 1-oxa-1,3-butadienes that are sterically hindered at the C(4) carbon, for example cycloalkylidene derivatives

of benzoylacetonitrile or 1,3-dimethylbarbituric acid can act as active heterodienes in hetero-Diels–Alder reactions.



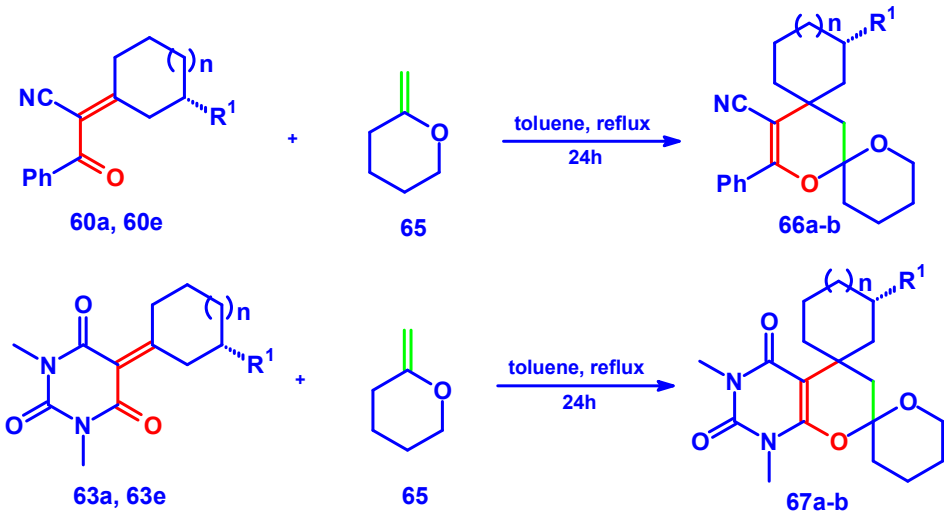
Hetero diene	n	R^1	Enol ether	R^2	R^3	Spiropyran	Yield %
60a	1	H	**61a**	C_2H_5	H	**62a**	89
60a	1	H	**61b**	*i*-Bu	H	**62b**	91
60a	1	H	**61c**	CH_3	CH_3	**62c**	84
60b	0	H	**61a**	C_2H_5	H	**62d**	87
60c	2	H	**61a**	C_2H_5	H	**62e**	86
60d	3	H	**61a**	C_2H_5	H	**62f**	83
60e	1	CH_3	**61a**	C_2H_5	H	**62g**	87
63a	1	H	**61a**	C_2H_5	H	**64a**	79
63b	0	H	**61a**	C_2H_5	H	**64b**	93
63c	2	H	**61a**	C_2H_5	H	**64c**	91
63d	3	H	**61a**	C_2H_5	H	**64d**	88
63e	1	CH_3	**61a**	C_2H_5	H	**64e**	78

Scheme 12. Synthesis of spiropyrans **62** and **64** by hetero-Diels–Alder reactions of 2-cycloalkilidene-3-oxo-3-phenylpropionitriles **60** or 5-cycloalkilidene-1,3-dimethylpyrimidine-2,4,6-triones **63** with enol ethers **61** [**H9**].

The cycloaddition reactions of 2-cycloalkylidene-3-oxo-3-phenylpropionitriles **60** or 5-cycloalkylidene-1,3-dimetylpyrimidine-2,4,6-triones **63** with enol ethers **61** were performed in toluene solution at 111°C (Scheme 12) [**H9**]. The spiropyrans **62** and **64** were obtained in good yields.

Encouraged by previous results, I next embarked on the inverse-electron-demand hetero-Diels–Alder reactions between cycloalkylidene derivatives **60** or **63** and cyclic enol ether – 2-methylidenetetrahydropyrane **65** (Scheme 13) [**H9**]. The cycloaddition reactions of appropriate compounds afforded dispiropyrans **66** and **67** in good yields. Only one

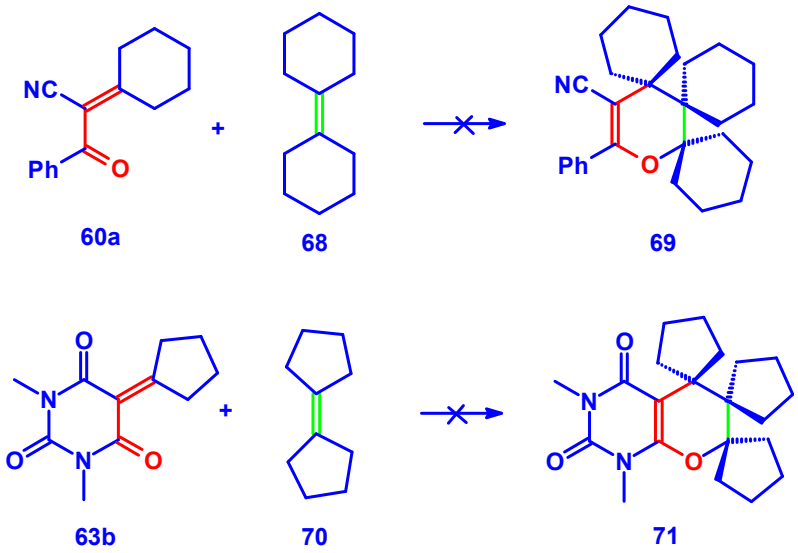
diastereoisomer **66** or **67** was obtained as product in the hetero-Diels–Alder reactions of selected compounds **60** or **63** with cyclic enol ether **65**. So, increase of steric hindrance in heterodiene or dienophile systems influences on increase of diastereoselectivity of cycloaddition reactions.



Heterodiene	n	R^1	Enol ether	Spiropyran	Yield %
61a	1	H	**66**	**67a**	93
61e	1	CH_3	**66**	**67b**	91
64a	1	H	**66**	**68a**	87
64e	1	CH_3	**66**	**68b**	89

Scheme 13. Synthesis of dispiropyrans **66** and **67** by hetero-Diels−Alder reactions of 2-cycloalkilidene-3-oxo-3-phenylpropionitriles **60** or 5-cycloalkilidene-1,3-dimethylpyrimidine-2,4,6-triones **63** with cyclic enol ether **65** [**H9**].

Trispiropyrans provide an unusual synthetic challenge, so in the next step, methodology for synthesis of dispiropyrans was applied to prepare trispiropyrans. The reaction mixture of 2-cyclohexylidene-3-oxo-3-phenylpropionitrile **60a** and cyclohexylidenecyclohexane **68** and the reaction mixture of 5-cyclopentylidene-1,3-dimethylpirymidine-2,4,6-trione **63b** and cyclopentylidenecyclopentane **70** were first heated to reflux in toluene solution for 24h but the trispiropyrans **69** and **71** were not formed (Scheme 14) [**H9**]. The reaction conditions were changed and the reaction mixtures were heated in xylene solution in the presence of catalytic amounts of the Lewis acids, such as $ZnCl_2$ or $CoCl_2$ and no reaction occurred, even after 24h at reflux.



Scheme 14. Test-reactions of cycloalkilidene derivatives **60a** and **63b** with cycloalkilidenecycloalkanes **68** and **70** [**H9**].

The cycloaddition reactions appear to be under frontier molecular orbital (FMO) control. In order to confirm the experimental results, frontier orbital (HOMO and LUMO) energies of selected heterodienes **60** and **63**, and selected dienophiles **61**, **65**, **68** and **70** were calculated by semi-empirical AM1 and PM3 methods, and *ab initio* Hartree-Fock calculations using the Gaussian 03 suite of programs [**H9**]. Investigated cycloadditions are an inverse-electron-demand hetero-Diels–Alder reactions. In hetero-Diels–Alder reactions with inverse-electron-demand, the HOMO orbital of the dienophile (D) overlaps with the LUMO orbital of the heterodiene (H), so energy gaps $E_{LUMO}(H) - E_{HOMO}(D)$ were discussed. In all the studied cases, the energy gaps for the interaction of the HOMO orbital of heterodiene and the LUMO orbital of the dienophile were higher (from 11.181 to 15.699 eV) than energy differences for the interaction of the LUMO orbital of heterodiene and the HOMO orbital of the dienophile (from 8.537 to 11.392 eV). For an inverse-electron-demand hetero-Diels–Alder cycloaddition the presence of an electron-withdrawing group in the heterodiene and an electron-releasing substituent in the dienophile contracts the LUMO(H) – HOMO(D) energy separation through raising the energy of the HOMO(D) and lowering the energy of the LUMO(H) and hence increases the reactivity. Energy gaps $E_{LUMO}(H) - E_{HOMO}(D)$ for reaction of ethyl-vinyl ether **61a** were slightly lower for the cycloalkylidene derivatives of 1,3-dimethylbarbituric acid **63** than for the cycloalkylidene derivatives of benzoylacetonitrile **60**. For the studied cycloadditions, the reactivity of cyclic enol ether **65** was comparable with the reactivity of ethyl-vinyl ether **61a**. The calculated energy gaps for the interaction LUMO orbital of selected heterodienes and HOMO orbital of dienophile **65**

are similar to the appropriate energy gaps for selected heterodienes and dienophile **61a**. However, the frontier molecular orbital model did not seem capable of explaining the observed reactivity for cycloadditions of heterodienes **60a** or **63b** with cycloalkylidenecycloalkanes **68** or **70** (Scheme 14). The energy differences for the interaction of the LUMO orbital of **60a** or **63b** and the HOMO orbital of **68** or **70** were comparable or slightly lower than energy gaps for reaction of **60a** or **63b** with dienophiles **61a** or **65**. Probably, steric effects dictated that heterodienes **60a** and **63b** can not react with sterically hindered dienophiles **68** or **70** and trispiropyrans **69** or **71** did not arise under these conditions [**H9**].

5. In search of hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes and alkenes with potential application in bioorthogonal chemistry

For chemical biologists discovering new reactions which can expand the toolbox of bioorthogonal chemistry is current challenge. Development of new orthogonal methods for labeling in the biosystems is still continued, although effective bioorthogonal reactions such as copper-free click chemistry have been developed. Bioorthogonal ligations have been widely used in biomedical research since they can selective label of biomolecules in living systems. The term bioorthogonal chemistry refers to any chemical reaction that can occur inside of living systems without interfering with native biochemical processes. The term was coined by Carolyn Bertozzi in 2003. Reactions which can be used in bioorthogonal click chemistry should meet the requirements:

1. The reactions should be carried out in water under physiological conditions (36-40 ^{o}C and pH 6-7).
2. Reagents and products should characterize chemical stability in aqueous solutions *in vivo*.
3. High reaction rate under physiological conditions. The reaction must be fast, on the time scale of cellular processes (minutes).
4. Reagents as well as products should not be toxic.
5. Reagents and resulting products should not possess any mode of reactivity capable of disrupting the native chemical functionality of the organism under study.

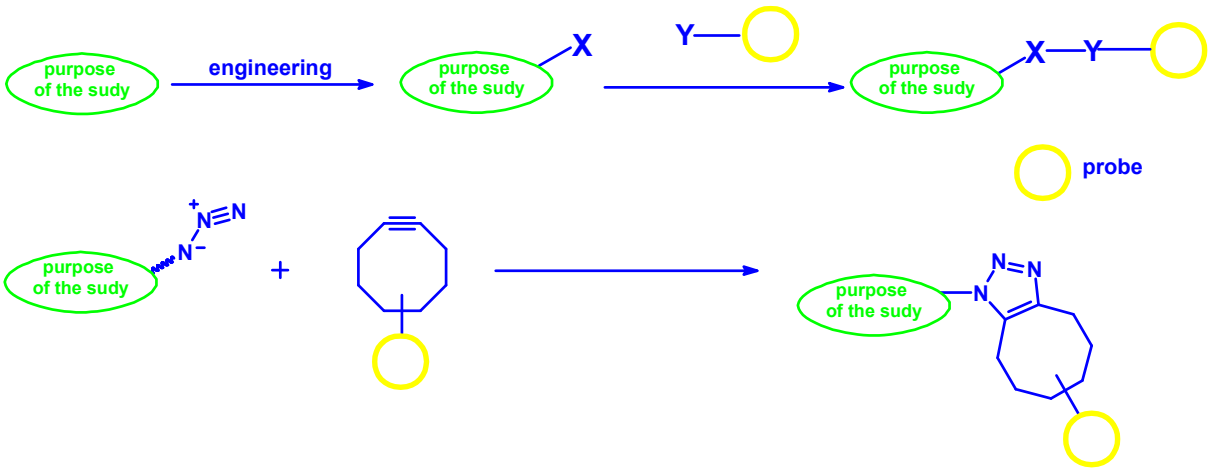
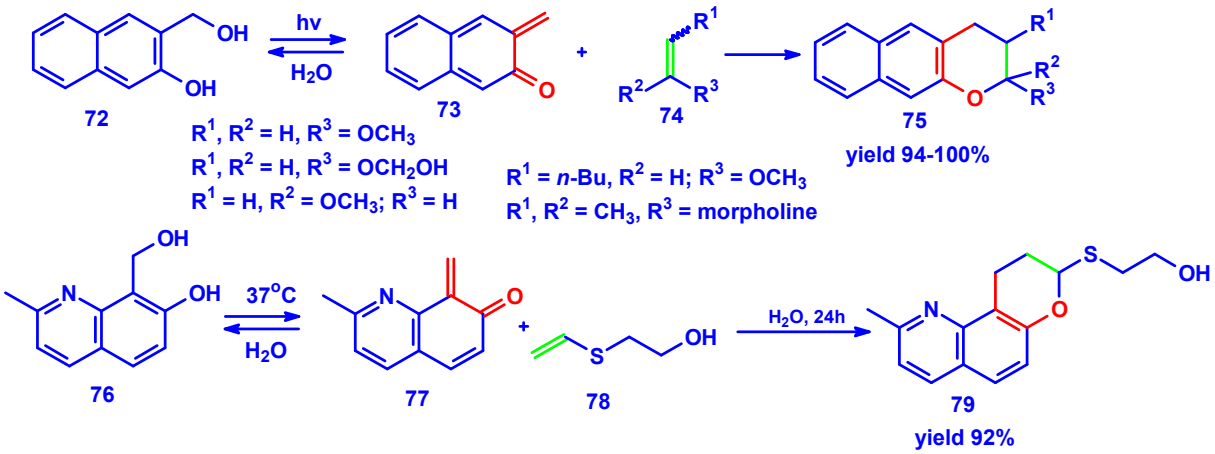


Fig.**7**. Scheme of the bioorthogonal reaction. 1,3-Dipolar cycloaddition of azide and cyclooktyne.

On Figure 7 is shown a bioorthogonal ligation between biomolecule X and reactive partner Y. These reactive partners X and Y cannot perturb other chemical functionality naturally found within the cell. The classic copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition has been an extremely fast and effective click reaction for bioconjugation, but it was not suitable for use in live cells due to the toxicity of Cu(I) ions. Instead of the application of Cu(I) ions as catalyst in 1,3-dipolar cycloaddition of azides and alkynes, strain promoted azide alkyne cycloaddition (SPAAC) is widely used in bioorthogonal ligation as.

There is only one example in literature of application of inverse-electron-demand reactions of 1-oxa-1,3-butadienes in bioorthogonal chemistry. *o*-Quinone methides represent 1-oxa-1,3-butadiene system which can undergo quick and selective inverse-electron-demand hetero-Diels–Alder reactions. Cycloadditions of photochemically generated *o*-naphthoquinone methides **73** with vinyl ethers or enamines **74** as dienophiles were described by Arumugam and Popik (Scheme 15) [A3]. They used UV light to generate 1-oxa-1,3-butadienes **73**. It is important that generation of the *o*-quinone methides can't be conducted in harsh reaction conditions because it could be harmful for the cell of organism. Lei and co-workers described a new bioorthogonal ligation by click hetero-Diels–Alder cycloaddition of in situ-generated *o*-quinolinone quinone methides and vinyl thioethers [A4]. High selectivity and the fact that this cycloaddition, can proceed smooth under aqueous conditions, make it suitable for bioorthogonal chemistry.



Scheme 15. Example of hetero-Diels−Alder reaction of 1-oxa-1,3-butadienes and alkenes which was applied in bioorthogonal chemistry [A3, A4].

Li at al. optimized both reaction partners to make it suitable for bioorthongal ligation [A4]. Introduction of more electronegative nitrogen into heterodiene system **77** improved its reactivity and hydrophilicity (Scheme 15). As dienophile was used small and chemically stable *in vivo* vinyl thioether **78**. *o*-Quinolinone quinine methide **77** was prepared from 8-(hydroxymehyl)-2-methylquinolin-7-ol **76** without use of catalyst and UV light. Cycloreactants **77** and **78** underwent a click HDA cycloaddition under physiological conditions (37 ^{o}C, H_2O). Authors used this bioorthonogal cycloaddition for labeling of proteins and imaging of taxol derivative inside live cells.

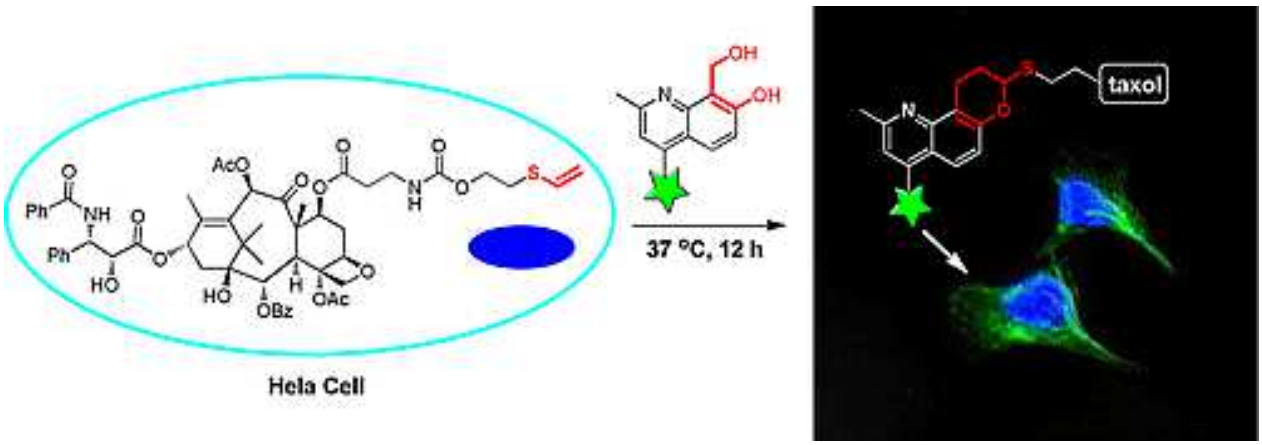
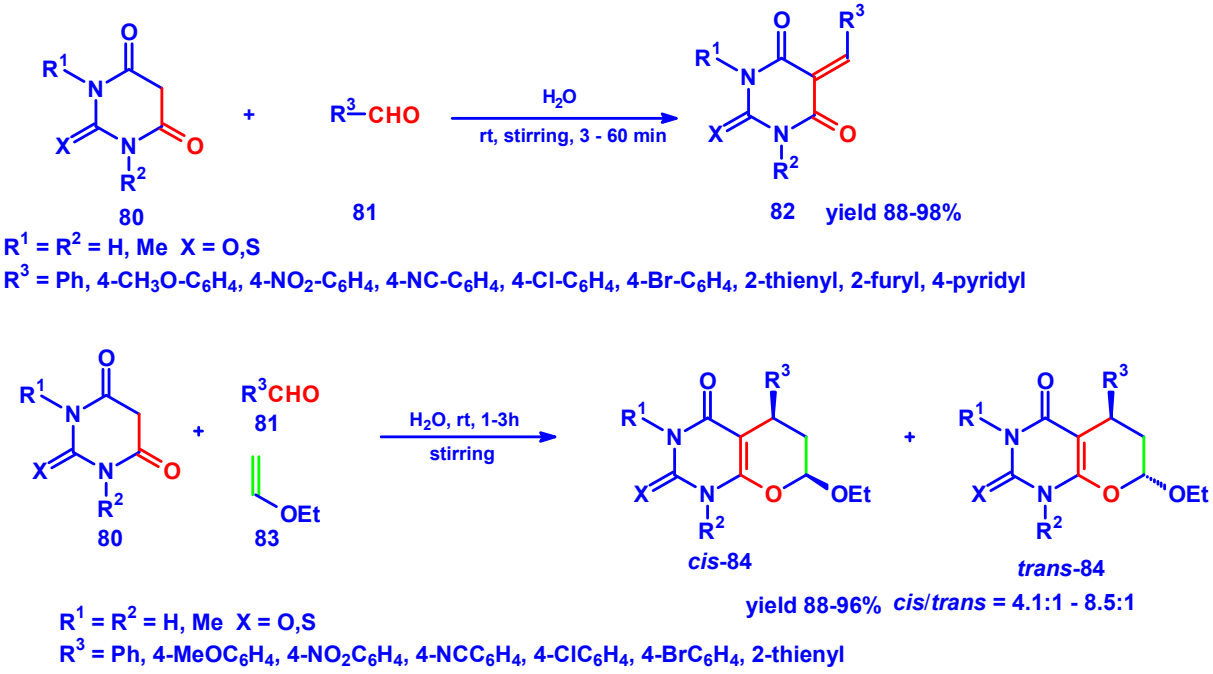


Fig. **8**. Application of hetero-Diels−Alder reaction of *o*-quinolinone methide with vinyl thioether as bioorthonogal cycloaddition for imaging of taxol derivative inside live cells HeLa. [A4].

Application of inverse-electron-demand hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes in bioorthogonal chemistry is still challenge because there is only one example

of this bioorthogonal cycloaddition in literature. Therefore, the next aim of my work was research of hetero-Diels–Alder reactions in water as solvent and in mild conditions similar to physiological conditions. High reactivity of 5-arylidene derivatives of 1,3-dimethylbarbituric acid in hetero-Diels-Alder reactions with enol ethers (Scheme 11), in methylene chloride solution at room temperature, prompted me to study these reactions in water as solvent. On-water Knoevenagel condensations of barbituric acids **80** with aromatic and heteroaromatic aldehydes **81** were carried out without a catalyst and at room temperature. Condensations in aqueous suspensions occurred rapidly, giving pure products **82** with almost stoichiometric yields (Scheme 16) [**H10**, **H11**].

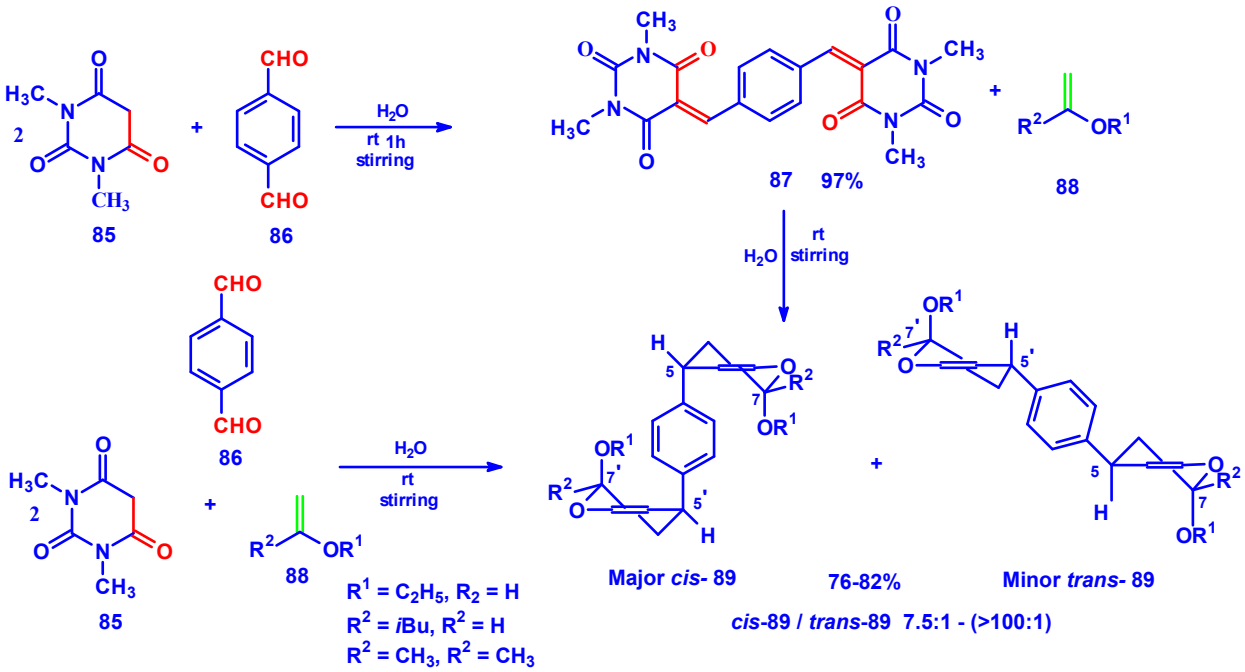


Scheme 16. Domino Knoevenagel/hetero-Diels–Alder reactions in „on water" conditions [**H10**, **H11**].

Solvent-free hetero-Diels–Alder reactions of 5-arylidene derivatives of barbituric acids with enol ethers were investigated at room temperature but the diastereoselectivity of these reactions was not high [**H10**,**H11**]. Therefore, I examined the cycloadditions in water. Three-component one-pot reactions of barbituric acids **80**, aldehydes **81**, and etyl-vinyl ether **83** were carried out in aqueous suspensions at ambient temperature. Formation of the unexpected derivatives in small amounts is explained in the publications **H10** and **H11**.

In the next step of my research, terephthalaldehyde containing two formyl groups in *para* position in aromatic ring was used in domino Knoevenagel/hetero-Diels–Alder reactions carried out in „on water" conditions (Scheme 17) [**H11**]. Condensation of 1,3-dimethylbarbituric acid **85** with terephthalaldehyde **86** was carried out in water without

catalyst and at room temperature, giving Knoevenagel product **87** with 97% yield after 1h (Scheme 17).



Scheme 17. Domino Knoevenagel/hetero-Diels–Alder reactions of 1,3-dimethylbarbituric acid **85**, terephthalaldehyde **86** and enol ethers **88** in „on water" conditions [**H11**].

1,4-Bis(pyrano[2,3-*d*]pyrimidinyl)benzens **89** were prepared as the result of the cycloaddition reactions presented on Scheme 17. Cycloadducts *cis*-**89** were the major products. The highest diastereoselectivity was observed for ethyl-vinyl ether. The unexpected derivatives of pyrano[2,3-*d*]pyrimidines were also obtained in small amounts. Formation of these compounds is explained in the publication **H11**.

On the basis of my research results I can state that „on-water" cycloadditions of 5-arylidene derivatives of barbituric acids with enol ethers characterized by high diastereoselectivity and high rate in contrast to reactions carried out without solvent or in homogenous organic media such as dichloromethane or toluene. I think that, hetero-Diels–Alder reactions of 5-arylidenebarbituric acids and enol ethers can potentially be applied in bioorthogonal chemistry.

6. Synthesis of uracil derivatives containing a sugar moiety of potential biological activity by hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes and alkenes

In review **H12** published in *European Journal of Medicinal Chemistry* I described the methods of synthesis, biological activity and pharmacological applications of uracils and fused uracils having uracil ring annulated with other heterocyclic ring. Uracils are considered as privileged structures in drug discovery with a wide array of biological activities and synthetic accessibility. Antiviral and anti-tumor are the two most widely reported activities of uracil analogs however they also possess herbicidal, insecticidal and bactericidal activities. Their antiviral potential is based on the inhibition of key step in viral replication pathway resulting in potent activities against HIV, hepatitis B and C, the herpes viruses etc. Uracil derivatives such as 5-fluorouracil or 5-chlorouracil were the first pharmacological active derivatives to be generated. Poor selectivity limits its therapeutic application, resulting in high incidences of gastrointestinal tract or central nervous toxicity. Numerous modifications of uracil structure have been performed to tackle these problems resulting in the development of derivatives exhibiting better pharmacological and pharmacokinetic properties including increased bioactivity, selectivity, metabolic stability, absorption and lower toxicity. Researches of new uracils and fused uracil derivatives as bioactive agents are related with modifications of substituents at N(1), N(3), C(5) and C(6) positions of pyrimidine ring (Fig. 9).

Recently, I have shown that fused uracils such as pyrano[2,3-*d*]pyrimidines with an aryl substituent at carbon C(5) in the ring system can be efficiently synthesized by hetero-Diels–Alder reactions of 5-arylidene derivatives of barbituric acids with vinyl ethers [**H8**, **H10**, **H11]**. Introducing a sugar moiety instead of an aryl group at the C(5) position of pyrano[2,3-*d*]pyrimidine can probably increase the potential pharmacological activity of the fused uracil. Therefore, efforts to construct 5-ylidene barbituric acids bearing the carbohydrate substituent were undertaken [**H13**]. A convenient procedure for Knoevenagel condensation of barbituric acids and unprotected sugars in water was described. The Knoevenagel condensations of different sugars **90**: L-(-)-xylose, L-(+)-arabinose, D-(+)-glucose, D-(+)-galactose and D-(-)-ribose with 1,3-dimethylbarbituric acid **91** in water solution in the presence of sodium carbonate were performed at 80 ^{o}C for 5 hours (Scheme 18) [**H13**].

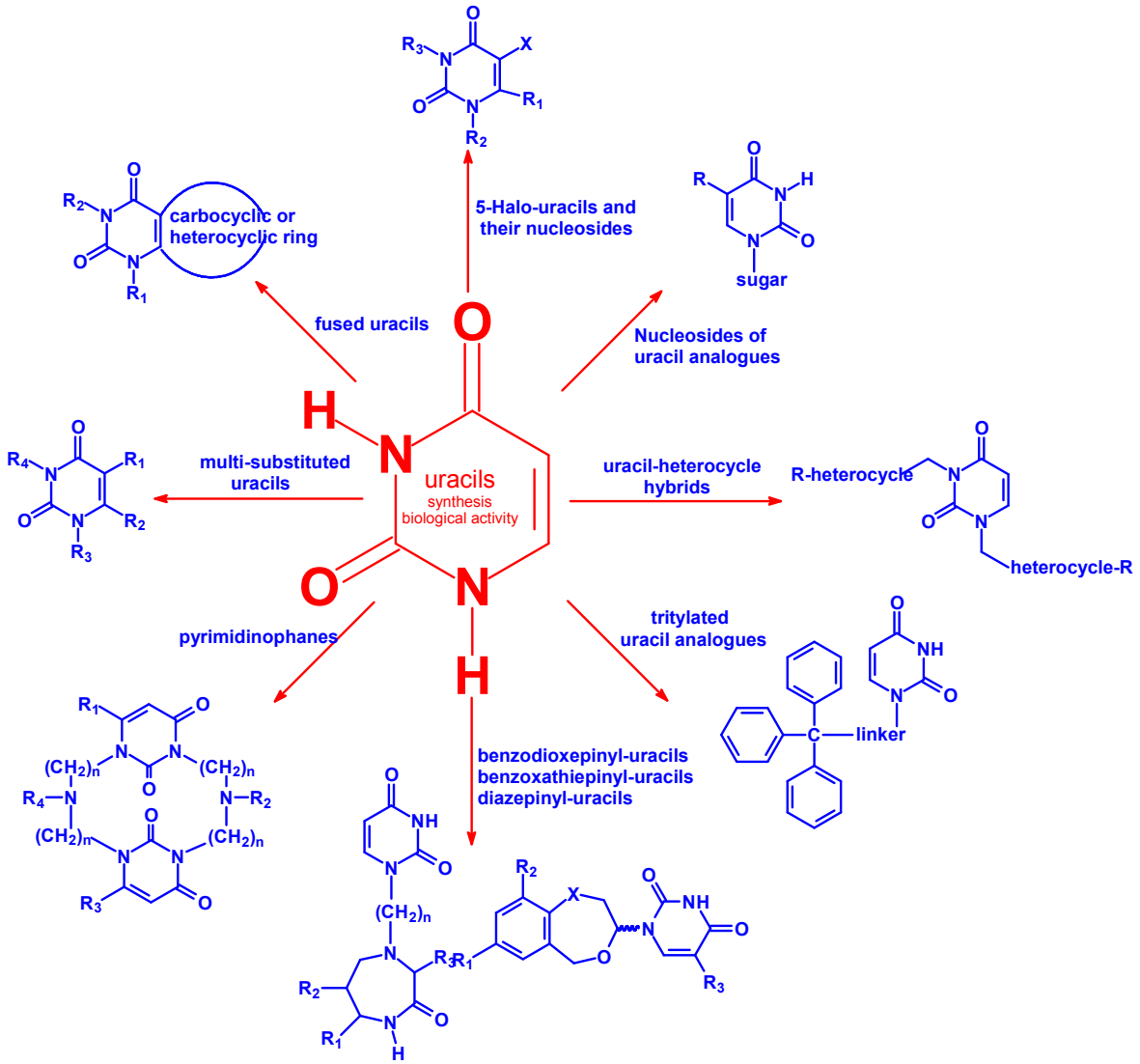
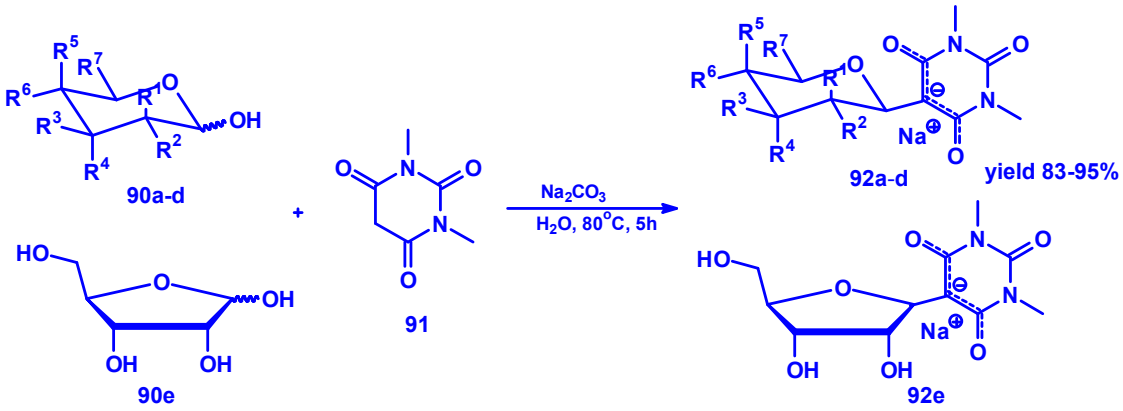


Fig. **9**. Uracil derivatives of biological activity with different substituents at N(1), N(3), C(5) and C(6) positions [**H12**].

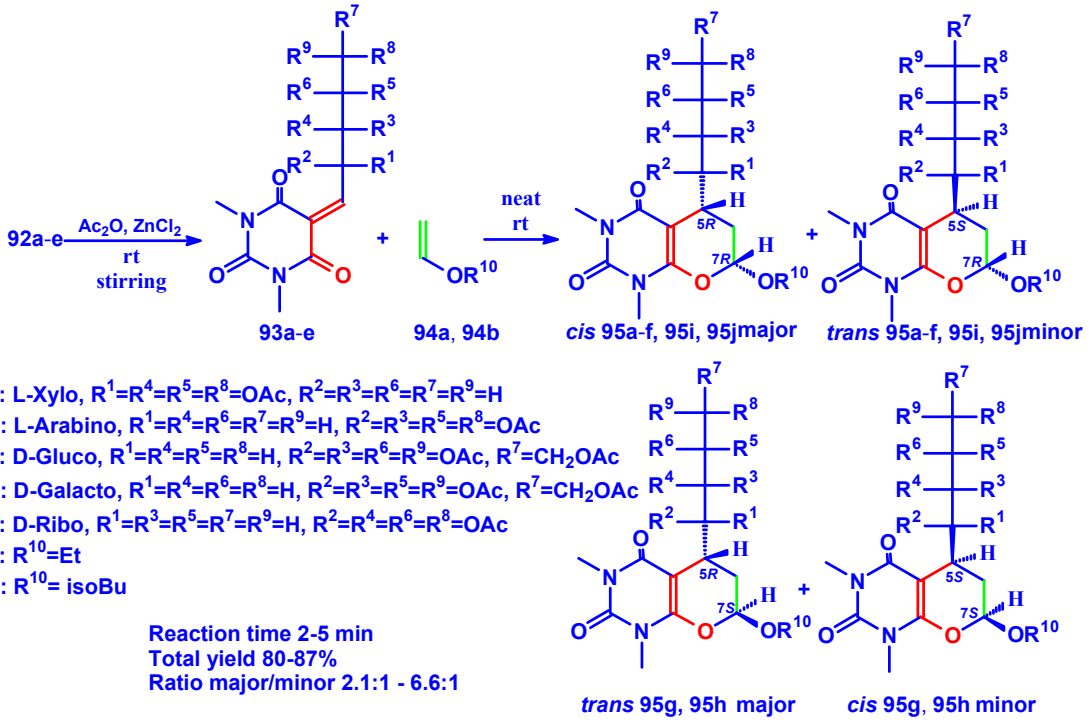
Sodium 5-glycopyranosyl-1,3-dimethylbarbiturates **92a-d** and sodium 1,3-dimethyl-5-*β*-D-ribofuranosyl-barbiturate **92e** as condensation products, did not represent a 1-oxa-1,3-diene system. Therefore, they did not react as active heterodienes in hetero-Diels–Alder reaction. However, treatment of compounds **92a-e** with acetic anhydride and a large excess of zinc chloride gave the *O*-acetylated 1,3-dimethyl-2,4,6-trioxo-pyrimidin-5-ylidene derivatives **93a-e** (Scheme 19) [**H13**]. Products **93a-e** possess a 1-oxa-1,3-diene system and additionally the introduction of the electron-withdrawing acetyl groups, as protection of each of hydroxy groups, could enhance their reactivity in hetero-Diels–Alder reactions.



90a: L-(-)-Xylose, $R^1=R^4=R^5=OH$, $R^2=R^3=R^6=R^7=H$
90b: L-(+)-Arabinose, $R^1=R^4=R^6=R^7=H$, $R^2=R^3=R^5=OH$
90c: D-(+)-Glucose, $R^1=R^4=R^5=H$, $R^2=R^3=R^6=OH$, $R^7=CH_2OH$
90d: D-(+)-Galactose, $R^1=R^4=R^6=H$, $R^2=R^3=R^5=OH$, $R^7=CH_2OH$
90e: D-(-)-Ribose

Scheme 18. Knoevenagel condensation of 1,3-dimethylbarbituric acid **91** and unprotected sugars **90** in water [**H13**].

The cycloaddition reactions of *O*-acetylated 1,3-dimethyl-2,4,6-trioxo-pyrimidin-5-ylidene derivatives **93a-e** with enol ethers **94a** or **94b** were performed in the absence of solvent at room temperature for 2-5 min and pyrano[2,3-*d*]pyrimidines **95a-j** were obtained in good 80-87 % yields (Scheme 19) [**H13**]. Cycloadducts *cis*-**95** were the major products in all reactions except of D-galactose derivatives **95g** and **95h**.



93a: L-Xylo, $R^1=R^4=R^5=R^8=OAc$, $R^2=R^3=R^6=R^7=R^9=H$
93b: L-Arabino, $R^1=R^4=R^6=R^7=R^9=H$, $R^2=R^3=R^5=R^8=OAc$
93c: D-Gluco, $R^1=R^4=R^5=R^8=H$, $R^2=R^3=R^6=R^9=OAc$, $R^7=CH_2OAc$
93d: D-Galacto, $R^1=R^4=R^6=R^8=H$, $R^2=R^3=R^5=R^9=OAc$, $R^7=CH_2OAc$
93e: D-Ribo, $R^1=R^3=R^5=R^7=R^9=H$, $R^2=R^4=R^6=R^8=OAc$
94a: R^{10}=Et
94b: R^{10}= isoBu

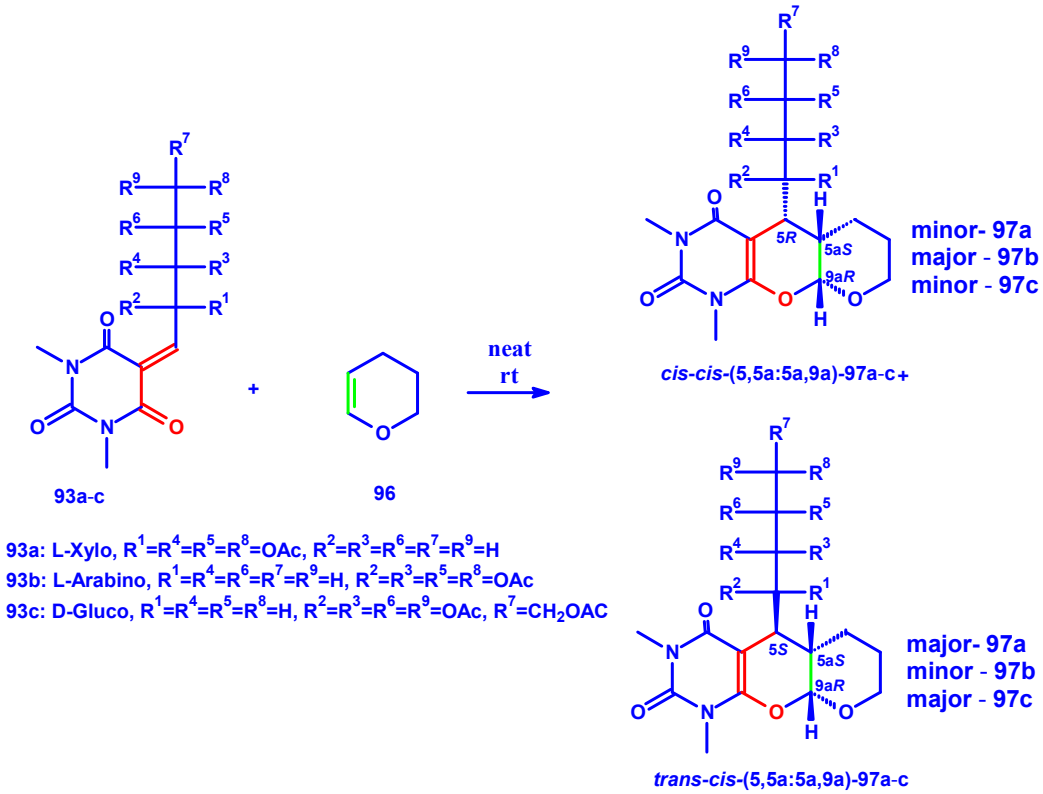
Reaction time 2-5 min
Total yield 80-87%
Ratio major/minor 2.1:1 - 6.6:1

Scheme 19. Synthesis of pyrano[2,3-*d*]pyrimidines **95** with sugar moiety by hetero-Diels−Alder reactions of alditols **93** with enol ethers **94** [**H13**].

It is worth noting that barbituric acid 5-ylidene alditols are extremely reactive because they underwent smooth hetero-Diels–Alder reactions at a temperature of –80 ^{o}C as well as at room temperature. The relative *cis* and *trans* configurations of the substituents at the stereogenic centers C(5) and C(7) of compounds **95** and *R*, *S* absolute configurations at these centers were assigned on the basis of the X-ray structure analysis and ^{1}H NMR spectra [**H13]**. Four different diastereoisomers could be formed in the hetero-Diels–Alder reactions of compounds **93** and **94**. Only two diastereoisomers were obtained in each of studied cycloaddition. Thus, the examined reactions characterized high diastereoselectivity that resulted in two diastereoisomers.

Next, the inverse-electron-demand hetero-Diels–Alder reactions of *O*-acetylated 5-ylidene derivatives **93a-c** with cyclic enol ether - 3,4-dihydro-2*H*-pyrane **96** were performed in solventless conditions at room temperature for 30 min and pyrano[3',2':5,6]pyrano[2,3-*d*]pyrimidines **97a-c** were obtained in good yields (Scheme 20) [**H13**]. Eight different diastereoisomers of cycloadducts **97** could be formed in the hetero-Diels–Alder reactions of compounds **93a-c** and **96**. Only two diastereoisomers were obtained in each of the studied cycloadditions and both diastereoisomers were formed in similar quantities.

These studies showed that *O*-acetylated 1,3-dimethyl-2,4,6-trioxo-pyrimidin-5-ylidene alditols can act as active heterodienes in hetero-Diels–Alder reactions and their using in cycloadditions allow to prepare the diastereoisomers of pyrano[2,3-*d*]pyrimidines possessing a sugar moiety. I have developed a convenient and efficient procedure for the preparation of fused uracils with a sugar moiety by the reaction sequence: Knoevenagel condensation, acetylation of *C*-glycoside and next hetero-Diels-Alder reaction.

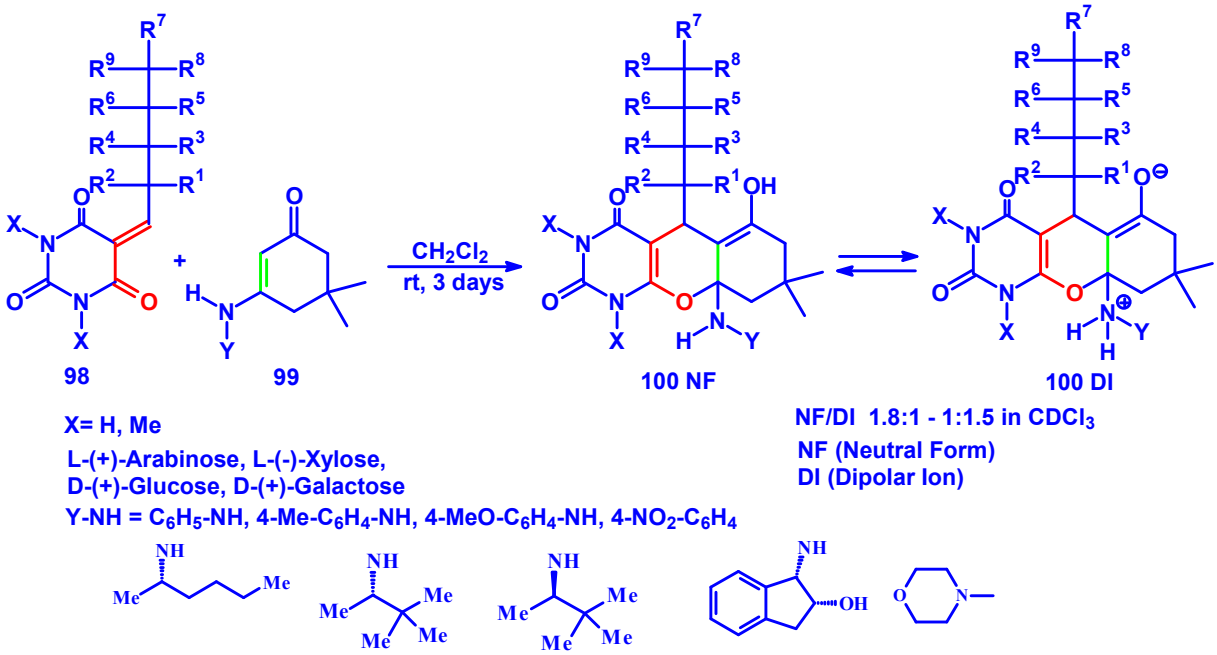


alditol	enol ether	cycloadduct	reaction time /min	yield/%	major/minor
93a	**96**	**97a**	30	78	1.2:1
93b	**96**	**97b**	30	76	1.1:1
93c	**96**	**97c**	30	78	1.2:1

Scheme 20. Synthesis of pyrano[3',2':5,6]pyrano[2,3-*d*]pyrimidines **97** possessing sugar moiety by hetero-Diels–Alder reactions of alditols **93** and cyclic enol ether **96** [**H13**].

Development of new cycloreactants is a continuous challenge in the field of pericyclic reactions, thus efforts were undertaken to find new dienophiles for hetero-Diels–Alder reactions with inverse-electron-demand which could concomitantly introduce important functional groups such as amino or carbonyl groups into the prepared compounds. Reports in the area of hetero-Diels–Alder cycloadditions mainly concern the use of vinyl ethers or simple enamines, but none have reported the use of cyclic enamines possessing carbonyl function in position alpha to the ene. The aim of the study was to investigate if different enamines of dimedone - 5,5-dimethyl-3-amino-cyclohex-2-en-1-one can act as active dienophiles in hetero-Diels–Alder reaction with inverse-electron-demand. I also wanted to determinate the influence of substituents on the amino group on reactivity and diastereoselectivity of cycloadditions. 2,4,6-Trioxo-pirymidin-5-ylidene alditols **93**, prepared by the Knoevenagel condensation and next the acetylation reaction (Scheme 19), were also used as heterodienes in hetero-Diels–Alder reactions with dimedone enamines **99**

(Scheme 21) [**H14**]. Dimedone enamines **99** were applied for the first time as new dienophiles in hetero-Diels-Alder reactions with inverse electron demand. Cycloadditions of barbituric acid 5-ylidene alditols **98** with dimedone enamines **99** were performed in dichloromethane at room temperature for 3 days and fused uracils - chromeno[2,3-*d*]pyrimidine-2,4-diones **100** were obtained in good 73–87% yields. Prepared cycloadducts **100** have three stereocenters, so eight stereoisomers could be formed. Only one enantiomerically pure stereoisomer was obtained in each studied cycloaddition of compounds **98** and **99** so examined cycloadditions were completely stereoselective. Analysis of ^{1}H NMR and 2D NMR spectra allowed for the determination that cycloadducts **100** exist in solution as mixture of the neutral form **NF** and dipolar ion **DI** (Scheme 21). The prepared fused uracils **100** contain both amine and enol functional groups, so share amphiprotic properties and they are zwitterions in solid state. The new class of compounds – amino enols was synthesized, which similarly to amino acids exists as zwitterions. In obtained cycloadducts amino groups and sugar moieties are close each other and they both are in *cis* configuration and in *axial* position. It was also shown that different alkenes can be used as dienophiles towards barbituric acid 5-ylidene alditols, for example styrene or 1-amino-2-thiocarbamoyl-cyclopent-1-ene.



Scheme 21. Stereoselective synthesis of amino enols of fused uracils **100** containing a sugar moiety by hetero-Diels–Alder reactions of barbituric acid 5-ylidene alditols **98** with dimedone enamines **99** [**H14**].

In summary, a convenient and efficient method for the synthesis of fused uracils, namely chromeno[2,3-*d*]pyrimidine-2,4-diones containing different sugar moieties, enol moiety and different amino groups of potential pharmacological activity, was described. These studies show that different enamines of dimedone can act as active dienophiles in hetero-Diels–Alder reaction with inverse-electron-demand. By this simple hetero-Diels–Alder reaction we can introduce into fused uracil systems such important for biological interaction groups as: different sugar moieties, enol moiety and different amino groups.

7. Summary

In conclusion, a increase of the reactivity of the heterodienes and the dienophiles was observed in order depicted in the Figure 10. Taking into account the heterodienes, I compared the reaction conditions and reaction time for cycloadditions with the same dienophile, namely ethyl-vinyl ether. *O*-Acetylated 2,4,6-trioxo-pyrimidin-5-ylidene alditols **F** characterized the highest reactivity. The heterodienes **F** underwent smooth hetero-Diels–Alder cycloadditions with enol ethers and reactions were completed after few minutes. It was due to the presence of an electron-withdrawing acetyl groups which influence on lowering the energy of the LUMO of the heterodiene. In hetero-Diels–Alder reactions with inverse-electron-demand, the HOMO orbital of the dienophile (D) overlaps with the LUMO orbital of the heterodiene (H), so energy gaps $E_{LUMO}(H)–E_{HOMO}(D)$ are discussed. The presence of an electron-withdrawing acetyl groups in heterodiene contracts $E_{LUMO}(H)–E_{HOMO}(D)$ energy separation through lowering the energy of the LUMO(H) and hence increase of the reactivity. The lowest reactivity was observed for enaminocarbaldehyde **A**, which reaction with ethyl-vinyl ether was performed at 111^{o}C for 36 h. The presence of the electron-withdrawing cyano group in the 1-oxa-1,3-diene system of compound **A** enhances its reactivity. However, the electron-donating function of the amino group raises the LUMO energy of the oxabutadiene system and only *N*-acetylated derivative **A** was capable to undergo hetero-Diels–Alder reactions. 5-Arylidene derivatives of barbituric acids **E** were found to be less reactive than alditols **F** because reactions of the heterodienes **E** occurred at room temperature and required 1-7 h whereas reactions of the heterodienes **F** were completed after few minutes. Cycloaddition reactions of 3-aryl-2-benzoylprop-2-enenitries **D** with ethyl-vinyl ether were carried out at room temperature for 24-48 h. The heterodienes **D** are less reactive than the heterodienes **E**. The presence of the electron-withdrawing carbamoyl group at C(3)

position of 1-oxa-1,3-butadienes **E** has a stronger impact on lowering of LUMO energy than the presence of the electron-withdrawing cyano group at C(3) position of 1-oxa-1,3-butadienes **D**. Electron-withdrawing groups: NO_2, CN, Cl, Br, in *para* position of aromatic ring of 1-oxa-1,3-butadienes **E** or **D** influence on raising of the reactivity. In contrast to this, the presence of an electron-donating groups: OCH_3, CH_3, in *para* position of aromatic ring of the heterodienes **D** and **E** influences on lowering of the reactivity. Hetero-Diels–Alder reactions of 5-cycloalkilidene-1,3-dimethylpyrimidine-2,4,6-triones **C**, 2-cycloalkilidene-3-oxo-3-phenylpropionitriles **B** and enaminocarbaldehyde **A**, required heating in boiling toluene and they needed more and more time to be completed in order: **C**, **B** and **A**. On the basis of the reaction times analysis, I can state that electron-donating alkyl groups at C(4) position of 1-oxa-1,3-butadienes **B** and **C** influence on lowering of the reactivity of the heterodienes **B** and **C** but an electron-donating impact of the amino group at C(4) position in heterodiene **A** is stronger.

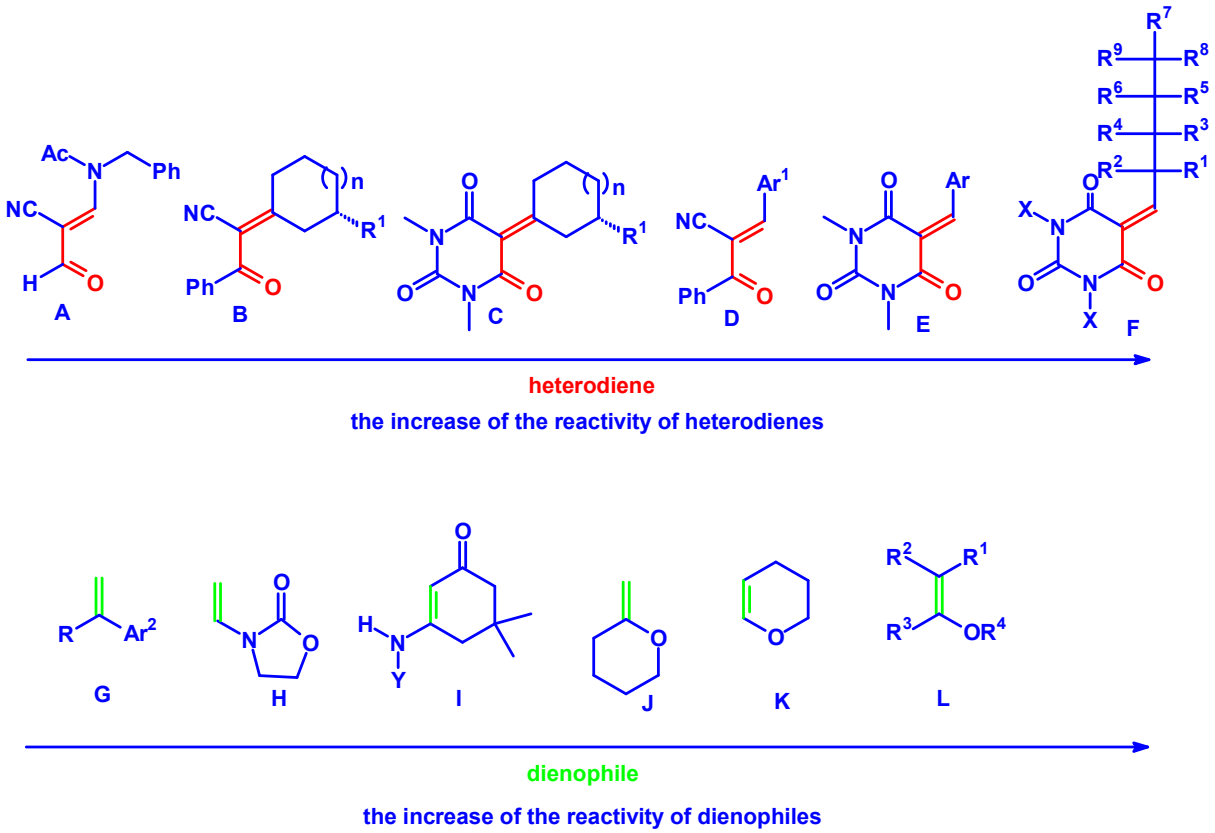


Fig. **10**. Reactivity comparison of investigated heterodienes and dienophiles.

Taking into account the dienophiles, I compared the reaction conditions and reaction time for cycloaddition reactions different dienophiles with 5-arylidene derivatives of 1,3-dimethylbarbituric acids **E**. On the basis of the analysis of the obtained results I proposed

for dienophiles **G-L** the reactivity order presented in the Figure 10. Styrenes **G** are alkenes without electron-donating groups and therefore the reactions of heterodienes **E** with styrenes **G** were performed in boiling toluene for 15-24 h. Styrenes **G** characterized the lowest reactivity. The presence of an electron-withdrawing substituent in *para* position of aromatic ring of heterodienes **E** was necessary to accomplish the cycloaddition with styrenes **G**. Cycloaddition reactions of *N*-vinyloxazolidin-2-one **H** also required heating in boiling toluene but reaction times were decreased (3-5 h) in comparison to styrenes **G**. Compounds **E** both with an electron-donating groups and with an electron-withdrawing groups in *para* position of aromatic ring can act as active heterodienes in reactions with dienophile **H**. The presence of an electron-donating amino group (substituted by an electron-withdrawing carboalkoxy group) at double bond of dienophile **H** increase the energy of HOMO dienophile **H**, contracts the E_{LUMO}(H)-E_{HOMO}(D) energy separation and hence increase the reactivity. Enol ethers **L** characterized the highest reactivity in cycloaddition reactions with 5-arylidene derivatives of 1,3-dimethylbarbituric acids **E**, because the reactions of these compounds were carried out at room temperature for 1-5 h. High reactivity of enol ethers **L** is due to the presence of an electron-donating alkoxy groups in dienophile system. Cycloaddition reactions of dimedone enamines **I** and reactions of 3,4-dihydro-2*H*-pyran **K** were carried out only with 5-ylidene derivatives of barbituric acids **F**. Similarly, the cycloaddition reactions of cyclic enol ether **J** were investigated only with 5-cycloalkylidene derivatives of 1,3-dimethylbarbituric acids **C**. Comparison of the reaction conditions and reaction time allowed on determination of the reactivity order: **I**, **J** and **K** (Fig. 10). Enol ethers **J** and **K** possessing an electron-donating alkoxy group characterized higher reactivity than dimedone enamines **I** equipped in an electron-donating amino group and electron-withdrawing carbonyl group.

My the most important achievements:

1. I applied for the first time in domino Knoevenagel/hetero-Diels–Alder reactions such active methylene compounds as: benzoylacetonitrile, methyl cyanoacetate, ethyl benzoylacetate, cyclohexane-1,3-dione derivatives, sulfide, sulfoxide and sulfone derivatives.
2. I showed that styrenes and *N*-vinyloxazolidin-2-one can act as valuable dienophiles in hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes with inverse-electron-demand.
3. I investigated cycloadditions of sterically hindered cycloalkylidene derivatives of benzoylacetonitile and 1,3-dimethylbarbituric acid with sterically hindered dienophiles.

4. I examined that 5-arylidene derivatives of barbituric acids can act as active heterodienes in hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes with inverse-electron-demand. I studied these reactions in water at room temperature. These reactions can potentially be applied in bioorthogonal chemistry.
5. Knoevenagel condensations of unprotected sugars and barbituric acids were carried out in water. A simple and efficient method for the synthesis of uracil derivatives containing a sugar moiety of potential pharmacological activity was described.
6. Dimedone enamines were applied for the first time as new dienophiles in hetero-Diels–Alder reactions with barbituric acid 5-ylidene alditols. By this simple cycloaddition reaction I introduce into fused uracil system such important for biological interaction groups as: different sugar moieties, enol moieties and different amino groups.
7. I determined configurations and conformations of the prepared cycloadducts on the basis of analysis of NMR and 2D NMR spectra and X-ray structure analysis.
8. I prepared a lot of uracil derivatives of potential biological activity.

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A1-A4 articles not belonging to the monothematic series of publications

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[H12] **A. Pałasz**, D. Cież, *Eur. J. Med. Chem*., **2015**, *97*, 582-611.

[H13] **A. Pałasz**, J. Kalinowska-Tłuścik, M. Jabłoński, *Tetrahedron*, **2013**, *69*, 8216-8227.

[H14] **A. Pałasz**, D. Cież, B. Musielak, J. Kalinowska-Tłuścik, *Tetrahedron* **2015**, *71*, 8911-8924.

II. Information on scientific outputs and teaching

1. Contact details

Dr Aleksandra Pałasz

Heterocyclic and Organometallic Chemistry Research Group

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2. Academic and research carieer

1985	graduate at Secondary Technical School of Chemistry in Cracow
1985-1990	graduate studies, chemistry, Faculty of Chemistry of Jagiellonian University
1990	MSc Thesis: Application of α,β-unsaturated cycloalkanones in synthesis of fluorine and phenanthrene derivatives", thesis supervisor professor Krystyna Bogdanowicz-Szwed, dr habil.
1990	MSc - Faculty of Chemistry, Jagiellonian University
1990-1997	employment as assistant trainee, postgraduate studies, in 1995 maternity leave
1997	PhD Thesis: „Synthesis of polyfunctionalized 3,4-dihydro-2*H*-pyrans by hetero-Diels–Alder reactions", thesis supervisor professor Krystyna Bogdanowicz-Szwed, dr habil.
1997	PhD - Faculty of Chemistry, Jagiellonian University
1997-2009	employment as assistant, Faculty of Chemistry, Jagiellonian University, 2001-2003 maternity leave and post-maternity leave. I was a member of Enamines Chemistry Research Group, head of group, Professor Krystyna Bogdanowicz Szwed, dr habil.

since 2009 as assistant professor in Faculty of Chemistry, Jagiellonian University. I was a member of Organic Physicochemistry Research Group (head of group, Barbara Rys, dr habil). Now, I work in Heterocyclic and Organometallic Chemistry Research Group (head of group, Dariusz Cież, dr habil).

3. List of publications in a chronological order

* Corresponding author

Articles published before a obtainment of Ph. D.

[1] K. Bodganowicz-Szwed*, M. Krasodomska, M. Lipowska, **A. Skonecka** (A. Pałasz), *Monatsh.Chem*., **1993**, *124*, 721-731: „Synthesis of pyridine derivatives by reactions of α,β-unsaturated nitriles with 2-oxo-cycloalkano carbothioic acid anilides".

5-Year IF (2014): **1.326**, the number of citations **5**

Approximate own contribution 20%

I synthesized some products. I did a spectroscopic analysis of the synthesized compounds. I prepared the date of some compounds to the experimental part of the article.

[2] K. Bodganowicz-Szwed*, M. Krasodomska, **A. Skonecka** (A. Pałasz), *Monatsh.Chem*., **1994**, *125*, 441-449: "Reaction of CH acids with 2-arylidenecycloalkanones – Synthesis of β–keto acid anilide derivatives of naphtalene, indene, fluorene, and phenanthrene".

5-Year IF (2014): **1.326**, the number of citations **0**

Approximate own contribution 30%

I synthesized some products. I did a spectroscopic analysis of the synthesized compounds. I prepared the date of some compounds to the experimental part of the article.

[3] K. Bogdanowicz-Szwed*, **A. Pałasz**, *Monatsh.Chem*., **1995**, *126*, 1341-1348: „Synthesis of functionalized 3,4-dihydro-2*H*-pyrans by hetero-Diels−Alder reaction of an enaminoketone with enol ethers".

5-Year IF (2014): **1.326**, the number of citations **17**

Approximate own contribution 50%

I synthesized all products. I did a spectroscopic analysis of the synthesized compounds. I prepared all schemes to the publication. I prepared the date to the experimental part of the article.

[4] K. Bogdanowicz-Szwed*, J. Grochowski, **A. Pałasz**, B. Rys, P. Serda, D. Soja, *Liebigs Ann*., **1996**, *9*, 1457-1462: „The conjugate addition of benzoyl(thioacetanilides) to nitroalkenes – synthesis of functionalized thiophenes and pyrroles". (*European Journal of Organic Chemistry*)
5-Year IF (2014): **3.034**, the number of citations **5**
Approximate own contribution 10%
I synthesized some products. I did a spectroscopic analysis of the synthesized compounds. I prepared the date of some compounds to the experimental part of the article.

[5] K. Bogdanowicz-Szwed*, **A. Pałasz**, *Wiad. Chem*., **1996**, *50*, 213-239: „Synteza układów piranowych w reakcjach cykloaddycji heterodienowej".
Journal without IF
Approximate own contribution 40%
I prepared all schemes for publication. I participated in proofreading of the manuscript.

[6] K. Bogdanowicz-Szwed*, **A. Pałasz**, *Monatsh.Chem*., **1997**, *128*, 1157-1172: „Hetero-Diels−Alder reactions of 3-aryl-2-benzoyl-2-propenenitriles with enol ethers. Synthesis of 2-alkoxy-3,4-dihydro-2*H*-pyran- 5-carbonitriles".
5-Year IF (2014): **1.326**, the number of citations **16**
Approximate own contribution 50%
I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared the date to the experimental part of the article.

Articles published after a obtainment of Ph. D.

[7] K. Bogdanowicz-Szwed*, **A. Pałasz**, *Monatsh.Chem*., **1999**, *130*, 795-807: „Intramolecular hetero-Diels−Alder reactions of functionalized α,β-unsaturated carbonyl compounds: Polycyclic 2*H*-pyran derivatives".
5-Year IF (2014): **1.326**, the number of citations **15**
Approximate own contribution 50%
I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared the date to the experimental part of the article.

[8] K. Bogdanowicz-Szwed*, **A. Pałasz**, *Z. Naturforsch. B.*, **2001**, *56*, 416-422: "Synthesis of 3,4-dihydro-2*H*-pyrans by hetero-Diels−Alder reactions of functionalized α,β-unsaturated carbonyl compounds with styrenes".
5-Year IF (2014): **0.690**, the number of citations **10**
Approximate own contribution 50%
I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared the date to the experimental part of the article.

[9] K. Bogdanowicz-Szwed*, **A. Pałasz**, *Monatsh.Chem.*, **2001**, *132*, 393-401:„ Polycyclic 2*H*-pyran derivatives by intramolecular hetero-Diels−Alder reactions of α-*s*ulfur-substituted–α,β-unsaturated carbonyl compounds".
5-Year IF (2014): **1.326**, the number of citations **8**
Approximate own contribution 50%
I synthesized all products. I prepared all schemes to the publication. I did a spectroscopic analysis of the synthesized compounds. I prepared the date to the experimental part of the article.

[10] A. Pałasz*, *Org.Biomol.Chem.*, **2005**, *3*, 3207-3212: „Synthesis of 3,4-dihydro-2*H*-pyrans by hetero-Diels−Alder reactions of functionalized unsaturated carbonyl compounds with *N*-vinyl 2-oxazolidinone".
5-Year IF (2014): **3.382**, the number of citations **24**
Unassisted work
My own idea to take up this topic in my research. I made plans of the synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[11] A. Pałasz*, K. Jelska, M. Ożóg, P. Serda, *Monatsh.Chem.*, **2007**, *138*, 481-488: „5-Arylidene derivatives of Meldrum's acid as synthons in pyrano[4,3-*b*]pyran synthesis".
5-Year IF (2014): **1.326**, the number of citations **8**
Approximate own contribution 60%.

My own idea to take up this topic in research. I made plans of the synthesis. I synthesized the majority of the products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[12] A. Pałasz*, K. Bogdanowicz-Szwed, *Monatsh.Chem*., **2008**, *139*, 647-655:„Hetero-Diels–Alder reaction of propenenitriles with enol ethers: a convenient approach to functionalized 3,4-dihydro-2H-pyrans".
5-Year IF (2014): **1.326**, the number of citations **5**
Approximate own contribution 70%.
I synthesized all products. I did a spectroscopic analysis of the synthesized compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[13] A. Pałasz*, *Monatsh.Chem*., **2008**, *139*, 1397-1404:„Three-component one-pot synthesis of fused uracils – pyrano[2,3-*d*]pyrimidine-2,4-diones".
5-Year IF (2014): **1.326**, the number of citations **10**
Unassisted work
My own idea to take up this topic in my research. I made plans of synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[14] A. Pałasz*, *Synthesis*, **2010**, 4021-4032: "A green approach to the synthesis of fused uracils: Pyrano[2,3-*d*]pyrimidines. On – water one-pot synthesis by domino Knoevenagel/Diels–Alder reactions".
5-Year IF (2014): **2.389**, the number of citations **12**
Unassisted work
My own idea to take up this topic in my research. I made plans of synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[15] A. Pałasz*, T. Pałasz, *Tetrahedron*, **2011**, *67*, 1422-1431: ”Knoevenagel condensation of cyclic ketones with benzoylacetonitrile and *N,N’* – dimethylbarbituric acid. Application of sterically hindered condensation products in the synthesis of spiro and dispiropyrans by hetero-Diels–Alder reactions”.

5-Year IF (2014): **2.675**, the number of citations **9**

Approximate own contribution 80%.

My own idea to take up this topic in research. I made plans of the synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[16] A. Pałasz*, *Monatsh.Chem*., **2012**, *143*, 1175-1185:„Synthesis of fused uracils: pyrano[2,3-*d*]pyrimidines and 1,4-bis(pyrano[2,3-*d*]pyrimidinyl)benzenes by domino Knoevenagel/Diels–Alder reactions”.

5-Year IF (2014): **1.326** , the number of citations **3**

Unassisted work

My own idea to take up this topic in my research. I made plans of synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[17] A. Pałasz*, J. Kalinowska-Tłuścik, M. Jabłoński, *Tetrahedron*, **2013**, *69*, 8216-8227: „Application of 2,4,6-trioxo-pyrimidin-5-ylidene alditols in the synthesis of pyrano[2,3-*d*]pyrimidines containing a sugar moiety by hetero-Diels–Alder reactions and by conjugate Michael addition-cyclizations”.

5-Year IF (2014): **2.675**, the number of citations **6**

Approximate own contribution 80%.

My own idea to take up this topic in research. I made plans of the synthesis. I synthesized all products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[18] A. Pałasz*, D. Cież, *Eur. J. Med. Chem*., **2015**, *97*, 582-611: “In search of uracil derivatives as bioactive agents. Uracils and fused uracils: Synthesis, biological activity and applications”.

5-Year IF (2014): **3.946**, the number of citations **4**

Approximate own contribution 85%.

My own idea to take up this topic in review. I did overview of scientific literature. I wrote article. I prepared the majority of schemes. I corresponded with editor and reviewers.

[19] A. Pałasz*, D. Cież, B. Musielak, J. Kalinowska-Tłuścik, *Tetrahedron* **2015**, *71*, 8911-8924: "Application of dimedone enamines as dienophiles: Stereoselective synthesis of amino enols of fused uracils containing a sugar moiety by hetero-Diels–Alder reactions of barbituric acid 5-ylidene alditols with dimedone enamines".

5-Year IF (2014): **2.675**, the number of citations **1**

Approximate own contribution 65%.

My own idea to take up this topic in research. I made plans of the synthesis. I synthesized the majority of the products. I did a spectroscopic analysis of the prepared compounds. I wrote the whole manuscript with all schemes and the experimental part of the article. I corresponded with an editor and reviewers.

[20] D. Cież*, **A. Pałasz**, B. Trzewik, *Eur. J. Org. Chem.* **2016**, 1476-1493: "Titanium Enolate Chemistry at the Beginning of the 21th Century".

5-Year IF (2014): **3.034,** the number of citations **0**

Approximate own contribution 15%

I was involved in overview of scientific literature. I prepared some schemes in the publication.

[21] A. Pałasz* *Top. Curr. Chem.*, **2016**, *374 (3)*, 1-37: „Recent advances in inverse-electron-demand hetero-Diels−Alder reactions of 1-oxa-1,3-butadienes". DOI: 10.1007/s41061-016-0026-2, First online: 20 April 2016 as Open Access Article

5-Year IF (2014): **5.325,** the number of citations **0**

Unassisted work

My own idea to take up this topic in review. I did an overview of the scientific literature. I wrote the whole article and I corresponded with an editor and reviewers.

4. Information on the number of citations, summary IF and the H-index

Indeks Hirscha*: **8**

The number of citations: **158**

Summary IF: **43.085** (5-Year IF, 2014)

Summary IF of **14** publications **H1-H14**: **31.713**

*Data from Web of Science for Aleksandra Pałasz and Aleksandra Skonecka (maiden name) 26. 04. 2016

5. Research projects

List of the proposals for financing of scientific projects in the field of basic research – OPUS submitted to the NCN

I was an author and planned principal investigator of five scientific projects submitted to the NCN. Projects **No. 1**, **No. 2**, **No. 3**, **No. 5** were not qualified by panel I, whereast project **No. 4** was not qualified by panel II.

1) Project title: „Research of hetero-Diels–Alder cycloadditions leading to asymmetric synthesis of uracil derivatives and aimed at potential application in bioorthogonal chemistry."
ID: 309043, December **2015,** not qualified by panel I.

2) Project title: „Synthesis of *C*-glycosides by Knoevenagel condensation of unprotected sugars and 1,3-dicarbonyl compounds in water and their application as precursors in stereocontrolled synthesis of new *C*-glycosides."
ID: 235484, December **2013**, not qualified by panel I.

3) Project title: „Synthesis of *C*-glycosides by Knoevenagel condensation of carbohydrates and 1,3-dicarbonyl compounds in water and their application as precursors for synthesis of new *C*-glycosides with potential pharmacological activity."
ID: 218087, June **2013**, not qualified by panel I.

4) Project title: „Synthesis of *C*-glycosides by Knoevenagel condensation of carbohydrates and 1,3-dicarbonyl compounds in water and their application in hetero-Diels–Alder reactions as precursors for synthesis of new *C*-glycosides."

ID: 202127, December **2012**, not qualified by panel II.

5) Project title: „Asymmetric synthesis of potential pharmacological activity fused uracils by Knoevenagel condensations and hetero-Diels–Alder reactions."
ID: 150676, June 20**11**, not qualified by panel I.

Grants from Faculty Reserve of Own Research (Polish WRBW) of Faculty of Chemistry of Jagiellonian University

I was an author and principal investigator of the five scientific projects:
1) Project title: „Synthesis of fused uracils with potential pharmacological activity by domino Knoevenagel/Diels-Alder reactions."
Project ID: WRBW/WCH/6/2010, grant 1164 PLN
Publication: A. Pałasz „A green approach to the synthesis of fused uracils: pyrano[2,3-*d*]pyrimidines. On water one – pot synthesis by domino Knoevenagel/Diels–Alder reactions", *Synthesis*, **2010**, *23*, 4021-4032.

2) Project title: „Diastereo- and enantioselective synthesis of spiropyrans by hetero-Diels-Alder reaction. Synthesis of new heterocycles with potential biological activity."
Project ID: WRBW/WCH/7/2009, grant 1000 PLN
Publication: A. Pałasz, T. Pałasz, „Knoevenagel condensation of cyclic ketones with benzoylacetonitrile and *N,N′*-dimethylbarbituric acid. Application of sterically hindered condensation products in the synthesis of spiro and dispiropyrans by hetero-Diels–Alder reactions", *Tetrahedron*, **2011**, *67*, 1422-1431.

3) Project title: „Diastereo- and enantioselective synthesis of spiropyrans by hetero-Diels–Alder reaction. Synthesis of new heterocycles with potential biological activity."
Project ID: WRBW/WCH/7/2008, grant 1719 PLN
Publication: A. Pałasz, K. Bogdanowicz-Szwed „Hetero-Diels–Alder reaction of propenenitriles with enol ethers: a convenient approach to functionalized 3,4-dihydro-2*H*-pyrans", *Monatsh*. *Chem*., **2008**, *139*, 647-655.

4) Project title: „Diastereoselective synthesis of 2*H*-pyrano[2,3-*d*]pyrimidine-2,4-diones by hetero-Diels–Alder reaction. Synthesis of new biological activity heterocycles."

Project ID: WRBW/WCH/7/2007, grant 1000 PLN

Publication: A. Pałasz „Three-component one-pot synthesis of fused uracils- pyrano[2,3-*d*]pyrimidine-2,4-diones", *Monatsh*. *Chem*., **2008**, *139*, 1397-1404.

5) Project title: „Diastereoselective synthesis of pyrano[4,3-*b*]pyranes by hetero-Diels-Alder reaction"

Project ID: WRBW/WCH/7/2006, grant 1200 PLN

Publication: A. Pałasz, K. Jelska, M. Ożóg, P. Serda "5-Arylidene derivatives of Meldrum's acid as synthons in pyrano[4,3-*b*]pyran synthesis", *Monatsh*. *Chem*., **2007**, *138*, 481-488.

Grant ACK Cyfronet

Calculation of frontier molecular orbital FMO energies of selected heterodienes and dienophiles for hetero-Dielsa–Alder reactions of 1-oxa-1,3-butadienes and alkenes by semi-empirical AM1 and PM3 methods and ab initio Hartree-Fock method using HF/3-21G basis set.

Grant No. MNiSW/SGI3700/UJ/084/2009. Computing on SGI Altix 3700 (Gaussian 03 suite of programs).

6. Research experiences

I have performed all my scientific research as assistant trainee, PhD student, assistant and assistant professor at Department of Organic Chemistry of Faculty of Chemistry of Jagiellonian University. I have no other research experience – long term research stays in polish and foreign scientific centers.

I participated in following scientific conferences:

1. IX Symposium of Heteroorganic Chemistry PTChem, Łódź, 2006, poster: "Application of 5-arylidene derivative of Meldrum acid in synthesis of pyrano[4,3-*b*]pyrans".

2. VIII Symposium of Heteroorganic Chemistry PTChem, Łódź, 2005 poster: "Diastereoselective synthesis of 3,4-dihydro-2*H*-pyrans by hetero-Diels–Alder reactions of *α,β*-unsaturated carbonyl compounds and *N*-vinyl-2-oxazolidynone".

3. 17th International Congress of Heterocyclic Chemistry 1-6 August 1999, Vienna, K. Bogdanowicz-Szwed, A. Pałasz poster: "Synthesis of policyclic 2*H*-Pyran Derivatives by intramolecular hetero-Diels–Alder Reaction".

4. 40th Congress of PTChem 22-26. 09.1997 Gdańsk, K. Bogdanowicz-Szwed, A. Pałasz poster „ Synthesis of polyfunctional 3,4-dihydro-2*H*-pyrans by hetero-Diels–Alder reactions".

5. 12th Symposium on Chemistry of Heterocyclic Compounds and 6th Blue Danube Symposium on Heterocyclic Chemistry 1-4 September 1996 Brno, K. Bogdanowicz-Szwed, J. Grochowski, A. Pałasz, B. Rys, P. Serda, D. Soja poster: " Synthesis of functionalized thiophenes and pyrroles by the coniugate addition of benzoyl(thioacetanilides) to nitroalkanes".

6. 39th Congress of PTChem, Poznań 23-26 September 1996, K. Bogdanowicz-Szwed, J. Grochowski, A. Pałasz, B. Rys, P. Serda, D. Soja poster: "Reactions of addition-cyclization of nitroalkenes to benzoylthioacetanilides".

7. I Symposium "New directions in heterocycle synthesis", Kraków 17-18 November 1995, K. Bogdanowicz-Szwed, A. Pałasz komunikat: „ Hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes with vinyl ethers and enamines".

8. 3rd Blue Danube Symposium on Heterocyclic Chemistry, 25-28th April, 1993, Sopron, Hungary, K. Bogdanowicz-Szwed, M. Krasodomska, M. Lipowska, B. Rys, A. Skonecka (Pałasz) poster: Synthesis of functionalized pyridines by Michael addition of CH acids to α,β-unsaturated nitriles".

9. II Symposium of Organic Chemistry Arturówek k/ Łodzi 3-4. 06. 1993, K. Bogdanowicz-Szwed, A. Skonecka (Pałasz) poster: „ Reactions of enaminoaldehydes with vinyl ethers and enamines".

7. Reviews for scientific journals

I was reviewer of 6 papers submitted to the following scientific journals:

1) Monatschefte fur Chemie (Springer) 2 papers

2) Molecular Diversity (Springer) 1 paper

3) European Journal of Medicinal Chemistry (Elsevier) 1 paper

4) Comprehensive Organic Chemistry Experiments for the Laboratory Classroom (Royal Society of Chemistry) 2 chapters in the book

8. Teaching

I lectured courses for students from: Faculty of Chemistry of the Jagiellonian University in Kraków, Faculty of Biology and Earth Sciences of the Jagiellonian University in Kraków and Faculty of Biochemistry, Biophysics and Biotechnology of the Jagiellonian University in Kraków.

Courses lectured:

1) Course: Organic Chemistry, Laboratory class for the students of II-year of chemistry (five-year graduate studies)

2) Course: Organic Chemistry, Discussion class for the students of I-year of chemistry (five-year graduate studies)

3) Course: Organic Chemistry, Discussion class for the students of I-year of chemistry (five-year graduate studies)

4) Course: Organic Chemistry, Laboratory class for the students of II-year of environmental studies

5) Course: Organic Chemistry, Discussion class for the students of II-year of environmental studies

6) Course: Organic Chemistry – Part II: Long Course, Laboratory class for the students of I-year of biology

7) Course: Organic Chemistry – Part II: Basic Course, Laboratory class for the students of I-year of biology

8) Course: Organic Chemistry – Part I, Discussion class for the students of I-year of neurobiology

9) Course: Organic Chemistry – Part II, Laboratory class for the students of I-year of neurobiology

10) Course: Organic Chemistry, Discussion class for the students of I-year of biology and geology. I coordinated this course.

11) Course: Organic Chemistry, Laboratory class for the students of I-year of biology and geology. I coordinated this course.

12) Laboratory class for graduate students of chemistry.

I described the example of application of 2,4,6-trioxo-pyrimidin-5-ylidene alditol in the synthesis of pyrano[2,3-*d*]pyrimidine possessing a sugar moiety by hetero-Diels–Alder reaction. The hetero-Diels–Alder reaction of xylose derivative with etyl-vinyl ether (Scheme

19, page 34) was desrcibed in detail in chapter of the book titled: „Comprehensive Organic Chemistry Experiments for the Laboratory Classroom" C. A. M. Afonso, R. Franzen, B. Tan, D. Simao, A. Trindade, J. Coelho, N. Candeias, Royal Society of Chemistry, **2016**. Chapter 171, page 769-773, **A. Pałasz**, D. Cież: „Application of 2,4,6-trioxo-pyrimidin-5-ylidene alditol in the synthesis of pyrano[2,3-*d*]pyrimidine containing a sugar moiety by hetero-Diels–Alder reaction." (ISBN: 9781849739634, Advance Book Information – Royal Society of Chemistry, Publishing date: 07/07/2016). Students can synthesize *cis* and *trans* diastereoisomers of fused uracil by simple and efficient method. This practical textbook contains organic chemistry experiments for teaching in the laboratory at the undergraduate level. The editorial team have collected contributions from around the world and standardized them for publication.

I was a thesis supervisor of the six master's thesis:

1) Katarzyna Jelska, „Synthesis of functionalized pyrano[4,3-*b*]pyrans by heterodiene cycloaddition reactions of 5-arylidene Meldrum's acid derivatives with vinyl compounds", 2006, Faculty of Chemistry of the Jagiellonian University, chemistry.

2) Monika Ożóg, „Synthesis of 5-arylidene Meldrum's acid derivatives, theirs application in hetero-Diels–Alder reaction and in conjugated addition-cyclization", 2006, Faculty of Chemistry of the Jagiellonian University, chemistry.

3) Anna Bednarek, „Knoevenagel condensation reaction of cyclic ketones with *N*,*N*-dimethylbarbituric acid. The use of sterically hindered condensation products in the reactions of the Diels–Alder cycloaddition", 2011, Faculty of Chemistry of the Jagiellonian University, chemistry.

4) Anna Górak, „Green Chemistry - reactions of Knoevenagel condensations between barbituric acid and carbohydrates in water. Application of condensation products in addition-cyclization and Diels–Alder reactions", 2012, Faculty of Chemistry of the Jagiellonian University, environmental studies.

5) Ewelina Chwałek, „Green Chemistry – synthesis of 5-pyrimidinylidene derivatives of sugars "in water" conditions and their application in cycloaddition reactions", 2012, Faculty of Chemistry of the Jagiellonian University, environmental studies.

6) Agnieszka Koczyk, „Green Chemistry – Diels–Alder reactions in water and on water", 2014, Cardinal Stefan Wyszyński University in Warsaw, Department of Mathematics and Natural, School of Science.

I was a thesis supervisor of the six bachelor thesis compiled on Faculty of Chemistry of the Jagiellonian University:

1) Anna Górak, „Green chemistry - synthesis of fused uracils by Knoevenagel condensations "on water" and Diels–Alder reactions without solvent", 2010, environmental studies.

2) Ewelina Chwałek, „"Green chemistry" - synthesis of fused uracils by Knoevenagel condensations "on water" and Diels–Alder cycloadditions", 2010, environmental studies.

3) Justyna Celka, „Green chemistry – Knoevenagel condensations and Diels–Alder cycloaddition reactions", 2011, environmental studies.

4) Michał Bocheński „Green chemistry – synthesis of fused uracils with potential pharmacological activity" 2012, environmental studies

5) Anna Bogacka, „Green chemistry - Knoevenagel condensation reaction carried out in the aqueous environment", 2011, environmental studies.

6) Karolina Lorek, „The study of the reactions of Diels–Alder cycloaddition of different chiral heterodienes with dienophiles with electron - donating substituents", 2015, chemistry.

I was a thesis supervisor of the three projects compiled on Faculty of Chemistry of the Jagiellonian University:

1) Agnieszka Koczyk, „Green chemistry - Diels–Alder reactions in water and on water", 2010, chemistry.

2) Monika Zapart, „Application of barbituric acid and its derivatives in synthesis of potential pharmacological activity compounds", 2010, chemistry.

3) Anna Bednarek, „Application of 5-cycloalkilidene derivatives of barbituric acid as dienes in Diels–Alder reactions", 2010, chemistry.

I was a reviewer of the nine master's thesis and bachelor thesis compiled on Faculty of Chemistry of the Jagiellonian University:

1) master's thesis, Grzegorz Łopatkiewicz, „Asymmetric synthesis of ketohexoses with the use of dihydroxyacetone", 2013, thesis supervisor: prof. dr habil. Jacek Młynarski, chemistry.

2) master's thesis, Anna Adamkiewicz, „Examination of regio- and enantioselectivity of asymmetric vinylogous Mukaiyamy aldol reaction", 2013, thesis supervisor: prof. dr habil. Jacek Młynarski, chemistry.

3) master's thesis, Izabela Mac, „Studies on the stereoselective addition of organomagnesium and organocerium reagents to chiral ketimines and cyclic ketones", 2014, thesis supervisor:

dr habil. Dariusz Cież, chemistry.

4) master's thesis, Mirosław Nawój, „Study of the effect of benzyl groups in the *O*-3,4,6 positions of monosaccharides on the stereoselectivity in glycosylation reaction", 2014, thesis supervisor: prof. dr habil. Jacek Młynarski, chemistry.

5) master's thesis, Marcin Szewczyk, „Chiral porphyrins synthesis and their application in asymmetric reduction of ketones", 2014, thesis supervisor: prof. dr hab. Jacek Młynarski, chemistry.

6) master's thesis, Magdalena Antkowiak, „Application of cellobiose and lactose in synthesis of some natural compounds", 2015, thesis supervisor: prof. dr habil. Jacek Młynarski, chemistry.

7) master's thesis, Matylda Stefaniak, „The synthesis of selectively protected derivatives of annose and mannosamine", 2015, thesis supervisor: prof. dr habil. Jacek Młynarski, chemistry.

8) bachelor thesis, Alicja Kozak, „Synthesis of benzoxazocines derivatives", 2014, thesis supervisor: dr habil. Barbara Rys, chemistry.

9) bachelor thesis, Dominik Sadzik, „Synthesis of the small molecule interaction of PD1-PDL1 inhibitors", 2015, thesis supervisor: prof. dr habil. Tadeusz Holak, chemistry.

Moreover:

1) I prepared a set of questions in organic chemistry to the undergraduate exam for the students of chemistry of Faculty of Chemistry of the Jagiellonian University in Kraków.

2) I prepared script in organic chemistry for students of II-year of environmental studies.

3) I prepared demonstration during Open Days of Faculty of Chemistry of the Jagiellonian University in Kraków.

4) I participated in preparing of celebrations of 120-year of Department of Organic Chemistry of Faculty of Chemistry of the Jagiellonian University in Kraków.

5) I was a member of the exam commission at studies recruitment on Faculty of Chemistry of the Jagiellonian University in Kraków.

Aleksandra Pastuch