BULGARIAN ACADEMY OF SCIENCES

INSTITUTE OF ORGANIC CHEMISTRY WITH CENTER OF PHYTOCHEMISTRY

HABILITATION THESIS

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Application for the academic position of Professor in the Professional Field 4.2. Chemical Sciences according to the Classifier of the Areas of Higher Education and the Professional Fields (Scientific Specialty “Organic chemistry”)
for
Laboratory “Organic Synthesis and Stereochemistry”

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I. Introduction

The presented herein habilitation thesis covers the period of my independent research career after I was appointed as an Associate professor at IOCCP-BAS (2017-2022). Five of the scientific publications (Q1) are dedicated to the development of the biogenic furanic platform and are included in indicator "B".[i] Eleven publications Q1 and one Q4 are included in indicator "Г".[ii] For clarity of the discussion, the scientific contributions from the publications, included in indicator "B" are discussed in more details. The presented herein research falls into the area of organic synthesis and green chemistry. The scientific contributions are both fundamental and applied and can be summarized in the following main directions:

- New methods for the intensification of the furanic plataform;
- Synthetic modifications of natural products;
- Others.

II. Scientific contributions

1. New methods for the intensification of the furanic plataform

Nowadays, biorefinery is considered the most promising approach to reduce the use of fossil resources. Among other reported biorenewable platform molecules, the furan derivatives have attracted much attention due to their availability from the carbohydrate fraction of the lignocellulosic biomass. Two main platforms, namely furfural derived from pentoses and 5-hydroxymethyl furfural (HMF) derived from hexoses, have emerged as the most promising candidates. The production of furfural from lignocellulosic biomass is currently one of the notable examples of an industrialized biorefinery process. Alongside furfural, many of its derivatives, for instance furfuryl alcohol (FA) and tetrahydrofurfuryl alcohol (THFA), are also industrial products. On the other hand, HMF is still in a pre-industrial stage of development.

Despite their structural similarity, the drawbacks that hamper wider incorporation of furfural and HMF in the industry largely differ. Furfural and FA are relatively low functionalized organic compounds, which often limits the scope of their application. Owning an additional substituent in the furan ring HMF is undoubtedly endowed with a greater synthetic potential. Unfortunately, this potential is limited due to the unstable nature of this compound. The lack of thermal and storage stability and occurrence of side reactions during the processing of HMF limits its potential as biorenewable platform molecule.

1.1. Achmatowicz rearrangement as a tool for the synthesis of pentane-1,2,5-triol from furfuryl alcohol[iii]

The biomass-derived alcohols are widely used as monomers in the production of polyesters, polyurethanes and polyethers, and as fuel additives. Currently, the portfolio of biorenewable

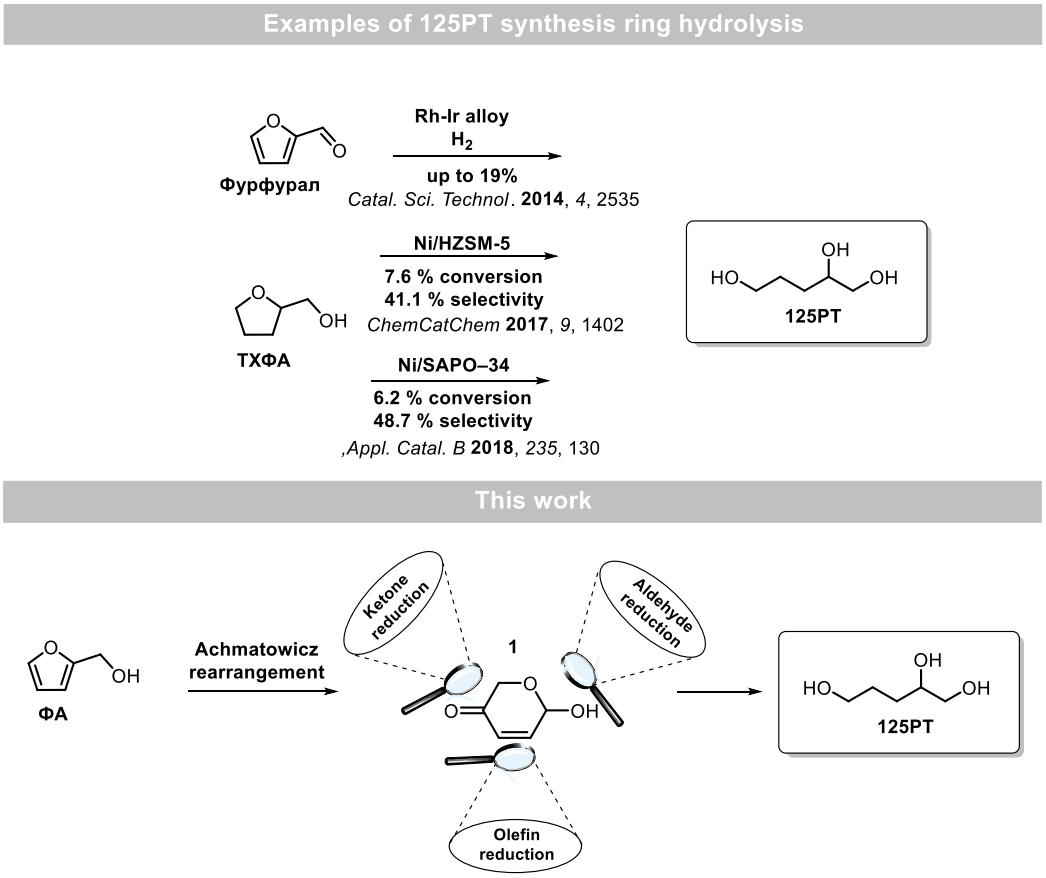
[i] Marked with B

[ii] Marked with Г

[iii] This scientific contribution has been recognized by “Acad. Bogdan Kurtev” 2017-2019 award for a Bulgarian scientific achievement in organic chemistry

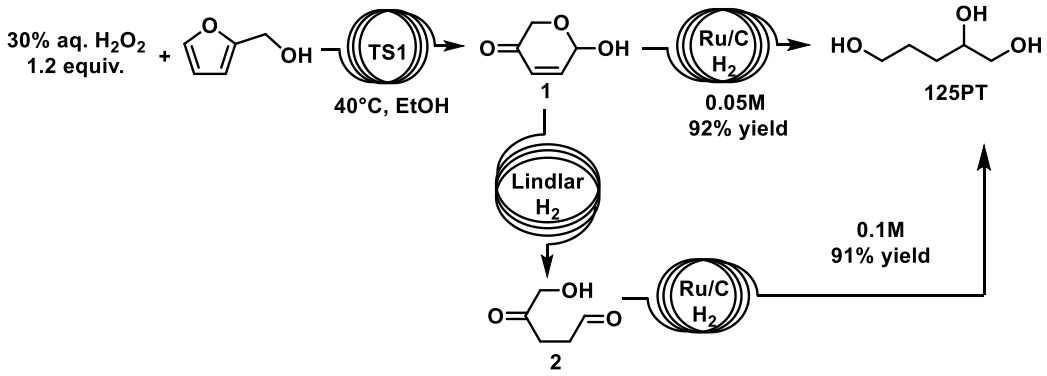
C5 alcohols available from furans includes 1,5-pentanediol, 1,2-pentanediol, 1,4-pentanediol., The direct synthesis of pentane-1,2,5-triol (125PT), a homolog of the industrially relevant butane-1,2,4-triol, from furfural and FA possess a great challenge. The reported methods for the preparation 125PT rely on the catalytic hydrolysis of the ring with C-O bond cleavage. This approach proved troublesome providing 125PT in low yields.

We have proposed a new and original synthetic strategy to achieve pentane-1,2,5-triol (125PT) from FA, which does not involve the hydrolytic ring cleavage (Scheme 1).



Scheme 1. New synthetic strategy for the synthesis of 125ПТ.

The strategy involves Achmatowicz rearrangement (Scheme 1) and subsequent hydrogenation of the reactive intermediate **1**. The transformation has been initially achieved in a liquid phase [1B] using commercial 5% Ru/C catalyst (Scheme 2). Aiming at a more attractive model for industrial application, we have developed a Flow chemistry method using ThalesNano H-Cube® Pro reactor. In a two-step continuous process 125PT was obtained in excellent yield using up to 0.05M solution of FA. The hydrogenation of the olefin in the structure of **1** was found to be the rate-determining step. Therefore, we included a third flow reactor containing a Lindlar catalyst. This allowed more efficient hydrogenation of **1** to intermediate **2** leading to two-fold increased productivity in up to 0.1M.

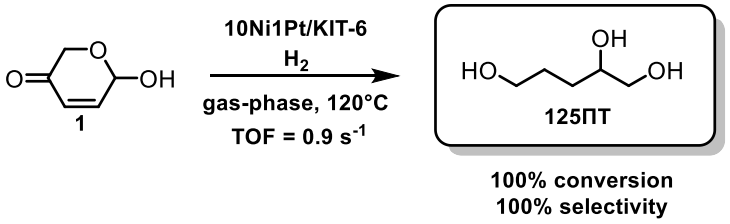


Scheme 2. Flow chemistry synthesis of 125PT.

Notwithstanding the high yield of 125PT and the implementation of flow chemistry methodology, several drawbacks remained namely, the high price of the catalysts, the very high catalyst/substrate ratios and the large influence of the solvent and the concentration of the feeding solution.

With the idea to overcome these drawbacks, we have developed a gas-phase hydrogenation of the Achmatowicz intermediate **1**.[2B] Six new mono- and bicomponent SBA-15 and KIT-6 mesoporous silicates containing Ni and/or Pt nanoparticles were prepared and fully characterized. All the newly obtained catalysts exhibited very high selectivity in the hydrogenation of **1** to 125PT. The catalytic activity was dominated by the metal components, while the type of mesoporous silica support exhibited a strong effect on the state and dispersion of the active sites. The monocomponent Pt-modified 1Pt/KIT-6 and 1Pt/SBA-15 catalysts show much higher catalytic activity compared to the monocomponent Ni modified 10Ni/KIT-6 and 10Ni/SBA-15. The highest TOF value was observed for 10Ni1Pt/KIT-6, indicating the favorable synergistic effect of the modifications with Ni and Pt nanoparticles and the pore structure of KIT-6. A drop in the activity was registered for the monocomponent Pt-modified 1Pt/KIT-6 and 1Pt/SBA-15 catalysts with time on stream 3 h, whereas the bicomponent samples exhibited stable activity.

These results led to the development of a highly selective process for the preparation of 125PT using 10Ni1Pt/KIT-6 as a catalyst. The method owns significant green chemistry merits, such as mild and simpler solvent free technology that operates at atmospheric pressure (Scheme 3).

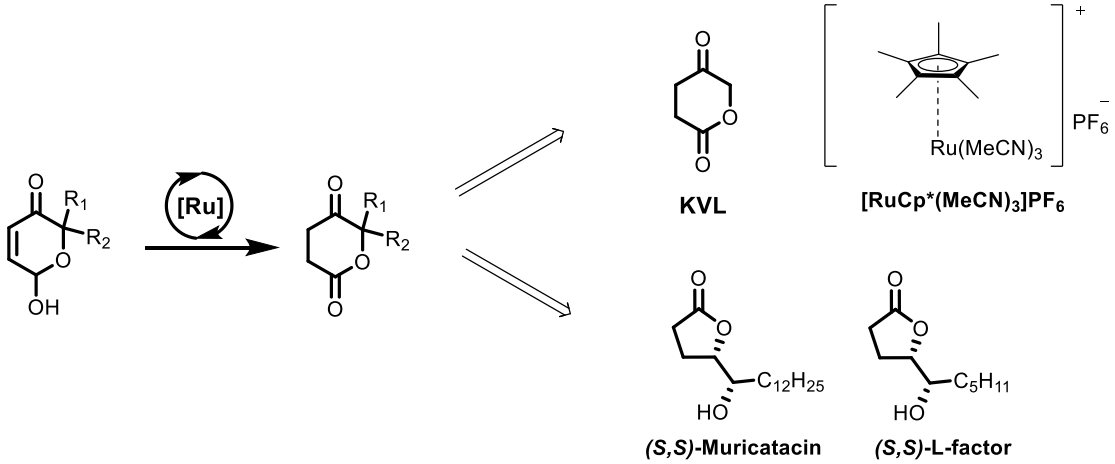


Scheme 2. Green chemistry synthesis of 125PT.

In collaboration with the Institute of Polymers, BAS 125PT was used as a monomer for the preparation of a new nanogel with an application drug delivery system for doxorubicin.[3Г] The nanogel is characterized by its biodegradability, high encapsulation capacity for doxorubicin and efficient drug protection against photolysis.

1.2. Ru-catalysed redox isomerization of Achmatowicz derivatives

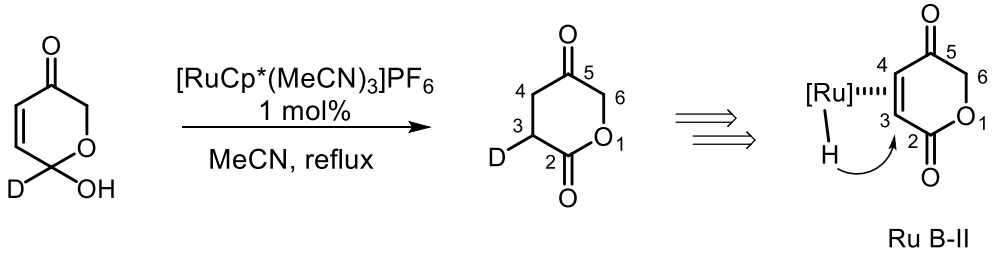
By using Ru-catalyzed allylic alcohol isomerization of Achmatowicz derivatives, we have developed a new synthetic route towards biorenewables and biologically active lactones. In contrast with the existing methods that employ reduction of the ketone, our approach involves reduction of the olefin resulting in 4-keto-δ-valerolactones (Scheme 4).[4B]



Scheme 4. Ru-catalysed isomerization of Achmatowicz derivatives and downstream applications.

The method was applied to the synthesis of the important monomer 4-ketovelerolactone and to the total asymmetric synthesis of two important biologically active natural acetogenins, namely (*S*,*S*)-Muricatacin and (*S*,*S*)-L-factor

The mechanistic insights of this formally redox-neutral intramolecular process were studied computationally and by deuterium labeling. The reaction was performed using D-labeled Achmatowicz product resulting in deuterium incorporation solely at position 3 (Scheme 5). This observation is in contrast with the reported mechanisms which operate via intramolecular 1,3-hydride shift leading to deuterium incorporation at position 4.



Scheme5. Mechanistic insights

It was found that, due to the specificity of the substrates the reaction proceeds via a different mechanism, which involves the formation of a Ru V-II complex. The later undergoes1,4-hydride addition relative to the ketone governed by electrophilic and/or thermodynamic reasons, which was also confirmed by DFT calculations.

1.3. New approaches to circumvent the instability of HMF.

The problems arising from the instability of the HMF molecule are well-known to both the scientific community and the industry. HMF tends to self-polymerase leading to the formation of tarry substances known as "humins." We pioneered a methodology for HMF stabilization

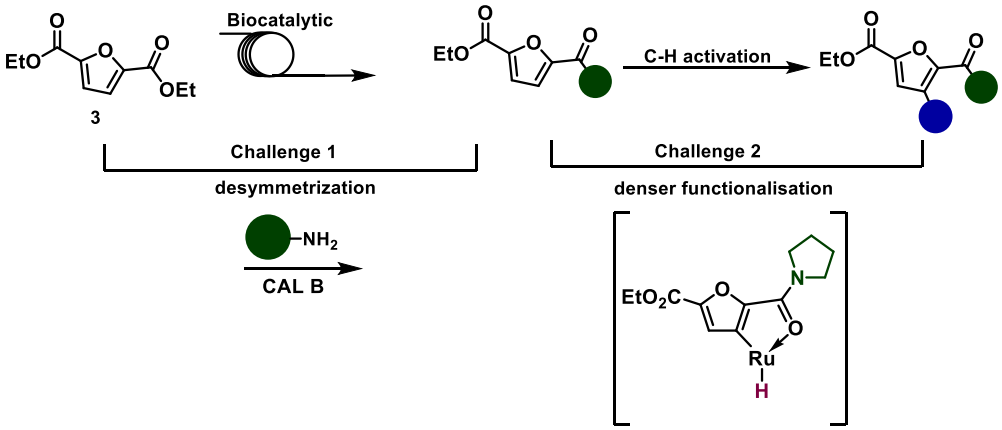
based on the use of the readily available and cheap sodium salt $Na_2S_2O_4$, which was shown to inhibit the undesired dimerization and polymerization reactions.[5B] It is known that, HMF forms a self-organized network that favors the self-polymerization. Some compounds, such as choline chloride, disrupt this self-assembly of HMF molecules and thus exhibit positive effect on its stability, which was also observed by us using NMR spectroscopy. However, NMR experiments uncovered that the stabilization mechanism of $Na_2S_2O_4$ is different and is not due to the disruption of this network. A possible cause for this stabilizing effect is the balanced antioxidant activity and weak basicity of $Na_2S_2O_4$, which brought us to the idea that, in contrast with other compounds, this stabilizer might be applicable to a number of processes related to the production and use of HMF.

We have shown that $Na_2S_2O_4$ is an effective stabilizer for HMF synthesis, leading to a significant increase in the yield and purity of the final product. Another major problem in HMF processing is its difficult purification. The reported distillation methods provide up to 45-60% distillation yield due to thermal degradation. The use of only 2 wt.% $Na_2S_2O_4$ vacuum distillation of HMF provided the remarkable >85% yield and >99.9% purity of the product. The versatility of the stabilization induced by $Na_2S_2O_4$ was demonstrate in several reaction, such as Knovenagel condensation, Cannizzaro reaction, and the synthesis of pyridine salts.

The utility of $Na_2S_2O_4$ as stabilizer for the biorefinery of HMF accompanied by its availability and low toxicity, outline the importance of this scientific contribution to practice. To the best of my knowledge, to date $Na_2S_2O_4$ remain the only reported versatile stabilizer for HMF. Its utility has been subsequently demonstrated by a number of authors.

Due to its application as a substitute for terephthalic acid in the production of polymers, furan-2,5-dicarboxylic acid (FDCA) became a major industrial product derived from HMF. The annual production capacity for FDCA is expected to reach 170, 000 tons. In contrast to HMF, FDCA is a stable compound, which provoke us to consider it as a possible platform for streamlining the synthesis of structurally complex furans. The development of such a strategy faced two major challenges. The presence of the two chemically equivalent carboxylic acid functions, is favorable for FDCA application in polymer chemistry. However, from the point of view of organic synthesis the desymmetrization of the two equivalent carboxyl groups is a serious challenge. On the other hand, the introduction of additional substituents into the furan ring requires the activation of non-reactive carbon-hydrogen bonds.

Driven by the aforementioned considerations, we developed a tandem bio/metal catalytic synthetic strategy based on the biocatalytic desymmetrization of the diethyl ester **3** using the enzyme CAL-B as a catalyst and the subsequent introduction of aromatic substituents by amide-directed Ru-catalyzed C-H activation.[6B] (Scheme 6). By tuning the reaction conditions, we achieved the modification of all possible positions in the molecule of FDCA.



Scheme 6. Streamlining the synthesis of structurally complex furans from FDCA

Apart from the diversification of the HMF platform this scientific contributions resulted in the development of new synthetic roads to achieve the synthesis of densely substituted furans, a class of compounds with diverse biological activity.

1.4. Other scientific contributions in the biorefinery of HMF.

Traditionally, fructose is the major source of HMF. Its dehydration is well studied and in many cases leads to high yields and selectivity. However, fructose is not widely abundant, and is used in the food industry. In contrast, glucose is the most bundant carbohydrate in nature and is readily available from cellulosic biomass, which has no nutritional value for humans. Therefore, it is a much more attractive source of HMF. Glucose exhibit high resistance to dehydration, which requires the use of bifunctional catalysts that efficiently catalyze its isomerization to fructose and subsequent dehydration to HMF. We developed a method for the synthesis of HMF from glucose in a tetraethyl ammonium bromide/water system as the reaction medium and Cr^{3+} modified commercial acid resins as catalysts. The product was isolated in high purity and 70% yield. The newly prepared bifunctional catalysts showed good stability. Amberlyst15/Cr^{3+} was used in up to 4 catalytic cycles without significant loss of activity. The loss of catalytic activity after the 5^{th} cycle was found to be due to the reduction of the active acid sites of the catalyst, which could be recovered by regeneration with HCl. [7Γ]

The dimer OBMF, obtained by the etherification of two HMF molecules, is attracting an increasing interest due to its potential use of biorenewable monomer. However, the unstable nature of HMF and the equilibrium of reaction present a serious challenge. In order to overcome these problems, a set of acid-modified silica gels was prepared and used in HMF dimerization. The reaction was carried out in the absence of solvent and under vacuum as a water removal tool, thus facilitating the etherification reaction. The desired product OBMF was obtained in good yields.[8Γ]

Another HMF ether of industrial interest is 5-tert-butoxymethyl furfural *t*-BMF, which finds application as a fuel additive. Using a large set of acidic heterogeneous catalysts and flow chemistry, we have developed a continuous process for the production *t*-BMF by etherification of HMF with t-BuOH.[9Γ]

2,5-diformyl furan DFF is a valuable product with a number of applications in industry. By using pyridine-N-oxide as oxidant and $CuSO_4$ as catalyst in flow reactor we obtained DFF in good yields from oxidation of 5-chloromethylfurfural.[10Γ]

2. Synthetic modifications of natural products

Lupanine is a widespread natural alkaloid and a waste product from the food industry during the production of Lupin beams. It is structurally similar to another spread alkaloid, sparteine, which is known to effectively block voltage-gated sodium channels (VGSCs) responsible for the rapid propagation of electrical impulses in nerves. The presence of an amide function in the lupanine structure was exploited in the synthesis of new C2-modified sparteine analogues. The obtained set of compounds was provided for biological studies in collaboration with the Department of Neurophysiology and Neuropharmacology, Medical University of Vienna. All the newly prepared C2-modified sparteine analogues exhibited a high level of irreversible block of VGSCs in up to 100%. This property could eventually be used for long acting local pain relief, representing a new class of therapeutic agents.1[11Г]

Due to the limited access and availability in only enantiometic form the natural sparteine has been replaced in the asymmetric synthesis by the use of "Sparteine surrogate" (+)-(*1R,5S,11αS*)-tetrahydrodeoxycytisine. Using natural (-)-(*1R,5S*)-cytisine as starting material, we prepared (+)-(*1R,5S,11aS*)-tetrahydrodeoxycytisine as free base, mono- and dihydrochloride. An unambiguous assignment of the signals in the proton and carbon NMR spectra was achieved alongside single crystal X-ray diffraction comparison with NMR data.[12Г]

Oleuropein is a natural product isolated from the leaves of the olive treeл Its high functionalization and availability are of interest for the synthetic chemistry. The structure of oleuropein consist of three main fragments: glucoside-monoterpene-hydroxytyrazole. By using tunable acid catalysis and precise control of the reaction conditions, we achieved selective methanolysis of only glucoside and simultaneous methanolysis of the glucoside and hydroxytyrazole fragments with subsequent cascade synthetic transformation of the monoterpene unit leading to the generation of biologically active compounds.[13Г]

3. Others

The development of effective approaches for CO2 capture and utilization is among the hot topics for scientific exploration in recent years. Among a number of approaches for the capturing of this greenhouse gas, nanoporous materials with high specific surface area gain their momentum. In order to be eventually commercialized, these materials must have an absorption capacity exceeding the value of 2 mmol/g while being chemically and thermally stable and selective to CO_2. Such nanoporous materials were obtained by us by modification of mesoporous silicates with organic amines. The CO_2 absorption capacity of the materials was determined in static and dynamic mode. The 1-methylpiperazine modified mesoporous silicate MCM-48-P exhibited a remarkable absorption capacity of 4.2 mmol/g. The mechanisms of CO_2 capture were studied by ^{13}C NMR spectroscopy, showing chemisorption of CO_2 leading to the formation of a bicarbonate ion.[14Г]

A new method for convenient and inexpensive preparation of amides from amines and esters using KOBu-t/DMSO or n-BuLi/THF basic systems was developed. The tolerates tolerates a variety of substituents and functional groups in the substrates. It is also applicable to the synthesis of phosphoramidates from triethyl phosphate, whose known preparation relies on expensive and toxic starting phosphorus compounds, as well as high temperatures, long reaction times and the presence of metal catalysts. A selective acylation of unprotected diamines possessing aliphatic and aromatic amino groups is demonstrated. A one-step autocondensation

of methylanthranilate has been achieved, leading to the preparation of a key intermediate for the total synthesis of a number of quinazolinone alkaloids. [15Г]

The scientific community was served with a comprehensive critical review that covers the main methods available for production of Shikimic acid and its epimers, including synthetic methods, extraction from plants and microbial production. The review also covers its synthetic modifications and related applications, including synthesis of Tamiflu and derivatives, synthetic manipulations of the main functional groups, its use in green chemistry, and in total synthesis.[16Г]

A second review is devoted to the existing noncovalent interactions used to exert control over the regioselectivity of transition metal-catalyzed C-H functionalization of arenes.[17Г]

III. Future directions

My future research interests falls in the field of organic synthesis and green chemistry. After a decade of intensive research dedicated to the chemistry of the furan derivatives alongside it, my future research plans involve the opening of new research avenues:

- Development of new methodologies for transition metal-catalyzed CH activations;
- Development of high value-added biorefinery products with applications in biochemistry and medicinal chemistry.
- Development of new photochemical methods for CO_2 activation.

The aforementioned work plans are an integral part of the implementation of the two main research projects coordinated by me, namely Biomass4Synthons funded by Horizon 2020 program and ReCat4VALUE funded by NSP VIHREN. The envisioned research will be carried out in close collaboration with the colleagues from IOCCP-BAS and other national research organisation. The developed by me through the years` international scientific network will be also heavily exploited. Those collaborations include: Prof. Giovanni Poli (Sorbonne University, Paris) and Prof. Nuno Candeias (University of Aveiro, Portugal) on transition metal catalysis. Prof. Gonzalo Bernardes (University of Cambridge, UK) on site-selective modifications of proteins. My long-standing collaboration with the group of Prof. Carlos Afonso (University of Lisbon, Portugal) will continue to be one of the main pillars in the biorefinery research.

The work with young researchers is and will be a top priority in my scientific career. Currently, I am a supervisor of one PhD student with a prospective for a second one in the frame of the NSP VIHREN project. The collaborations created within the framework of the Biomass4Synthons project, will be used in a search for foreign researchers willing to apply as postdoctoral fellows via NSP Peter Beron, NSP VIHREN and other funding mechanisms.

IV. Scientific publications

1B Simeonov, S. P.; Ravutsov, M. A.; Mihovilovic, M. D. Biorefinery via achmatowicz rearrangement: synthesis of pentane-1,2,5-triol from furfuryl alcohol. *ChemSusChem,* **2019**, *12*, 2748-2754.

2B Simeonov, S. P.; Lazarova, H. I.; Marinova, M. K.; Popova, M. D. Achmatowicz rearrangement enables hydrogenolysis-free gas-phase synthesis of pentane-1,2,5-triol from furfuryl alcohol. *Green Chem.,* **2019**, *21*, 5657-5664.

3Г Kamenova, K.; Radeva, L.; Yoncheva, K.; Ublekov, F.; Ravutsov, M. A.; Marinova, M. K.; Simeonov, S. P.; Forys, A.; Trzebicka, B.; Petrov, P. D. Functional nanogel from natural substances for delivery of doxorubicin. *Polymers,* **2022**, *14*, 3694.

4В Dangalov, M.; Fernández-Figueiras, A.; Ravutsov, M.; Vakarelska, E.; Marinova, M.; Candeias, N.; Simeonov, S. Ru-catalyzed isomerization of Achmatowicz derivatives: a sustainable route to biorenewables and bioactive lactones, *ACS catal.*, Accepted, DOI: 10.1021/acscatal.2c04867

5В Gomes, R. F. A.; Mitrev, Y. N.; Simeonov, S. P.; Afonso, C. A. M. Going beyond the limits of the biorenewable platform: sodium dithionite-promoted stabilization of 5-Hydroxymethylfurfural. *ChemSusChem,* **2018**, *11*, 1612-1616.

6В Ravasco, J. M. J. M.; Monteiro, C. M.; Siopa, F.; Trindade, A. F.; Oble, J.; Poli, G.; Simeonov, S. P.; Afonso, C. A. M. Creating diversity from biomass: a tandem bio/metal-catalysis towards chemoselective synthesis of densely substituted furans. *ChemSusChem,* **2019**, *12*, 4629-4635.

7Г Ravasco, J. M. J. M.; Coelho, J. A. S.; Simeonov, S. P.; Afonso, C. A. M. Bifunctional Cr^{3+} modified ion exchange resins as efficient reusable catalysts for the production and isolation of 5-Hydroxymethylfurfural from glucose. *RSC Adv.,* **2017**, *7*, 7555-7559.

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9Г Pardo Cuervo, O. H.; Simeonov, S. P.; Peixoto, A. F.; Popova, M. D.; Lazarova, H. I.; Romanelli, G. P.; Martínez, J. J.; Freire, C.; Afonso, C. A. M. Efficient continuous production of the biofuel additive 5-(*t*-butoxymethyl) furfural from 5-Hydroxymethylfurfural. *Energy Technology* **2019**, *7*, 1900780.

10Г Vicente, A. I.; Coelho, J. A. S.; Simeonov, S. P.; Lazarova, H. I.; Popova, M. D.; Afonso, C. A. M. Oxidation of 5-Chloromethylfurfural (CMF) to 2,5-Diformylfuran (DFF). *Molecules* **2017**, *22*, 329.

11Г Gawali, V. S.; Simeonov, S.; Drescher, M.; Knott, T.; Scheel, O.; Kudolo, J.; Kählig, H.; Hochenegg, U.; Roller, A.; Todt, H.; Maulide, N. C2-modified sparteine derivatives are a new class of potentially long-acting sodium channel blockers. *ChemMedChem,* **2017**, *12*, 1819-1822.

12Г S. P. Simeonovp, S. D. S., B. L. Shivachev, R. P. Nikolova, V. B. Kurteva. Solution and solid state characterization of "sparteine surrogate" (+)-(1R,5S,11aS)-tetrahydrodeoxocytisine. *Bul. Chem.Comm.* **2017**, *49*, 103-110.

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14Г Ravutsov, M.; Mitrev, Y.; Shestakova, P.; Lazarova, H.; Simeonov, S.; Popova, M. CO_2 Adsorption on modified mesoporous silicas: the role of the adsorption sites. *Nanomaterials,* **2021**, *11*, 2831.

15Г Slavchev, I.; Ward, J. S.; Rissanen, K.; Dobrikov, G. M.; Simeonov, S. Base-promoted direct amidation of esters: beyond the current scope and practical applications. *RSC Adv.*, **2022**, *12*, 20555-20562.

16Г Candeias, N. R.; Assoah, B.; Simeonov, S. P. Production and Synthetic Modifications of Shikimic Acid. *Chem. Rev.*, **2018**, *118*, 10458-10550.

17Г Fernández-Figueiras, A.; Ravutsov, M. A.; Simeonov, S. P. Site-Selective C–H Functionalization of Arenes Enabled by Noncovalent Interactions. *ACS Omega* **2022**, *7*, 6439-6448.