JAVAKHISHVILI TBILISI STATE UNIVERSITY
ASSOCIATION OF PROFESSIONAL CHEMISTS OF GEORGIA

ICOC-2014 | 25-28 September, 2014 | Tbilisi, Georgia

# Abstract Book Notebook


25-28 September, 2014
Tbilisi, Georgia

3-rd International Conference on Organic Chemistry

## Organic Synthesis- Driving Force of Life Development

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IVANE JAVAKHISHVILI TBILISI STATE UNIVERSITY

ASSOSIATION OF PROFESSIONAL CHEMISTS OF GEORGIA

# The 3-rd International Conference of Organic Chemistry (ICOC-2014)

# "Organic Synthesis - Driving Force of Life Development"


Tbilisi, Georgia

September 25-28, 2014

**Dear Colleagues,**

The Organizing Committee cordially invites you to the 3-rd International Conference of Organic Chemistry (ICOC-2014) "Organic Synthesis - Driving Force of Life Development" organized by the Javakhishvili Tbilisi State University and Association of Professional Chemists of Georgia. This forthcoming conference will be held in Tbilisi, Georgia on September 25-28, 2014.

The First Georgian Conference on Organic Chemistry was held on September, 2009 in Sighnaghi – in one of the loveliest regions of Georgia – Kakheti (old Kiziki). In Sighnaghi the organizing committee took the decision to carry out the following conferences on organic chemistry with the different outlined topics in various cities of Georgia.

The second conference on organic chemistry "Advances in Heterocyclic Chemistry" - GeoHet-2011 was held in the capital city of Georgia –Tbilisi on September 25-27, 2011. The Conference was sponsored by Rustaveli Science Foundation of Georgia and organized by Javakhishvili Tbilisi State University, Georgian Technical University and Association of Professional Chemists of Georgia and 150 attendees from 16 countries, including Armenia, Azerbaijan, Belarus, China, Georgia, Greece, India, Iran, Latvia, Pakistan, Russia, Switzerland, Turkey, Ukraine, USA and Uzbekistan have been participated. The Conference partners were hotel "D-Plaza", hotel "Prestige", Media promotion was supported by World scientific publishing, Journal "Chemistry of Heterocyclic compounds", ARKAT USA Inc. "Arkivoc", Digital Printing Center "ESPO".

The organizing committee cordially hopes that with the assistance of scientists from around the world The International Conference on Organic Chemistry will really become an interesting and attractive international conference on organic chemistry worldwide. We hope that the current conference will be a successful scientific meeting, summarizing the latest achievements of organic chemistry.

Again, we thank all of you for attending these conferences and wish you a pleasant, as well as memorable stay in Tbilisi.

*Organizing Committee*

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- Association of Professional Chemists of Georgia
- Shota Rustaveli National Science Foundation
- Internet Newspaper “Mastsavlebeli”
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# ⏩ PLENAR LECTURES

## PL 1. DOMINO REACTIONS. CONCEPTS FOR EFFICIENT ORGANIC SYNTHESIS

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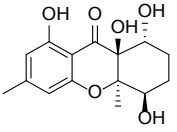
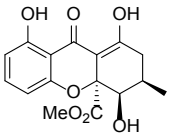
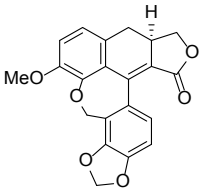
The efficient synthesis of natural products, drugs, agrochemicals and materials is a very important aspect in academia and industry. To allow an ecologically and economically favourable approach the former stepwise procedures must be replaced by domino reactions which allow the preparation of complex molecules starting from simple substrates in a straight forward way. Thus, the increase of complexity in correlation to the number of steps is a valuable criterion for the quality of a modern synthesis [1]. Domino reactions allow the reduction of the amount of waste being formed and the preservation of our resources. Moreover, the reactions can proceed via unstable intermediates which is almost never possible in a stepwise approach.



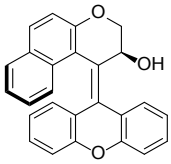

Diversonol




(-)-Blenolid A




Linoxepin




Molecular Switches

The usefulness of the domino concept is demonstrated with the syntheses of the fungal metabolites diversonol [2] and blennolide A [3a] as well as blennolide C [3b] and gonytolide [3b] using an enantioselective domino-Wacker/carbonylation/methoxylation reaction as well as of the natural aryldihydronaphthalene lignan linoxepine [4] employing a domino-carbopalladation/Heck reaction. The approach has also been applied for the synthesis of novel materials such as molecular switches [5a-d] and fluorescence dyes [5e] using a domino-Sonogashira/carbopalladation/CH-activation reaction.

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## PL 2. SYNTHESIS OF MUCIN GLYCOPEPTIDE ANTITIGENS FOR THE DEVELOPMENT OF ANTITUMOR VACCINES

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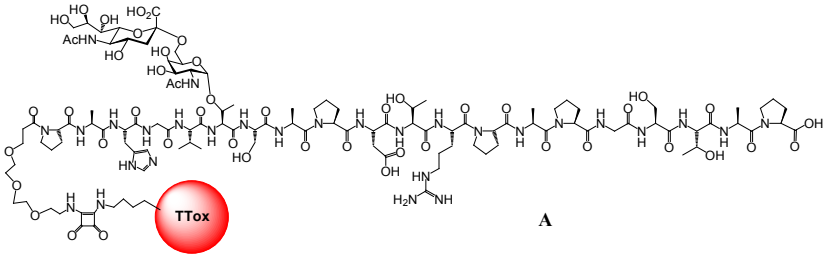
Tumor-associated mucin MUC1 over-expressed on tumor cell membranes shows glycan patterns quite different from those of MUC1 on normal cells. Glycopeptides of the extracellular region of tumor-associated MUC1 with Tn- T-, Sialyl-Tn-, and Sialyl-T-antigen saccharides are promising target structures for the design of antitumor vaccines. In order to construct such vaccines, Fmoc-protected O-glycosyl threonine and serine building blocks were synthesized and applied to solid-phase syntheses of tumor-associated MUC1 glycopeptides.

The obtained glycopeptide antigens were conjugated to immunostimulating components, e. g. T-cell epitopes [1] and/or lipopeptide toll-like receptor ligands [2] to give fully synthetic vaccines. Alternatively, the synthetic tumor-associated glycopeptide antigens were coupled to carrier proteins, in particular to tetanus toxoid, as for example in vaccine **A**. [3]




**A**

Immunization of mice with vaccines of type A induced very strong immune responses of IgG antibodies and, thus, an immunological memory. The induced antibodies recognized human breast tumor cell of cell lines MCF-7 and T47-D and also bound to breast and pancreas tumor tissues.

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# ⏩ INVITED LECTURES

## IL 1. CHEMOSELECTIVE NUCLEOPHILIC ADDITION TO *N*-ALKOXYAMIDES: DEVELOPMENT AND APPLICATION TO THE TOTAL SYNTHESIS OF GEPHYROTOXIN

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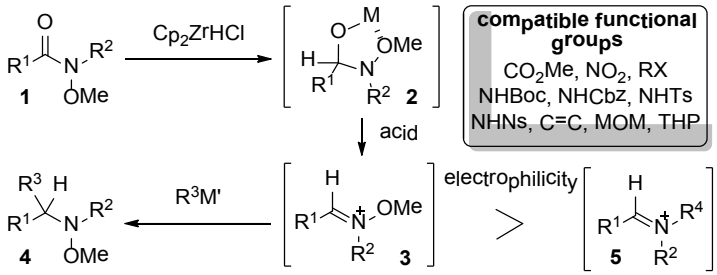
Modern organic synthesis especially for drug discovery has resulted in the need for compounds of ever-increasing complexity. However, transformation of a specific functional group in such complex molecules is not trivial. Extra steps to protect more reactive functional groups are often required in the course of synthesis, and results in decreases in total yields. Therefore, the highly chemoselective reaction to eliminate the protecting group manipulation increasingly become recognized as a crucial tool in organic synthesis.

Nucleophilic addition to amide carbonyls is the simple and promising way to access multi-substituted amines. However, chemoselective version of this reaction remained an unsolved challenge due to the poor electrophilicity of amide carbonyls. The classical methods required harsh reaction conditions and prohibited high functional compatibility. To overcome this issue, we envisioned a chemoselective nucleophilic addition to *N*-methoxyamides (Scheme 1).[1] Treatment of *N*-methoxamide **1** with the Schwartz reagent [$Cp_2ZrHCl$] is known to produce chelated intermediate **2**.[2] Although hydrolysis of **2** gives the corresponding aldehyde, our nucleophilic addition would afford *N*-oxyiminium ion **3** upon treatment of **2** with acid. The generated **3** would then react with nucleophiles to provide substituted *N*-methoxyamine **4** in one-pot process. The first key to achieve functional-group compatibility is the high reactivity of the Schwartz reagent with amide groups. The second feature of this reaction is the high electrophilicity of *N*-oxyiminium ion **3**, which enables use of mild nucleophiles. Combination of these properties would result in high compatibility with a number of sensitive functional groups such as esters.

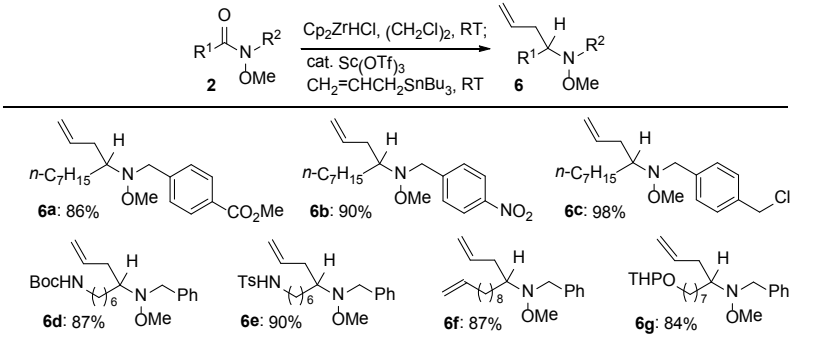



**Scheme 1.** Plan for chemoselective reductive nucleophilic addition to N-methoxyamides.

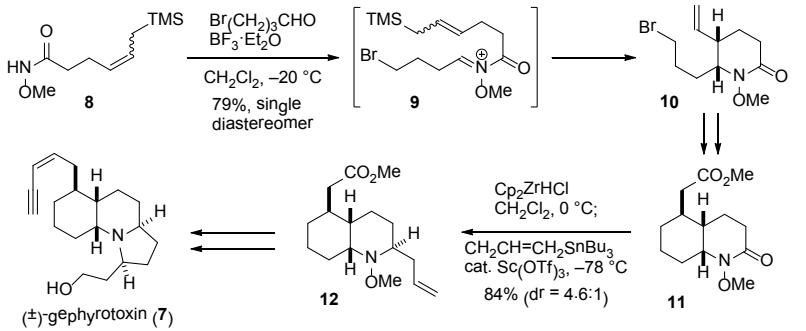
Our hypothesis was confirmed when allyltributylstannane and a catalytic amount of $Sc(OTf)_3$ were employed (Scheme 2). The reduction of *N*-methoxyamide with a methyl ester took place in high yield without affecting the methyl ester (**6a**: 86%). It is noteworthy that a number of extra steps would be required if conventional methods were used. For example, the reduction of a more electrophilic ester and the subsequent protection of the resulting alcohol would be essential prior to the nucleophilic addition. Additionally, deprotection and re-oxidation of the hydroxy group would be required to provide the corresponding amine **6a**. Thus, our method eliminates a number of extra steps including the protecting group manipulations and redox reactions. The developed transformations were found to be compatible with not only esters but also a variety of functional groups.

Our chemoselective nucleophilic addition was successfully applied to the total synthesis of (±)-gephyrotoxin **7** (Scheme 3).[1b] Our central strategy toward the total synthesis was based on use of the *N*-methoxy group as a reactivity control element. The first key reaction was direct coupling reaction between *N*-methoxyamide **8** and 4-bromobutanal via acyliminium ion **9**, giving *cis*-piperidone **10** in 79% yield as a single diastereomer.[3] In general, intermolecular coupling of an ordinary amide with an aldehyde is challenging due to the poor nucleophilicity of the nitrogen atom of the amide. However, the *N*-methoxy group enhanced the nucleophilicity of the nitrogen and rendered the direct condensation with the aldehyde feasible. The second key step was chemoselective reductive allylation of *N*-methoxylactam **11** in the presence of the methyl ester. The reaction

provided **12** in completely chemoselective fashion, and obviated a number of extra steps from the total synthesis. Thus, we accomplished the total synthesis in 14 steps with an overall yield of 9.4%, which represents the most concise and efficient synthesis to date.




**Scheme 2.** Scope of the chemoselective reductive allylation to *N*-methoxyamides.




**Scheme 3.** Total synthesis of (±)-gephyrotoxin (7).

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## IL 2. PALLADIUM-CATALYZED CYCLIZATION OF PROPARGYLIC ESTERS WITH NUCLEOPHILES

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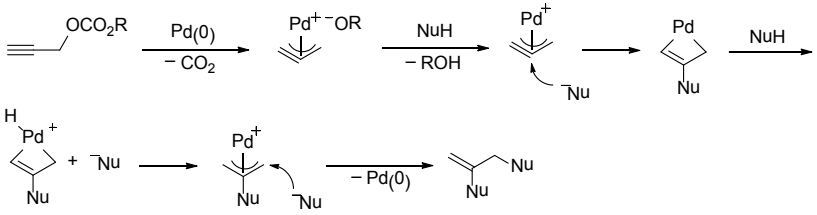
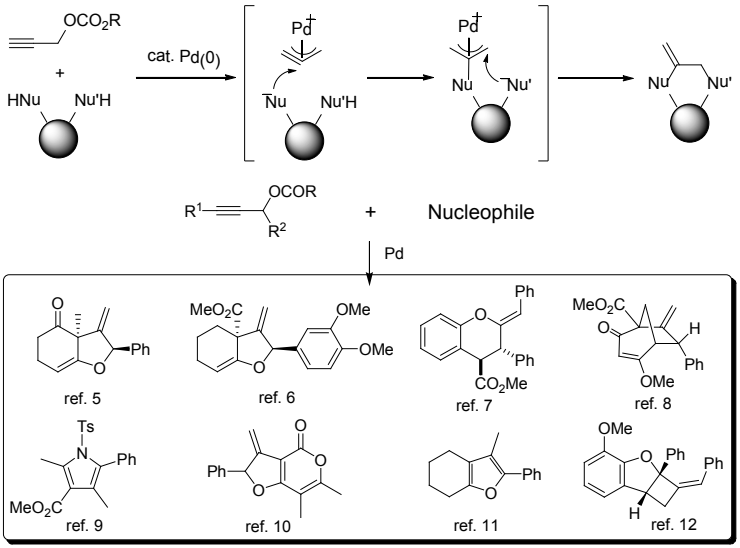
Propargylic compounds containing an ester or a halide at the propargylic positions are known as useful intermediates in organic synthesis, and a number of reactions utilizing the properties of propargylic compounds have been reported. For example, propargylic carbonates react with palladium complex leading to π-propargylpalladium complexes, which further cause various transformations in the presence of soft nucleophiles to produce the 1,2-disubstituted allylic compounds along with the regenerated palladium complexes [1,2]. In the reaction, a nucleophile initially attacks to the central carbon of π-propargylpalladium to transform the π-allylpalladium complex via the palladacyclobutene, which further reacts with another nucleophile to afford the disubstituted products. Various transformations including cyclization reactions have been developed by the design of propargylic substrates and nucleophiles.




As another type of the palladium-catalyzed cyclization of propargylic compounds with nucleophiles, it is known that the use of bis-nucleophiles, which contain two nucleophilic parts within the molecules. In this reaction, the initially formed π-propargylpalladium intermediate is subjected to consecutive nucleophilic attacks by the bis-nucleophilic part to give the cyclized product [3,4].

This type of cyclization is useful for the synthesis of various heterocyclic compounds in one step, and extensive studies about this process have been examined in recent years. In this lecture, a comprehensive overview of our studies on palladium-catalyzed reactions of propargylic esters with bis-

nucleophiles is described, in which various functionalized cyclic molecules can be synthesized in a regio- and stereoselective manner [5–12]

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## IL 3. NOVEL MOLECULAR PHOTOSENSITIZERS FOR DYE-SENSITIZED SOLAR CELLS AND PHOTODYNAMIC THERAPY APPLICATIONS

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In the past few decades, transition-metal complexes have attracted intense scientific interest. Besides their catalytic [1] and energy-converting potential, for example in dye-sensitized solar cells applications [2], this is due to their ability to be introduced in health-related applications such as photodynamic therapy (PDT) [3].

Dye-sensitized solar cells (DSCs) provide an appealing alternative to the conventional solid-state cells. This is mainly due to their ability to work indoors and under subdued light conditions, their potential transparency and flexibility, their invariant efficiency to the operating temperature, and their relatively low production cost [2]. Photodynamic therapy (PDT) [3] is a light-triggered, non-surgical protocol for the treatment of various malignant cancers including lung, cervical, bladder, oesophagus, and skin, as well as of age-related macular degeneration. Moreover, photodynamic therapy has been applied in killing microbial cells including bacteria, fungi, and viruses.

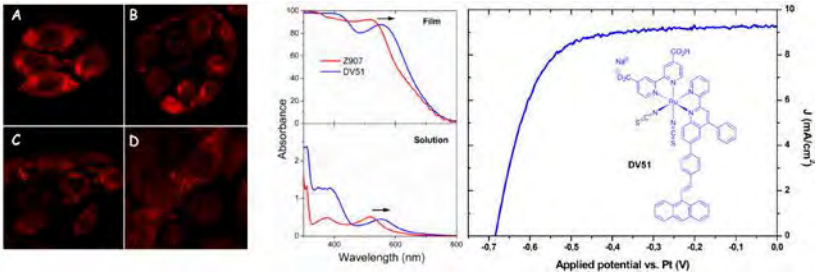


**Figure 1:** Confocal microscopy images of human prostate cancer cells following 4 h incubation with one of the novel ruthenium photosensitizers (images A-D, left) and UV-Vis spectra and J-V curves of DSCs encompassing photosensitizer DV51 (right).

The talk deals with the synthesis, characterization, and applications of a variety of tailor-designed organic ligands and the corresponding ruthenium-based photosensitizers. The lecture will begin with a quick overview of the dye-sensitized solar cells and photodynamic therapy fields, followed by an in-depth discussion on the applications of the newly-synthesized molecular photosensitizers in these fields [4-7].

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## IL 4. SYNTHESIS OF CARBOCYCLES AND HETEROCYCLES VIA CASCADE REACTIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS OF NITROALKENES

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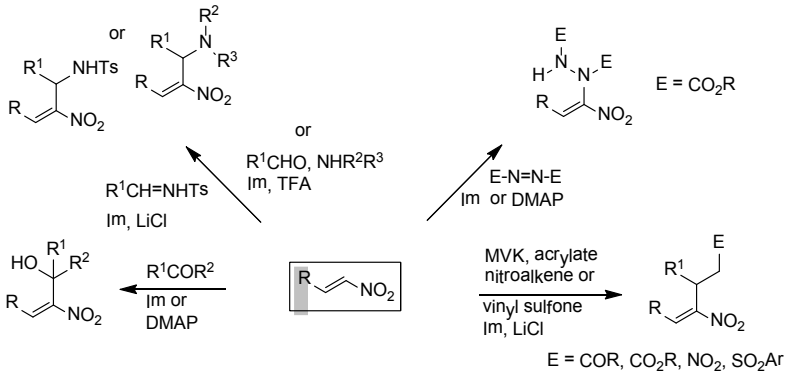
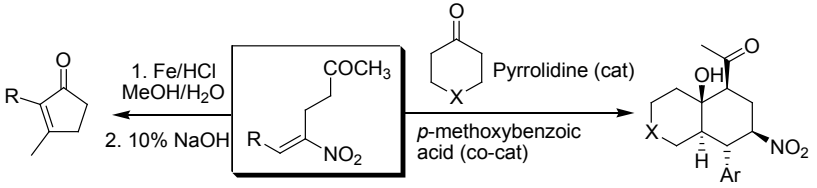
The Morita-Baylis-Hillman (MBH) reaction of activated alkenes with various electrophiles such as formaldehyde, activated carbonyl compounds and imines provides novel multi-functional molecules through a one-pot, room temperature, multi-component and atom economical reaction. Analogous Rauhut-Currier (RC) type dimerization of nitroalkenes and their coupling with other electron deficient alkenes such as MVK, acrylate, vinyl sulfone as well as heteroatom centered electrophiles such as azodicarboxylates also lead to novel molecules with fabulous functional group diversity (Scheme 1) [1].

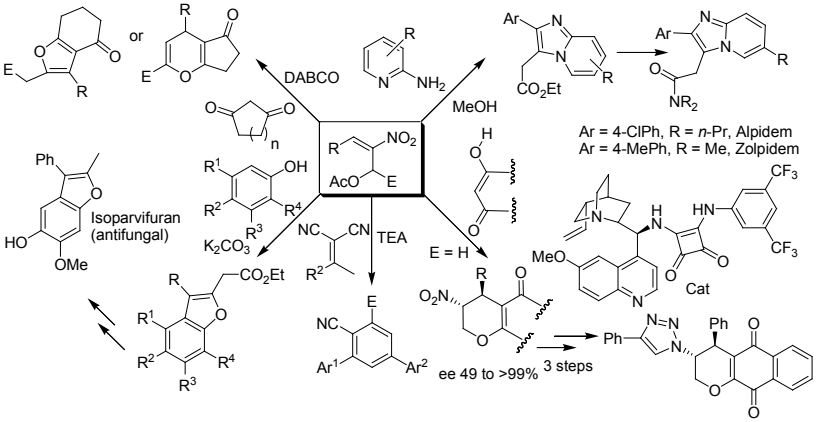



**Scheme 1**

Applications of the MBH and RC adducts in the synthesis of carbocycles such as terphenyls, cyclopentenones and decalins as well as heterocycles such as furans, pyrans, imidazopyridines and pyranonaphthaquinones via cascade reactions will be discussed (Schemes 2-3).[2-7]




**Scheme 2**




**Scheme 3**

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## IL 5. TRANSITION METAL-CATALYZED ALLYLIC ALKYLATIONS - VERSATILE TOOLS FOR AMINO ACID AND PEPTIDE SYNTHESES

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Based on their central position between chemistry and biology, amino acids and peptides play a dominant role in life sciences. Besides the few proteinogenic amino acids, around 1000 unusual amino acids are found in nature, many of them in natural products showing interesting biological properties. Therefore, stereoselective syntheses of these amino acids and peptides are a real challenge for synthetic organic chemists.

During the past couple of years, transition metal catalyzed reactions became one of the most powerful tools in asymmetric syntheses and the syntheses of natural products and drugs. Our group is involved in amino acid and peptide synthesis, based on reactions of chelated amino acid ester enolates [1]. Besides typical enolate reactions, these chelated structures also serve as versatile nucleophiles e.g. in palladium catalyzed allylic alkylations [2]. Based on their high reactivity, these enolates react under very mild conditions, normally at –78°C. At this temperature undesired side reactions, can be suppressed, what enlarges the potential of this synthetic protocol [3].

The Palladium-catalyzed allylation is easily transferable to peptides [4]. In this case, the stereochemical outcome of the reaction can be controlled by the peptide chain. Such stereocontrolling effects are also observed in many other reactions, such as Claisen rearrangements. Subsequent modifications at the unsaturated side chain allows the easy generation of small libraries of structural related unusual peptides [5]. Therefore, this approach is highly suitable for natural product and drug synthesis.

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## IL 6. THE THREE-CENTER-FOUR-ELECTRON HALOGEN BOND

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Halogen bonding is the noncovalent interaction of halogens in which they act as electron acceptors [1]. Its geometry, energy, and dominantly electrostatic nature resemble that of the hydrogen bond. The phenomenon was first reported two centuries ago [2], and its crystallographic description was awarded a Nobel prize in 1969 [3], but it was largely neglected and the exploration of its potential has just recently begun [4]. Recent studies revealed its immense potential for applicability in supramolecular chemistry, in organocatalysis, in structural biology, and in medicine, for example [4].

Halogen bond strength critically depends on the electron deficiency of the halogen. Accordingly, halonium ions that bear a formal positive charge are the strongest halogen bond donors known so far. Halonium ions, similar to $H^+$, are capable of simultaneously interacting with two Lewis bases and may form three-center bonds (Figure 1). Three-center-four-electron (3c4e) halogen bonds possess a series of unusual properties. They are held together by a hypervalent, partially positively charged halogen simultaneously interacting with two electron donors and are among the strongest known secondary interactions. Whereas similar three-center hydrogen bonds [5] and $[C\text{-}X\text{-}C]^+$ halonium ions [6] have been critically evaluated for decades, the investigations of the analogous three-center halogen bonds are only at an early stage [7].

**Figure 1.** The surface electrostatic potential of a three-center-four-electron halogen bond, as demonstrated on the example of the $[bis(pyridine)iodine]^+$ complex. The antiparallel p-holes of $I^+$ (blue) are separated by an equatorial of neutral charge (yellow). Each p-hole interacts with the nonbonding electron pair of a pyridine nitrogen.

We performed a systematic evaluation of the $[N\text{-}X\text{-}N]^+$ 3c4*e* halogen bonds in solution, in the solid state and *in silico*. The importance of the central halogen and the environmental factors such as solvent, counter ion and steric strain were studied [8-11]. The geometry of the iodine- and bromine-centered 3c4e halogen bonds were assessed with the NMR technique isotopic perturbation of equilibrium, which is capable of distinguishing a static symmetric structure, $[N\cdots X\cdots N]^+$, from rapidly interconverting asymmetric geometries, $[N–X\cdots N]^+ \leftrightarrow [N\cdots X–N]^+$, in solutions [12]. Iodine- and bromine-centered 3c4e halogen bonds possessing nitrogenous donors were demonstrated to prefer a static, symmetric geometry in which the central halogen accepts electrons from both Lewis bases to an equal extent (Figure 2)]. The symmetry of the $[N\text{-}I\text{-}N]^+$ and $[N\text{-}Br\text{-}N]^+$ bonds is not perturbed by alteration of environment polarity, i.e. changing the solvent from dichloromethane ($\varepsilon$=8.9) to acetonitrile ($\varepsilon$=37.5) [10]. Diffusion NMR studies revealed the solvent polarity dependent degree of counter ion coordination that may have an impact on the reactivity of the systems [10]. Neither is the symmetric arrangement destabilized by the strain introduced by a bis(ethynyl)benzene linker [9]. The symmetric arrangement remains highly preferred even in the solid state, and is undisturbed by strongly coordinating or sterically demanding counter ions [7]. These spectroscopic-based conclusions were supported by DFT geometry optimizations on the B3LYP/LANL08d level. Computational studies supported by NMR relaxation and chemical shift measurements at low temperatures revealed the preference for the symmetric arrangement also for the $[N\text{-}Cl\text{-}N]^+$ system [11]. In contrast, the corresponding fluorine-centered 3c4e halogen bonded system adopts an asymmetric structure, similar to the analogous $[N–H\cdots N]^+$ hydrogen bond. However, in contrast, its interconversion, $[N–F\cdots N]^+ \leftrightarrow [N\cdots F–N]^+$, is hindered by a high energy barrier and its formation is thermodynamically disfavored, in line with F being a poor halogen bond donor. The charge transfer from the coordinating nitrogenous electron donors to the central halogen(I) is extensive and is shown to follow the order of electronegativity, i.e. F > Cl > Br > I.

The studied model systems provide valuable insights into the fundamentals of reaction and chemical bonding theories. In addition to the value of reaching an improved understanding of 3c4e halogen bonds from a theoretical perspective, the rapidly growing awareness of the wide synthetic applicability of electrophilic halogenating agents provides the practical importance of these studies.

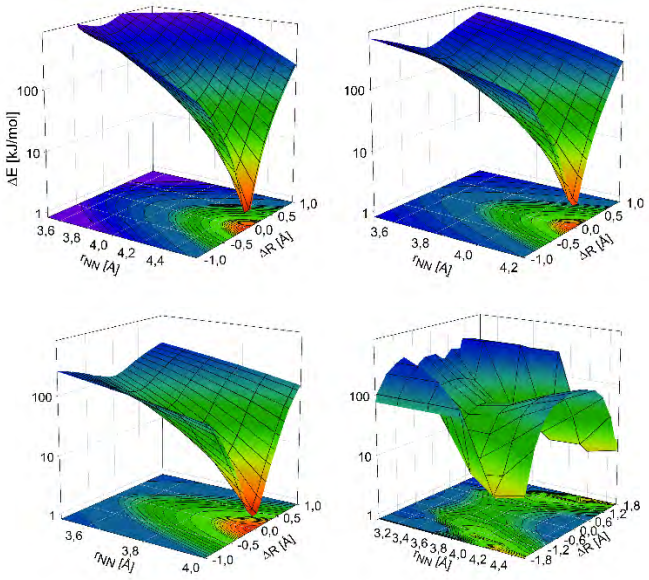


**Figure 2.** The computed potential energy surface of bis(pyridine)halonium complexes describes the relationship between their geometry and energy. The potential energy surfaces describing the halogen motion for the [bis(pyridine)iodine]$^+$, bromine and chlorine complexes, from the left to the right, possess a single energy minimum reflecting a static, symmetric geometry whereas that of the fluorine-centered complex shows two equal minima revealing its preference for an asymmetric arrangement.

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## IL 7. SYNTHESIS OF NOVEL PEPTIDES THROUGH MULTICOMPONENT REACTIONS AND INVESTIGATION OF THEIR BIOLOGICAL ACTIVITIES

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Multicomponent reactions (MCR) have become important tools in the preparation of structurally diverse chemical libraries of drug-like polyfunctional compounds. However, to ensure sufficient molecular diversity and complexity of new chemical entities, there is a continuous need for novel reactions with high efficiency and selectivity in novel reaction media [1,2].

The importance of peptides as pharmaceutical has increased significantly and peptide drugs have an essential role in pharmaceutical market. However, the pharmacokinetic profile and selectivity of peptide drugs is limited by their low metabolic stability due to the amide bond hydrolysis by peptidases and low bioavailability. In this way, finding of a suitable way for drug delivery and modification of peptide structure is the subject of the recent researches. Now, some glycopeptides and nucleopeptides are introduced as novel drugs.

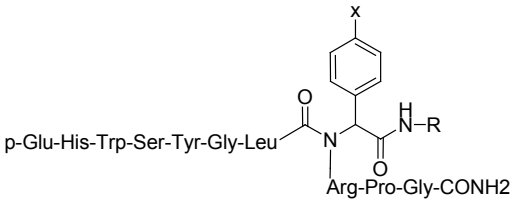
We intend to use the Ugi-4CR approach to construct products with further functional groups which have lipophilic moieties and in some cases are prone to carrying out further reactions such as additional ring closure reactions. This strategy allows us to prepare in a very economic and ecologic way complex systems.

During the past six years, we have been actively involved in the using of multicomponent reaction to access modified peptides and have developed a series of bioactive compounds.

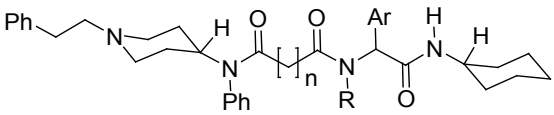
This lecture will highlight some of our contributions to this area which contained [3]:

a. Ugi-4CR as an approach for the synthesis of some novel GnRH analogues and investigation of their anti-cancer activity

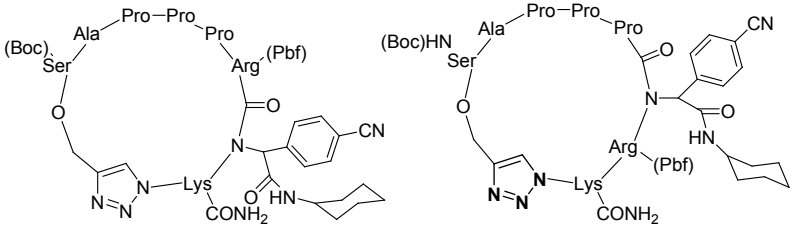
b. Design and synthesis of novel fentanyl analogues based on Ugi-4CR, and also functionalization of natural analgesic peptides
c. Synthesis of novel cyclopeptides through Ugi ligation/click reaction to construct the cyclopeptides which have a triazole moiety and also lipophilic moieties
d. Synthesis of azapeptides and combination of active heterocyclic backbones with peptides




**(A)**




(B)




**(C)**

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## IL 8. THE TALE OF TWO ENANTIOMERS - ORGANIC SYNTHESIS OF INHIBITORS OF ENZYMES AND PROTEIN-PROTEIN-INTERACTIONS

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In my presentation, I will present three case studies, how we used organic synthesis to develop inhibitors and mechanistic probes to investigate protein function. In the first part, I will present our collaborative effort with the group of Prof. Blankenfeldt (HZI Braunschweig, Germany) to investigate the biosynthesis of phenazines. Along these studies we have observed the first case that both enantiomers of a racemic ligand bind simultaneously to a protein.[1] In the second part of my talk I will describe our efforts to develop a comprehensive library of teraryl-based alpha-helix mimetics to address protein-protein interactions. Our synthesis relies on the use of Knochel-Turbo-Grignard reagents for the preparation of 5-substituted 3-pyridine boronic acids as building blocks and on a modular teraryl assembly using sequential Pd-catalyzed cross-coupling reactions.[2] Finally, I report about our journey to identify the first inhibitor of the physiologically relevant protein ATGL (adipose triglyzeride lipase). Atglistatin proved to be a useful tool compound to study ATGL function in vivo.[3]

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## IL 9. RIDING THE BEAST WITH A SMILES: A JOURNEY ALONG ISOCYANIDE-BASED MULTICOMPONENT REACTIONS

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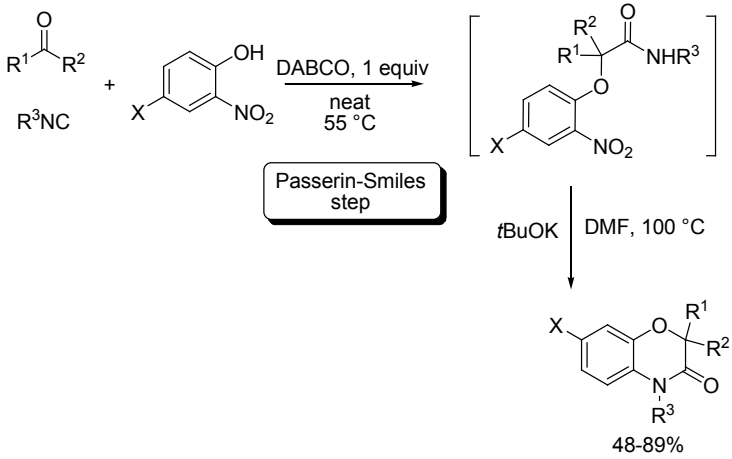
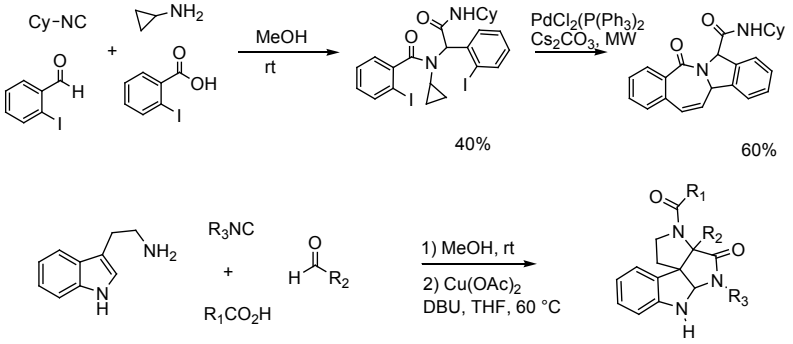
In the last twenty years, the field of isocyanide chemistry has been strongly influenced by the interest for multicomponent reactions. Our group has approched this domain with the goal of inventing new reactions through more or less important modifications of existing couplings. In the last ten years, we have been particularly successfull with the introduction of Smiles rearrangements in isocyanide couplings (Ugi-Smiles and Passerini-Smiles) [1]. These reactions have been applied to various syntheses of heterocyclic scaffolds such as the recent benzoazinones synthesis displayed in Scheme 1 [2].




**Scheme 1**

Beyond our interest for isocyanide chemistry, we consider that Ugi, Ugi-Smiles reactions and their Passerini analogues remain underestimated tools for reactivity studies. The ability to form in one step properly functionnalized starting materials expands the chance of finding new reactions and

interesting cascades. Scheme 2 gathers some of our studies trying to follow these lines working with organometallic or radical processes [3].




**Scheme 2**

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## IL 10. D-GALACTAL AS A SOURCE OF READILY AVAILABLE BENZOPYRANS, CHROMENES AND CHROMANS

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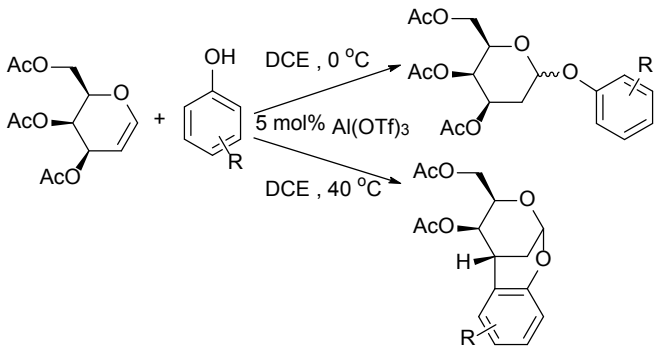
Carbohydrates have been used for many decades as a ready source of chirality and highly structured and reactive starting materials. They have been applied in the synthesis of a great number of derivatives, many of which are biologically active or are premised on biologically active structures [1]. Indeed, carbohydrates are part of glycolipids, glycoproteins and as other glycoconjugates such as glycosteroids.

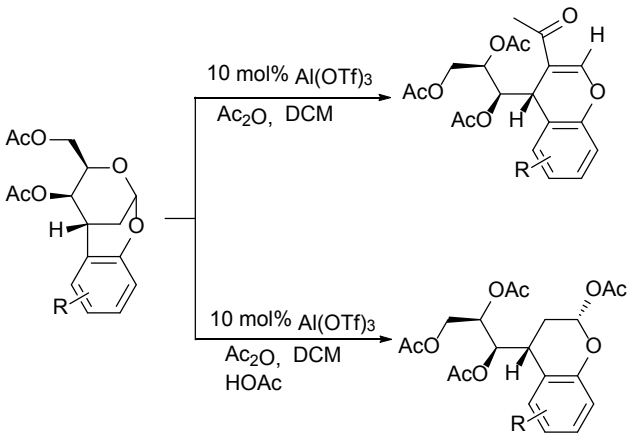
Glycals are interesting starting materials because they contain the usual hydroxyl functionality found in carbohydrates (as free OH groups or as protected OH groups) in addition to an enol ether. This gives them additional reactivity that can be harnessed to produce a range of useful products via powerful chemistry.

In this paper, we have employed tri-*O*-acetyl-D-galactal in various reactions catalysed by the Lewis acid aluminium triflate ($Al(OTf)_3$). We show that glucal and galactal can be used but not necessarily in the same type of transformation. We will further demonstrate that the mechanism of the reaction can be varied depending on the reaction conditions. With D-glucal, the reaction product is either the 1-*O*-aryl-2-deoxy glucoside product of the Ferrier rearranged product [2]. With D-galactal, altogether different outcomes emerge. Here, the reaction product is either the 1-*O*-aryl-2-deoxy galactoside of a chiral bridged benzopyran (Scheme 1) [3].

Quite usefully, the bridged benzopyran is a source either of the chromene derivative or its chroman analogue, in efficient ring-opening reactions catalysed by $Al(OTf)_3$ and acetic anhydride in the presence or absence of acetic acid (Scheme 2).




**Scheme 1**




**Scheme 2**

This presentation will explore the scope and limitations of the various reactions detailed above.

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# ⏩ ORAL PRESENTATIONS

## OP 1. STRUCTURE-BASED DESIGN AND SYNTHESIS OF ORGANIC LIGANDS - THE MILESTONE IN THE WAY FROM COORDINATION TO SUPRAMOLECULAR CHEMISTRY

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In this talk I will try to emphasize on the importance of the structure of the organic compounds, used as metal complexing ligands, in shaping not only the final geometry of the formed complexes, but also their properties and potential fields of applications. A possible approach in coordination chemistry is to select the ligands under interest by their intrinsic properties (physical or biological) and examine their modulation through metal ion complexation, whereas another one is to design and purposely synthesize ligands with pre-defined structure with the aim to obtain coordination compounds with the envisaged geometry and the desired properties. As both approaches have specific difficulties, some examples of our experience will be presented.

Initially, will be described the complexation properties of two types of compounds with interesting optical and/or biological properties that have been thoroughly studied in the last ten years in our group. The selected ligands, namely 2-acyl indan-1,3-diones and 5-spiro-thiohydantoins, belong to the classes of cyclic β-triketones and imidazolidines, respectivelly. The structure of the metal complexes of the indandiones were unambiguously determined by X-ray diffraction analysis and/or wide range of spectroscopic methods, which was easily possible due to the structural characteristics of the 2-acyl indan-1,3-dione unit that possesses well-defined coordination site **1** (Fig. 1). Yet, interesting periodic structures have been formed due to the several available types of intermolecular interactions, which, however, were not strong enough to modulate the physical (optical or magnetic) properties of the formed complexes [1,2]. On the other hand, the studied thio-

derivatives of the physiologically active hydantoin ligands have four possible sites for coordination that makes the structure determination of their metal complexes very difficult. Our recent results on Pt(II) and Ru(III) complexes of novel dithiohydantoin ligands showed that they exhibit concentration dependent **antitumor activity** against human cancer cell lines that motivated our further studies on their properties. As the important point for proper analysis of the biological activity of the complexes is the correct determination of their structure, most of our efforts were focused in this direction. Alas, no suitable single crystals for X-ray analysis could be obtained from the large series of metal complexes that we studied. Therefore, the structure of the metal complexes was investigated by use of multiple spectroscopic (IR, UV-Vis, NMR, EPR and XPS) and electrochemical methods. Structure determination was possible only by employing quantum chemical methods for modeling the possible geometries of the complexes followed by calculation of their spectroscopic properties (IR and NMR) that are known from the available experimental data. Direct comparison of the theoretical DFT results with the experimental data allowed for suggesting the best model structure of the complexes **2** (Fig. 1), similarly to earlier studies of ours demonstrating the successful application of the suggested integrated approach [3-5].

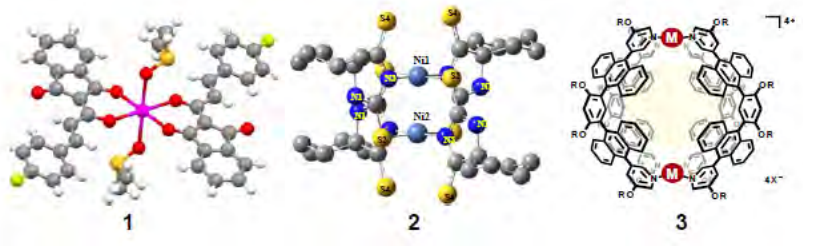


**Fig. 1. Ligand-defined structures of the metal complexes - optimized and experimental data; the ligands are (1) 2-acyl indan-1,3-dione; (2) cycloalkyl-spiro-5-dithiohydantoin; (3) bis-anthryl-pyridine**

The other approach in coordination chemistry relies on the synthesis of target ligands that render well-defined sites for coordination as well as for strong intermolecular interactions. Thus, a leap forward of the general coordination chemistry to the fascinating field of supramolecular chemistry has become possible in the past decades. Herein, I will shortly present the subject of coordination nano-capsules that I have been recently involved in

through collaboration with their inventors, Yoshizawa et al. that have recently reported the design and synthesis of anthracene based coordination capsules **3** (Fig. 1) [6]. The capsules have an $M_2L_4$ composition and provide large, hydrophobic cavity with an average volume of ~580 $Å^3$ making it ideal hosts for encapsulation of various organic molecules [7]. The purpose of the designed structure was to employ the hydrophobic cavity for catalysis of unique chemical reactions or stabilization of highly-reactive species [8, 9]. A new possible application of the capsules is their use as anticancer agents or dug carriers that is about to be proved in our ongoing studies.

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## OP 2. COMPLEXATION OF POLYETHER IONOPHORES AS A POTENTIAL TOOL FOR ENHANCEMENT OF THEIR BIOLOGICAL ACTIVITY

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The natural polyether ionophores Monensin and Salinomycin (Fig. 1) produced by *Streptomyces spp.* are worldwide applied in veterinary medicine due to their pronounced coccidiostatic and antibacterial properties [1-4]. The mode of action of ionophorous antibiotics relates to their ability to bind monovalent metal cations as neutral complexes, which penetrate cell membranes and disturb metal homeostasis in parasites and bacteria. Most of polyether ionophores possess high affinity to complex with alkali metal ions and for that reason they are known as monovalent polyether ionophores.

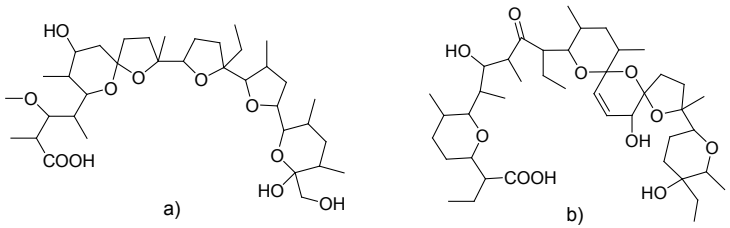


**Fig. 1. Structural formulae of: a) Monensin, b) Salinomycin**

In 1990s several studies repoNrted that biological activity of polyether ionophores is influenced by the presence of metal(II) ions, thus suggesting that the antibiotics could react with ions of valence higher than +1. In this respect we have started an extensive research on coordination properties of Monensin and Salinomycin towards divalent bio- and toxic metal ions.

On the other hand, a significant interest is recently aroused towards ionophorous antibiotics with respect to their antitumor activity due to reports that: i) Monensin significantly inhibits proliferation of cultured cell lines established from renal cell carcinoma, colon cancer, myeloma, lymphoma and myelogenous leukaemia; the antibiotic suppresses *in vivo* the growth of murine leukemia cells in BALB/c mice; ii) Salinomycin causes

apoptosis of breast cancer stem cells and it was found by Gupta et al. [5] to be much more effective than paclitaxel (traditional anticancer drug). These findings prompted us to study properties of biometal(II) complexes of polyether ionophores against human and animal tumor cell lines in order to examine the influence of metal(II) ion on cytostatic and cytotoxic activity of Monensin and Salinomycin.

The third point of view concerning biological properties of antibiotics refers to their *in vivo* toxicity in animals, which depends at high extent to the species studied, accompanied by the general opinion that relative chronic toxicity of ionophores decreases in the order of Maduramycin > Monensin > Narasin > Lasalocid > Salinomycin [6].

In this study we present a brief summary on chemical and biological properties of complexes of Monensin and Salinomycin with divalent ions of bio- and toxic metals [7-17]. Three types of complex species were obtained up to now depending both on the starting ligand (acidic or sodium form) and metal(II) ions used: i) $[ML_2Cl_2]$ (L = sodium Monensin; M = Cu, Co, Mn); ii) $[ML_2(H_2O)_2]$ (L = Monensin, Salinomycin; M = Mg, Ca, Sr, Ba, Mn, Co, Ni, Cu, Zn, Cd); iii) $[ML(H_2O)]$ (L = Monensin, Salinomycin; M = Hg, Pb) (Fig. 2).

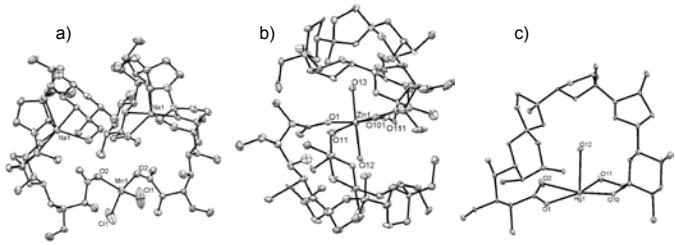


**Fig. 2. Coordination mode of polyether ionophores Monensin and Salinomycin: a) $[ML_2Cl_2]$; b) $[ML_2(H_2O)_2]$; c) $[ML(H_2O)]$**

Biometal(II) complexes of polyether ionophores exert stronger antimicrobial actiNvity against Gram-positve bacteria as compared to the non-coordinated ligands. Similar trends were observed testing their activity towards permanent human tumor / non-tumor cell lines and virus-transformed animal tumor cell lines. The acute toxicity was evaluated in mice to determine the effect of metal(II) ion on toxicity of ionophores. The results reveal that the presence of biometal(II) ion enhances significantly antimicrobial and antitumor activity of antibiotics, while acute toxicity

values are heterogeneous and still require more detailed studies. At the same time the formation of ionophores complexes with toxic metal(II) ions points out to the possible application of these ligands as antidotes in the case of acute/chronic intoxications.

**Acknowledgements.** This research was partially supported in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 „National Excellence Program – Elaborating and operating an inland student and researcher personal support system" key project. The project was subsidized by the European Union and co-financed by the European Social Fund.

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## OP 3. *YUCCA GLORIOSA* L. INTRODUCED IN GEORGIA, AS RICH SOURCE OF STEROIDAL COMPOUNDS

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The leaves of the decorative plant *Yucca gloriosa* L. introduced at the botanical gardens of Georgia, contains steroidal glycosides mostly derivatives of a genin – tigogenin, what facilitates simple technology for receiving it.

Tigogenin was converted into the key products for the synthesis of steroidal hormonal preparations: acetate-5α-androstanol and 5α-pregnenolone. There was carried out synthesis of anabolic, androgenic, miorelaxante, anti-inflammatory, antitumoral, antituberculosis steroidal hormonal preparations. Tigogenin was recognized as a suitable raw material for the synthesis of steroids of the 5α-series.

There was developed an efficient method for growing it vegetatively at the Pharmacochemistry Institute and for the providing the manufacture of tigogenin with raw material 200 ha plantation was established in the Eastern Georgia on the Shiraki field.

*Y. gloriosa* an evergreen abundantly flowering decorative plant widely takes part in planting of greenery of the various regions of Georgia. *Y. gloriosa* develops great mass of vegetative organs. There were isolated few ten steroidal glycosides from the leaves, flowers, rhizomes, stems of the plant. Among them furo- and spirostanols, cholestanols, pregnans with interesting structures and biological activities.

Spirostanol glycosides from the leaves drying on the living plants exhibit anti yeast and antidermatophytic fungi activity. On the basis them there was developed (for clinical approbation) fungicide remedy named “Gloriofucin”.

There was elaborated plant growth stimulant preparation – Alexin on the basis of the steroidal glycosides from the flowers of *Y. gloriosa*, which have found uses in Allelopathy. Pre-sowing seeds treatment or spraying of saplings with low concentrations aqueous solutions of Alexin produce 20-60% increases in the yields of cereal, leguminous and vegetable cultures and provides for ecologically clean production.

In the plantation of *Y. gloriosa* (East Georgia) on the few plants was marked fruiting, very rare occurrence for this species. There were isolated 8 new furo- and spirostanol glycosides from the pericarp of fruits derivatives of tigogenin with multi monosaccharides.

There were isolated new stilbenes with interesting spirostructure named as Gloriosaols A, B, C, D, E from the barks of the roots, rhizomes and stems of *Y. gloriosa*, their molecules consist three parts and represents diastereoisomers. Gloriosaols exhibit high antioxidant, pro-apoptotic and antiproliferative activities.

## OP 4. A NOVEL ONE-POT SYNTHESIS AND PRELIMINARY BIOLOGICAL ACTIVITY EVALUATION OF CIS-RESTRICTED POLYHYDROXYSTILBENES INCORPORATING PROTOCATECHUIC AND CINNAMIC ACID FRAGMENTS

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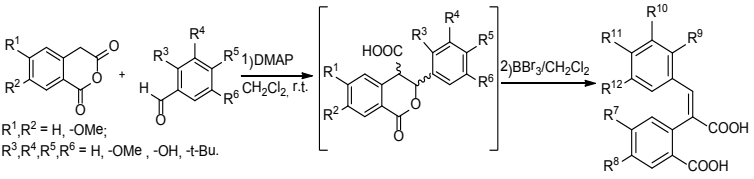
A series of 14 novel stilbenes was synthesized through a one-pot Perkin-like reaction between homophthalic anhydrides and various aromatic aldehydes, followed by treatment with $BBr_3$ [1]. This straightforward synthesis allows polyhydroxylated *cis*-stilbenes combining the two well-known pharmacophoric fragments of protocatechuic and caffeic acids, to be obtained in good yields and for short reaction times. The structure of the newly synthesized compounds was established by spectroscopic methods ($^1$H NMR, $^{13}$C NMR, IR and HRMS) and the double bond configuration was unequivocally elucidated by means of gated decoupling $^{13}$C NMR spectra and 2D NOESY experiments. Preliminary differentiating screening of their radical scavenging, antioxidant, antibacterial, anti-fungal and tyrosinase inhibitory activity was further performed. The results obtained suggest that the tested compounds possess a triple biological action as potent radical scavengers, antifungal agents and tyrosinase inhibitors in micromolar concentration. Moreover, it was shown that the combination of two different and independently acting fragments of well-known pharmacological profiles into one covalently bonded hybrid molecule can evoke synergistic effect resulting in higher than the expected activity.

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## OP 5. EFFICIENT SYNTHESIS OF PYRROLO[1,2-*A*]QUINOXALINE DERIVATIVES

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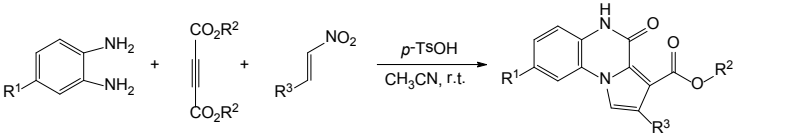
Quinoxaline derivatives are nitrogen-containing heterocyclic compounds and their importance has been reported in the literature [1]. They are a class of benzoheterocycles [2] displaying a broad spectrum of biological activities [3], and this has made them privileged structures in combinatorial drug discovery libraries [4]. The quinoxaline ring is part of various antibiotics such as echinomycin, levomycin, and actinoleutin [5,6] that are known to inhibit growth of Gram positive bacteria, and are active against various transplantable tumors [7]. They have also found applications as dyes [8], building blocks in the synthesis of organic semiconductors [9], efficient electron luminescent materials [10], building blocks for the synthesis of anion receptors [11], cavitands [12], dehydroannulenes [13], and DNA cleaving agents [14]. They also serve as useful rigid subunits in macrocyclic receptors for molecular recognition [15] and chemically controllable switches.

The pyrrolo[1,2-a]quinoxaline system is the skeleton of several heterocyclic compounds possessing interesting biological activity. This nucleus substituted at the C-4 with alkylpiperazines gives highly selective agonist affinity for the serotonine receptors.




| 1 | $R^1$ |
|---|---|
| a | H |
| b | Cl |

| 2 | $R^2$ |
|---|---|
| a | Me |
| b | Et |

| 3 | $R^3$ |
|---|---|
| a | Ph |
| b | 4-Me$C_6H_4$ |

| 4 | $R^1$ | $R^2$ | $R^3$ | Yield% |
|---|---|---|---|---|
| a | H | Me | Ph | 82 |
| b | H | Et | Ph | 85 |
| c | H | Me | 4-Me$C_6H_4$ | 70 |
| d | H | Et | 4-Me$C_6H_4$ | 75 |
| e | Cl | Me | Ph | 75 |
| f | Cl | Et | Ph | 73 |

**Scheme 1.**

In this work we wish to report a three-component reaction for the synthesis

of pyrrolo[1,2-*a*]quinoxalines in good yield. Intermediate dihydroquinoxalines, derived from the addition of *o*-phenylenediamine to dialkyl acetylenedicarboxylates, possess enamine character, and react with *β*-nitrostyrenes in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) to produce the title compounds (Scheme 1). It has been reported that p-toluenesulphonic acid (PTSA) acts as a mild, useful, non-toxic and inexpensive Lewis acid catalyst which makes the process convenient, more economic. The mild reaction conditions, operational simplicity and the excellent yields make the catalyst more versatile.

The structures of the isolated products were corroborated by $^{1}$H- and $^{13}$C-NMR spectroscopy. The procedure offers several advantages including high yields, operational simplicity and cleaner reaction which make it a useful and attractive process for the synthesis of these compounds.

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## OP 6. THE SYNTHESIS AND STUDY OF 5(6)-ALKOXY- AND 5(6)-CARBOXY-2-(1-ADAMANTYL)BENZIMIDAZOLES DERIVATIVES

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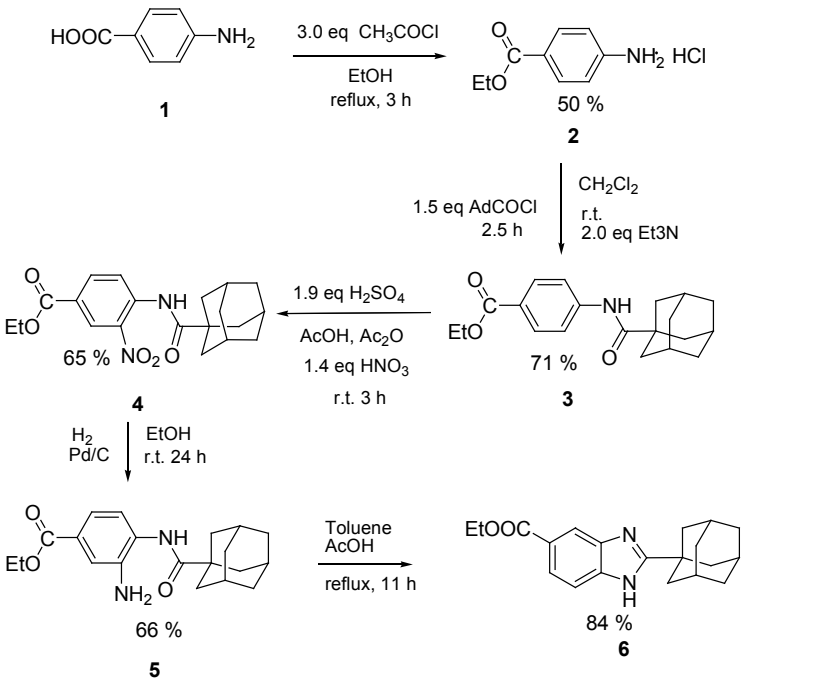
Wide spectrum of biological actions of adamantane derivatives makes promising research on the synthesis and pharmacological activity in a series of adamantyl amide derivatives and benzimidazoles [1-4].

The aim of our work was the synthesis of 5(6)–Carboxy– and 5(6)-Alkoxy-2–(1–adamantyl)benzimidazole derivetives. For supposed interesting biological activity and further chemical conversion we decided to synthesize the ethyl ester of 5(6)–Carboxy-2–(1–adamantyl)benzimidazole. For starting reagent was used p-Aminobenzoic acid (1). After esterification and adamantoyllation of compound 1 with Adamantane–1–carboxylic acid chloride was synthesized Ethyl 4-(adamantane-1-carboxamido)benzoate (3). Then was investigated nitration, catalytic reduction and aminoamide cyclization conditiones of obtained amide to give Ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate (6) (Scheme 1).

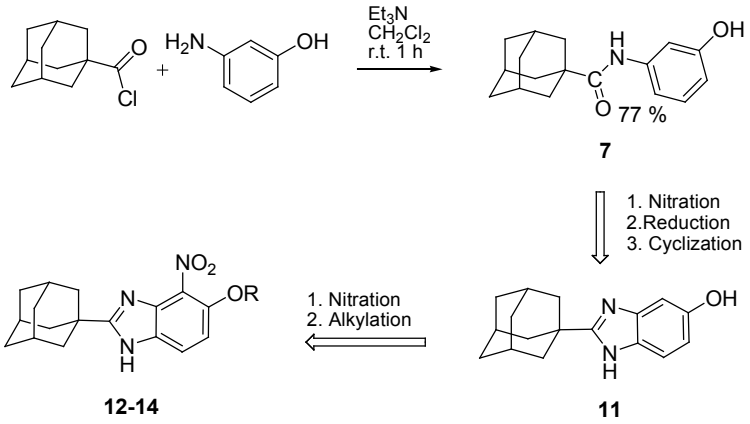
In direction of synthesis of 5(6)–Alkoxy–2–(1–adamantyl)benzimidazole derivatives initially was carried out the condensation of Adamantane carboxylic acid chloride with 3-Aminophenol to give N-(3-Hydroxyphenyl)adamantane-1-carboxamide (7). Subsequently, was fulfiled nitration, reduction and cyclization reactions of synthesized amide to obtain 5(6)–Hydroxy-2-(1–adamantyl)benzimidazoles(11). Afterwards, by nitration and alkylation of given Benzimidazole with aliphatic halogen reagents were synthesized 4-Nitro-5-alkoxy-2-(1-adamantyl)benzimidazole derivatives (12-14) (Scheme 2).




**Scheme 1.**

In direction of synthesis of 5(6)–Alkoxy–2–(1–adamantyl)benzimidazole derivatives initially was carried out the condensation of Adamantane carboxylic acid chloride with 3-Aminophenol to give N-(3-Hydroxyphenyl)adamantane-1-carboxamide (7). Subsequently, was fulfiled nitration, reduction and cyclization reactions of synthesized amide to obtain 5(6)-Hydroxy-2-(1-adamantyl)benzimidazoles(11). Afterwards, by nitration and alkylation of given Benzimidazole with aliphatic halogen reagents were synthesized 4-Nitro-5-alkoxy-2-(1-adamantyl)benzimidazole derivatives (12-14) (Scheme 2).

All synthesized compounds were identified by Infrared and Ultraviolet spectroscopes, $^{1}H$ NMR, $^{13}C$ NMR, DEPT, HMQC, HMBC, Mass spectroscopy and Elementary Analysis.




**Scheme 2.**

**Acknowledgment.** This work was fulfilled in the frame of **DAAD** (German Academic Exchange Service) PhD students' research scholarship (period 01.06.2013-01.12.2013 year). The author is very grateful to prof. Dr. Jens Christoffers, his scientific team and Carl von Ossietzky University of Oldenburg were this work was carried out.

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## OP 7. SYNTHESIS AND STUDIES OF SOME ADAMANTANE CONTAINING BENZYLIDENES, BENZIMIDAZOLES AND DIPEPTIDES

**Sh. Samsoniya[1], D. Zurabishvili[1], T. Bukia[1], M. Lomidze[1], I. Gogolashvili[1], G. Buzaladze[1], E. Elizbarashvili[2], U. Kazmaier[3]**

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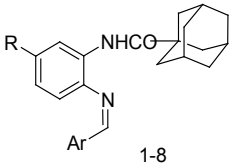
Adamantane fragment containing organic compounds possess antiviral, antibacterial, anticancer, anticataleptic, immunotropic, neuro-psychotropic and other activities. They amplify energy of the human body and significantly improve emotional and physical state in patients. Introduction of adamantane fragment into the molecule of a preparation changes or partly increases its biological activity, in most of the cases reduces toxicity, which can be explained by spatial structure of the compound, hydrophobia and lipophilicity. Also suitable conditions of transportation into the biological membranes, prolongation effect of preparations, high immunotropicity and others can be considered [1-4].

Aim of the research work is the development of synthetic method for adamantane-fragment containing some benzylidenes, benzimidazoles and dipeptides. Studying the effects of electron donor adamantane on reaction capacity and specific biological activity of obtained adamantane containing compounds.

We aimed to synthesize new derivatives of *o*-phenylenediamine in the molecule with adamantane-1-carboxamide (Ad−CONH) and arylidenimine (Ar−CH=N) groups [5].

For this aim we synthesized following structure:

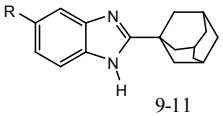



1-8

(1-8): R=H, $CH_3O$, Ar=$C_6H_4OH$, $C_6H_3BrOH$, $C_6H_2Br_2OH$, $C_6H_4NO_2$

2-(1-Adamantyl)benzimidazole (9) was synthesized with high yield. Afterwards, by nitration of 9 and reduction of 10 was formed compound 11. Some of new corresponding amides 12-14 were obtained by interaction of 5(6)-amino-2-(1-adamantyl)benzimidazole (11) with carboxylic acid chlorides and the condensation of 11 with aromatic aldehydes gave new Schiff bases 15-18 [6].

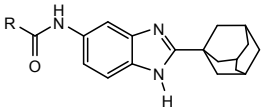
a




9-11

(9-11): R=H, $NO_2$, $NH_2$;

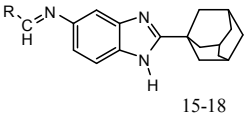
b




12-14

(12-14): R=Ad, $C_6H_5$, $CH_3$

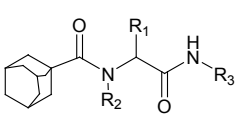
c



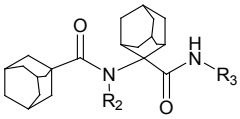

15-18

(15-18): R=2-OH-$C_6H_4$; 2-OH-5-$NO_2C_6H_3$, 2-OH-5-Br-$C_6H_3$, 2-OH-3,5-$Br_2C_6H_2$.

The Ugi four-component reaction (Ugi 4CR) was conducted by condensation of aldehyde or adamantane-2-on, amine, adamantane-1-carboxylic acid and isocyanide at 0-60 °C on the ethanol medium. Dipeptides 19 a-h and 20 a,b was obtained with 42 – 64 % yield [7].




**19 a-h**




**20 a, b**

**(19a-h):** $R_1$= i-$C_3H_7$, $C_4H_9$; $R_2$= i-$C_3H_7$, $C_4H_9$, $C_6H_5$, $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, Ad; $R_3$= $CH_2COOC_2H_5$, $C_6H_5$. **(20a,b):** $R_2$= $C_6H_5$, $C_6H_5CH_2$; $R_3$= $CH_2COOC_2H_5$.

The structure of some synthesized compounds was determined by IR, $^{1}H$ NMR,$^{13}C$ NMR spectral data.

**Acknowlegment.** The present project was supported by Shota Rustaveli National Science Foundation (Grant #GNSF/ST08/4-413) and (Grant #YS/33/6-420/12.)

The ideas expressed in this article belong to the authors and it may not reflect the position of the Georgia National Science Foundation

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## OP 8. PYRIMIDINE-BASED SYNTHESES OF BIS-HETEROARYL SYSTEMS FOR PRODUCING SELECTIVE CHEMOSENSORS OF METAL CATIONS

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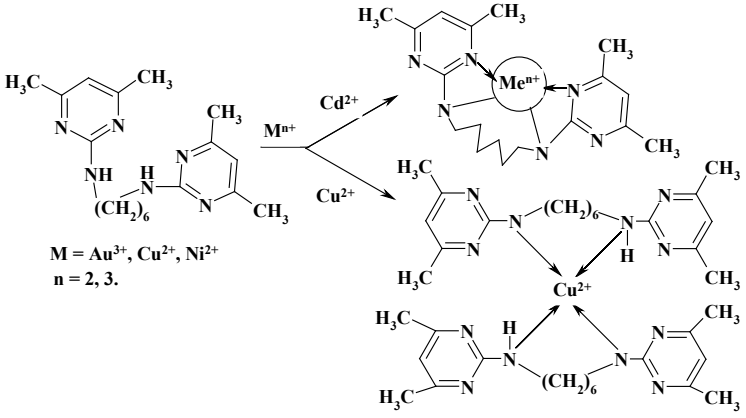
The presented research is devoted to the methods of synthesis of symmetric and asymmetric bis-heteroaryl systems.

The research is aimed to the synthesis of bis-heteroaryl derivatives of nitrogen-containing heterocycles that can find potential application as selective molecular sensors for colorimetric or luminescent detection of metal cations of a strictly definite type.

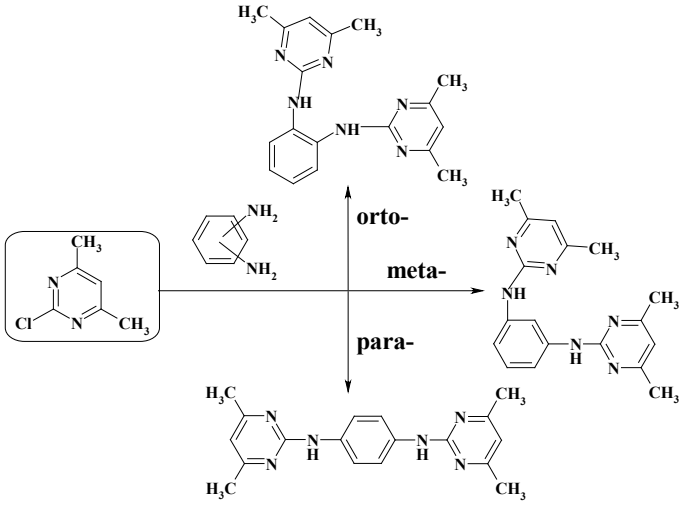
The research contains the following parts:

a) synthesis of symmetric bis(pyrimidin-2-ylamino)- and bis(pyrimidin-2-ylidenimino) alkanes as well as study of complex-forming ability of synthesized bis-arylalkanes;

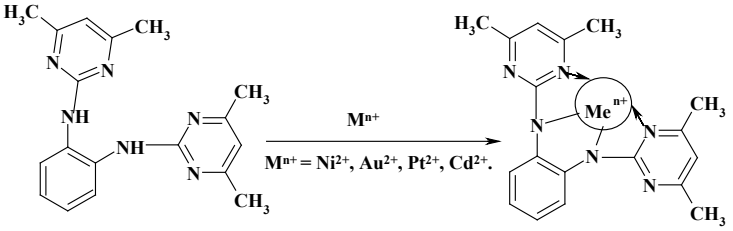



Bis[(pyrimidin-2-yl)amino]alkanes were synthesized by intereaction of 2-chloro-4,6-dimethylpyrimidine with hexamethylenediamine and ethylenediamine. The reaction of the obtained bis-pyrimidinylalkanes with methyliodide resulted in salts that in alcoholic KOH were transformed into anhydro bases.

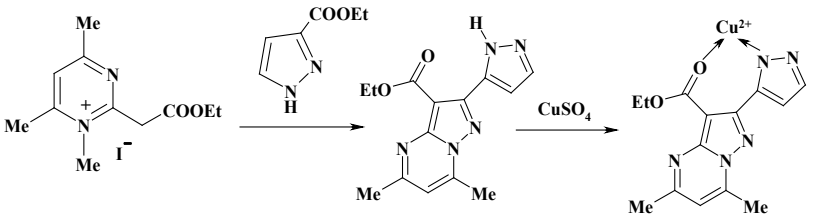
b) synthesis of substituted bis-N, N`-(pyrimidin-2-yl) phenylendiamines;



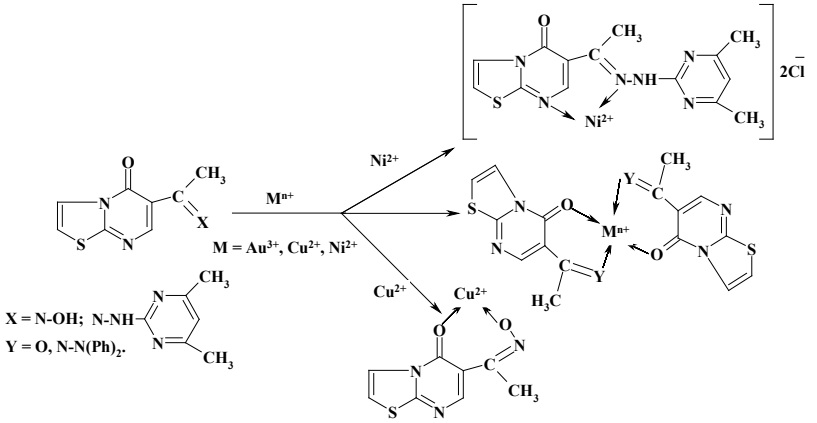

c) study of complex-forming ability of synthesized bis-N,N`-(pyrimidin-2-yl) phenylendiamines based thereon.




d) synthesis of asymmetric bis-arylalkanes with pyrazolo[1,5-a]pyrimidine and pyrazolyl fragments in their molecule via interclass recyclization of pyrimidinium salts and study of complex-forming ability of synthesized systems;



e) synthesis of hydrazones and oximes of 6-acetyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-one with a pyrimidine fragment in the functional group and study of complex-forming ability of synthesized systems.



This work was supported in part by State Committee of Science of the Ministry of Education and Science of the Republic of Armenia award No. 13-1D334, and by Armenian-Russian award No. 13RF-087 .

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## OP 9. THEORETICAL STUDY FOR THE EFFECT OF HYDROXYL RADICAL ON THE ELECTRONIC PROPERTIES OF CYCLOBUTADIENE MOLECULAR

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The present work deals with the electronic properties of organic molecules in form ring, containing semiconductor atoms. Cyclobutadiene is the original ring before replacing the hydrogen atom by hydroxyl radical**.** Density functional theory with B3LYP/6-21G level has been used to find the electronic structure and electronic properties of the studied molecules. The effect of substitute on cyclebutadiene molecule is discussed on the basis of the calculated electronic properties. It is included total energy, energy gap, ionization potential, electronic affinity and electrophilicity, with comprehensive analysis of the calculated highest-occupied and lowest-unoccupied orbital (HOMO and LUMO respectively) energies. The results in this study show that the calculated electronic properties for cyclebutadiene have been found a good agreement with the previous studies. For other molecules, we have not found a reference data, so this study supplies a new data in this aspect. These calculations have been performed using Gaussian 03 package.

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## OP 10. PHOTOCATALYTIC DEGRADATION OF ANILINE IN AQUEOUS SOLUTION USING ZnO NANOPARTICLES

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Aniline is a compound used by the chemical industry in several processes, such as the synthesis of pesticides, chemical brighteners, dyes, etc. It is also a common by-product of the petroleum, paper and coal industries. Due to the negative environmental impact of this refractory organic compound, there is a need to develop methods to carry out its degradation. Electrochemical oxidation is perhaps the most studied method for the degradation of aniline. However, some difficulties seem to arise in the practical use of this method, such as the need for high over-voltages and the poor efficiencies attained for the treatment of dilute effluents, which leads to only partial mineralization of the contaminant. A more recent method for the destruction of refractory organic compounds in mild conditions is photocatalysis.

Photocatalysis has been established as an efficient process for the mineralization of toxic organic compounds, hazardous inorganic constituents and bacteria disinfection owing to the strong oxidizing agent, i.e., hydroxyl radical (OH·). Some metal oxide semiconductors like titanium dioxide ($TiO_2$), zinc oxide (ZnO), tungsten oxide ($WO_3$), strontium titanate ($SrTiO_3$), and hematite ($\alpha$-$Fe_2O_3$) are proven to be dynamic photocatalysts. Most of these semiconductor photocatalysts have band gap in the ultraviolet (UV) region, i.e., equivalent to or larger than 0.2 ev ($\lambda$ = 387 nm). Therefore, they promote photocatalysis upon illumination with UV radiation. ZnO has emerged to be more efficient catalyst as far as water

detoxification is concerned because it generates $H_2O_2$ more efficiently; it has high reaction and mineralization rates. Also it has more numbers of active sites with high surface reactivity. ZnO has been demonstrated as an improved photocatalyst as compared to commercialized $TiO_2$ based on the larger initial rates of activities and its absorption efficacy of solar radiations. However, ZnO has almost the same band gap (3.2 ev) as $TiO_2$.

In this study, application of photocatalytic process of ZnO nanoparticle and ultraviolet light for aniline removal from synthetic effluent was investigated.

Several variables such as pH (3, 7 and 10), retention time (30-90 min), initial concentration of aniline (250-1000 ppm), ZnO concentration (0.2-0.5 g/L) and UV-A light intensity (10, 20 and 40 w) had been considered. A Plexiglas photocatalytic reactor was designed to treat aniline synthetic wastewater with net volume of 5 L. UV-A lamps were installed in the middle of the photocatalytic reactor (inside a quartz sleeve), respectively and ZnO nanoparticles slurry with specific concentrations were added in wastewater with initial aniline concentration of 250 ppm. The pH value of wastewater was adjusted to considered values by HCl and NaOH (3 M), then the UV-A lamp turned on. For better mixing, a magnet stirrer was installed under the reactor. Sampling was done after considered retention times and prepared for further analyses. Samples were first centrifuged in 8000 rpm for 20 min, then supernatant was filtered through 0.2 µm PTFE filters, after that extracted into $CH_2Cl_2$ by adding 2 mL of the solvent into 8 mL of filterd sample and 1 min shaking. Extracted sample was then collected from the bottom of the falcon tube and stored in 4oC in dark vessel, until further injection to a Gas Chromatograph (GC).

After measurement of removal efficiency of aniline pollutant, COD experiment was done for samples of optimum condition of aniline removal from synthetic effluent, for better measurement of aniline and its derivates removal.

Results showed that the nanophotocatalytic (ZnO+UV-A) reaction could efficiently oxide aniline pollutant from synthetic water. On the retention time of 90 min, removal efficiencies of aniline have been getting more than others. Although removal efficiency of aniline in concentration of ZnO nanoparticles of 0.5 g/L was a bit higher than others, statistical analyses (ANOVA) shows no significant difference between removal efficiencies in several concentration of ZnO nanoparticles ($Pvalue<0.05$). Moreover, by

increasing UV light intensity, the removal efficiency of Aniline from synthetic water was getting higher, significantly (Pvalue<0.05). The pH variable plays an important role in the removal of Aniline. In acidic pH, ZnO nanoparticles turn to soluble form and failed their photocatalytic effect. However, in alkaline pH, the most removal efficiency was measured in 90 min retention time, UV-A=40 W and 0.5 g/L ZnO, which was 80.77%. The optimum concentration of ZnO was chosen to 0.2 g/L, as result of ANOVA results, and in the UV-A intensity of 40 w, pH=10 and retention time of 90 min. COD results also showed that the removal efficiency of the COD in the optimum condition was about 47%, while the removal efficiency of aniline was about 73.22%. Therefore, it could be concluded that by oxidizing of aniline, some derivates had been created and removal of aniline is relatively independent from its derivates. Finally, it could be concluded that the nanophotocatalytic reaction of UV-A+ZnO could be applied for aniline removal from wastewater.

## OP 11. SYNTHESIS OF CYCLOHEXANE DERIVATIVES INCLUDING Br, Cl, N, O And S At 1,2,4,5-POSITIONS

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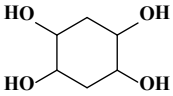
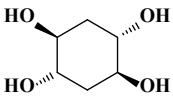
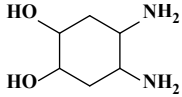
Cyclitols, especially those that are six members were studied by many chemists [1, 2]. 1,2,4,5-Tetrahydroxycyclohexane tetras (**1**) are cyclitols and their synthesis were carried out [3]. Betitol (**2**), naturally occurring cyclohexanetetrols [4], is found in very small amounts in sugar beet molasses. Diastereomeric 1,2-dihydroxy-4,5-diaminocyclohexanes (**3**) whose $Pt^{II}$ complexes have antitumor properties were reported [5].



**1**

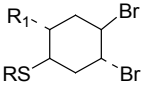


**2**

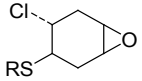


**3**

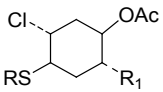
1,4-Cyclohexadiene [6] was used as starting material. Brominations of products, obtained from additions of 2,4-dinitrobenzenesulfenyl chloride to 1,4-cyclohexadiene in different conditions, gave **4** and **5** as the sole products. Epoxide **6** was synthesized and its reactions with reagents such as $Ac_2O/H^+$ and $NaN_3$ gave corresponding products **7-10**.



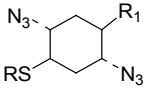
4 $R_1$ = Cl
5 $R_1$ = OAc



6

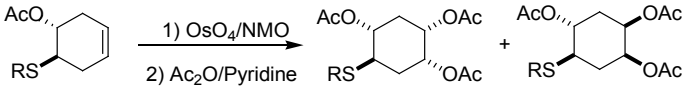


7 $R_1$ = Cl
8 $R_1$ = OAc



9 $R_1$ =OH
10 $R_1$ = OAc

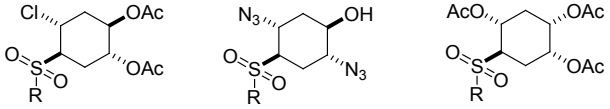
Cyclohexane derivatives with three OAc groups two of which are at *cis* may obtained from compound **11**. By this aim, we treated acetate **11** with catalytic $OsO_4$ and N-methylmorpholine N-oxide (NMO) as co-oxidant. From this reaction, the isomeric triacetates **12** and **13** were synthesized in 47% and 17% yield, respectively (Scheme 1).
Sulfones **14-16** were obtained from reactions of the corresponding sulfides with excess *m*-CPBA (*meta*- chloroperbenzoic acid) in $CH_2Cl_2$.




11 12 47% 13 17%

R = 2,4-Dinitrophenyl

**Scheme 1.**




14 15 16

R = 2,4-Dinitrophenyl

The products formed in these reactions were purified and their structures were characterized by spectroscopic methods such as NMR and X-ray analysis. Selectivity was observed in addition reactions.

**Acknowledgements.** We are grateful to Atatürk University and TÜBİTAK (104T354) for their financial supports.

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## OP 12. NEW CATIONIC POLYMERS COMPOSED OF NATURALLY OCCURING BUILDING BLOKS – ARGININE AND SPERMINE

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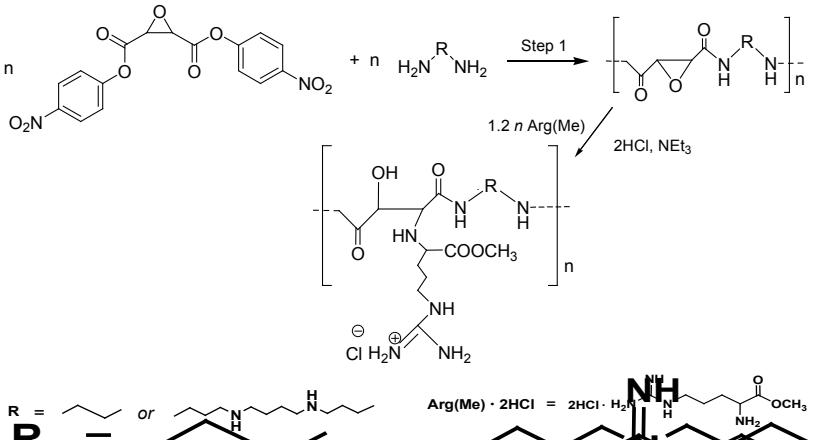
The battle against antibiotic resistant bacteria is a topical problem today. Among various synthetic antibacterials cationic polymers are considered as one of the most "powerful weapon" to beat emerging pathogens [1]. Cationic polymers are also promising as gene intracellular delivery (transfection) agents for the applications in both gene therapy and biotechnology [2,3]. The development of non-toxic and more efficient antimicrobial and gene transfection agents for *in vivo* applications requires polycations that can be cleared from the body after their function is fulfilled. For this reason biodegradable cationic polymers have attracted considerable interest [4]. The present study deals with the synthesis and biological study of new cationic polymers composed of naturally occurring building blocks such as α-amino acid arginine (for incorporating guanidine-groups that provide a low cytotoxicity and strong interactions with DNA [5] along with antibacterial activity) and endogeneous multi-amine spermine (for incorporating *sec*-amino groups like polyethyleneimine that show high transfection and antibacterial activities). To our best knowledge no attempt was made to combine these two naturally occurring cationic building blocks for constructing new highly charged polycations. The new polymers are obtained *via* original two-step/one-pot synthetic strategy comprising solution polycondensation of spermine (in combination with other diamines, e.g. ethylenediamine) with *trans*-epoxy-succinic acid and subsequent treatment of the intermediate epoxy-polyamides with arginine methyl ester dihydrochloride according to scheme 1:




***Scheme 1.*** Two step/one pot synthesis of cationic polymers

The obtained new polymers contain 1,2-diamide fragments in the backbones that provides biodegradation through anchimerically assisted hydrolysis. Some of the polymers of this series revealed virtually no cytotoxicity (with Chinese Hamster Ovary (CHO) and insect Schneider 2 (S2) cells) and showed a transfection activity [6]. The polymers revealed also antimicrobial activity (tested against *Bacillus cereus, Staphylococcus aureus*, *Mycobacterium phlei*). The new cationic polymers have a potential for the applications in gene therapy and biotechnology, as antimicrobial additives for food protection, etc.

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## OP 13. SYNTHESIS AND BIOLOGICAL PROPERTIES OF [1,3]THIAZOLO [4,5-*d*]-PYRIDAZIN-4(*5H*)-ONES

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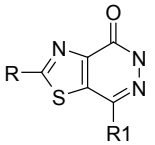
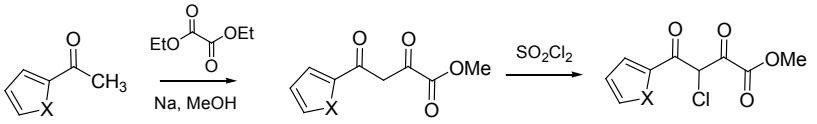
In order to search for new biologically active compounds we have synthesized a series [1,3]thiazolo[4,5-*d*]pyridazine-4(5*H*)-ones with various substituents in the 2-nd and 7-th positions of the heterocyclic system.



where R = $CH_3$, Ph, $NH_2$, NHMe, NHPh, pyrrolidine-1, piperidine-1, morpholine-4.
$R_1$ = Ph, $4FC_6H_4$, $4ClC_6H_4$, $4MeOC_6H_4$, $3,4(MeO)_2C_6H_4$, $3MeOC_6H_4$, $4MeC_6H_4$, $4EtC_6H_4$, $2,4Me_2C_6H_4$, α-furyl, α-thienyl

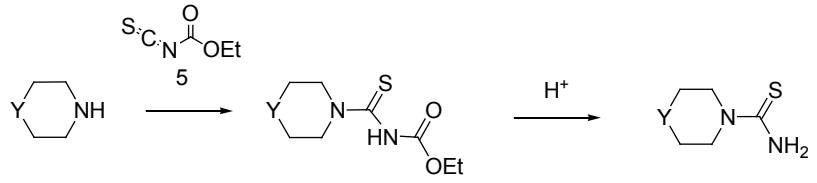
For example, 2,4-dioxo-4-furan(thiophen)-2-yl-butyric acid methyl esters **2a,b** were prepared by Knoevenagel condensation from ketones **1a,b** and diethyl malonate. 3-Chloro-2,4-dioxobutyric acid methyl esters **3a,b** was synthesized by refluxing compounds **2a,b** with $SO_2Cl_2$ in chloroform.




**1 a,b** **2 a,b** **3 a,b**

1-3 a) X = O, b) X=S

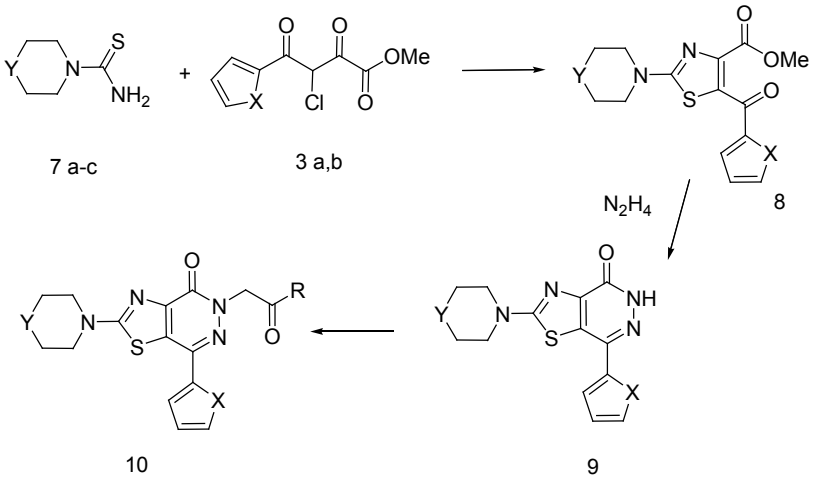
Pyrrolidine-(or piperidine, or morpholine)-1-carbothionic acid amides **7a-c** were prepared from cyclic amines **4a-c** and carboethoxyisothiocyanate **5**.



4 a-c 6 a-c 7 a-c

4-6 a) Y=bond, b) Y=$CH_2$, c) Y=O

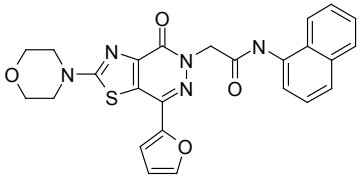
Through the condensation of 3-chloro-2,4-dioxobutyric acid methyl esters **3a,b** with carbothionic acid amides **7a-c** 5-(furan or thiophen-2-carbonyl)-2-R-thiazole-4-carboxylic acid methyl esters **8** were obtained. Thiazolo[4,5-*d*]pyridazines **9** were obtained by refluxing **8** with hydrazine hydrate in ethanol. Compounds **9** were alkylated with aryl halogenides, substituted phenacyl bromides and α-chloroacetanilides with the order to obtain a series of compounds **10**.



7 a-c 3 a,b 8 9 10

For 50 compounds of this series was studied antitumor activity at the National Cancer Institute (NCI, Bethesda, Maryland, USA) under the International Program of the National Institutes of Health - DTP (Developmental Therapeutic Program). The study was performed on 60 cancer cell lines (leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate, breast) by the action

of a substance in a concentration of $10^{-5}$ mol/l. The leader compound was found – 2-[7-(2-furyl)-2-morpholin-4-yl-4-oxo[1,3]thiazolo[4,5-*d*]pyridazin-5(4*H*)-yl]-N-1-naphthylacetamide (see below). This compound exhibits the highest activity against cell line NCI-H322M (lung cancer).



The value of mitotic activity reaches 83.99%. In addition, a high degree of reduction in the number of tumor cells was observed in experiments with cancer cell lines such as OVCAR-3 (ovarian cancer) and HOP-92 (lung cancer), and composed respectively 75.70% and 67.16%. It should be noted that this compound inhibits the growth or destroys 40 of the 55 studied cancer cell lines.

$[Ca^{2+}]_i$-desensitizing activity of 40 compounds was studied. It was found the compound, that relaxes smooth muscles in blood vessels (87.4±5)% at a constant concentration of intracellular calcium. Due to its LD50 is greater than 2000 mg/kg, it can be proposed to create on its basis a remedy for the treatment of hypertension with a new mechanism of action.

Antiviral activity of 38 compounds was studied. It was found that N-(2-chlorobenzyl)-2-[2-methyl-4-oxo-7-(2-thienyl)[1,3]thiazolo[4,5-*d*]pyridazin-5(4*H*)-yl]acetamide has showed activity against all investigated strains of viruses (H1N1, H3N2, H5N1, influenza B and SARS) with selectivity indices Si> 8.

## OP 14. DIRECT C-H BORYLATION OF ARENES WITH CARBORANE-BASED QUASZI-BORINIUM CATION

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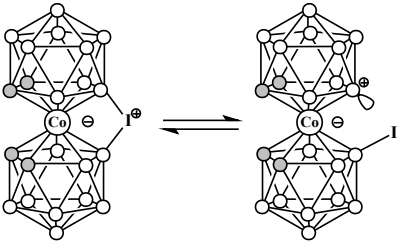
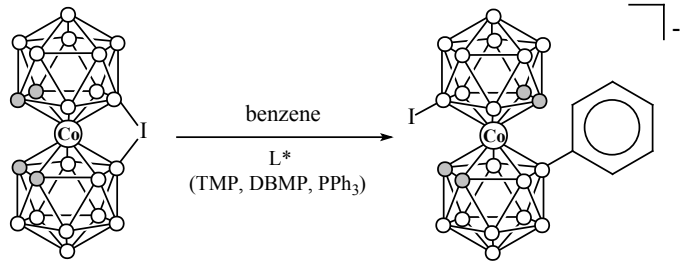
The reactions of the iodonium derivative of cobalt bis(dicarbollide) [8,8'-μ-I-3,3'-Co(1,2-$C_2B_9H_{10})_2$] with aromatic solvents were studied. It is assumed that reversible disclose of the iodonium bridge could result in the generation reaction center at boron atom demonstrating properties of both very strong electrophile and very strong Lewis acid.

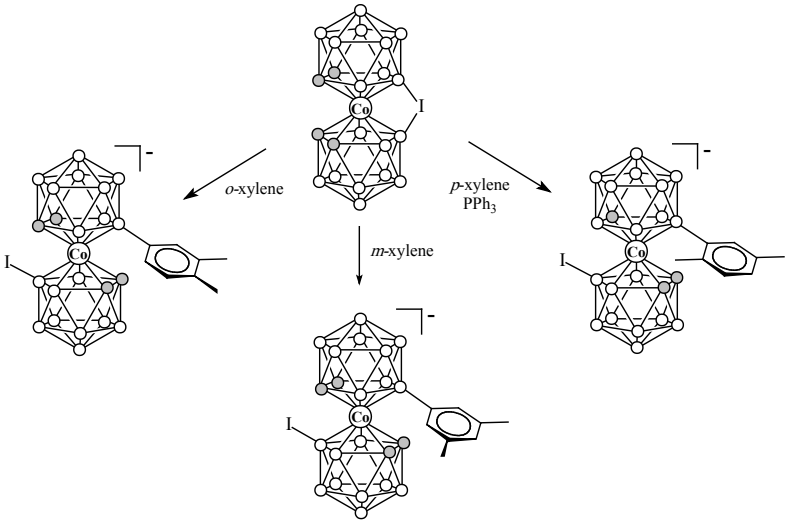



The reactions of [8,8'-μ-I-3,3'-Co(1,2-$C_2B_9H_{10})_2$] with "classical" Lewis bases such as pyridine and morpholine in benzene result in formation of the corresponding onium derivatives [8-L-8'-I-3,3'-Co(1,2-$C_2B_9H_{10})_2$]. However in the case of sterically hindered Lewis bases formation of onium derivatives of cobalt bis(dicarbollide) is not possible. As it is known, the reaction of frustrated Lewis acid – Lewis base pairs, in which the formation of the classical acid-base complex is not possible due to steric hindrance, can lead to activation of various small molecules.

We found that the reaction of [8,8'-μ-I-3,3'-Co(1,2-$C_2B_9H_{10})_2$] with 2,2,6,6-tetramethyl-piperidine, 2,6-di*(tert*-butyl)-4-methylpyridine and triphenylphosphine at room temperature does not proceed, but gentle heating for 20 minutes results in CH-borylation of benzene to form the corresponding phenyl derivative [8-Ph-8'-I-3,3'-Co(1,2-$C_2B_9H_{10})_2]^-$, the structure of which was established by NMR spectroscopy and confirmed by X-ray diffraction [1].




TMP = 2,2,6,6-tetramethylpiperidine
DBMP = 2,6-di(*t*-butyl)-4-methylpyridine




With activated aromatics such as toluene the borylation reaction takes place on heating even in the absence of sterically hindered Lewis bases resulting in a mixture of the corresponding tolyl derivatives. In the case of more activated aromatics such as *ortho*- and *meta*-xylene the borylation proceeds slowly (5-6 days) without Lewis base even at ambient temperature, whereas heating to 80 °C completes the reaction for 1 h. In the both cases the borylation proceeds at the positions that are the most distant from the primary substituents. In the case of *para*-xylene, where position for electrophilic attack is shielded by the methyl group, the reaction proceeds only in the presence of triphenylphosphine as Lewis base [2].

The borylation of more activated, but more sterically hindered mesitylene requires heating and Lewis base. However in this case the reaction with triphenylphosphine produces the corresponding phosphonium derivative [8-$Ph_3P$-8'-I-3,3'-Co(1,2-$C_2B_9H_{10})_2$], whereas the reaction with TMP gives the mesityl derivative [8-Mes-8'-I-3,3'-Co(1,2-$C_2B_9H_{10})_2]^-$ [1].

The Lewis acidity of the reaction intermediate forming on the iodonium bridge disclosure was determined using the Beckett-Gutmann method [3].

This work was supported by the Russian Foundation for Basic Research (14-03-31029 and 13-03-00581).

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## OP 15. EFFECT OF SPIPERONE BINDING ON A MEMBRANE-BOUND HUMAN GI-COUPLED $D_{2L}$ DOPAMINE RECEPTOR

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Tertiary structure determination of $D_{2L}$ dopamine receptor ($D_{2L}R$) is crucial for novel drug design for the treatment of schizophrenia and Parkinson Syndrome. Here, homology modelling and explicit solvent molecular dynamics (MD) methods were applied to determine the tertiary structure of Gi-coupled $D_{2L}R$ in complex with spiperone, an inverse agonist of $D_{2L}R$ (0.02 nM)[1], or dopamine, an agonist of $D_{2L}R$.

An activated human dopaminergic $D_{2L}R$ was constructed by homology modeling, which involved aa sequence modification of a recently published crystal structure of a human $D_3$ dopamine receptor [2] that possesses 73.4% sequence identity with that of $D_{2L}R$. X-ray coordinates for the α, β, and γ subunits of human Gi were obtained from Protein Data Bank, PDB ID: 2XNS [3] and PDB ID: 3SN6 [4] respectively. Dopamin and spiperone were docked into the binding site of $D_{2L}R$ by Autodock_vina v1.5.6 [5]. Intermolecular enthalpy of binding energies were determined by Molecular Mechanics-Poisson Boltzman Surface Area (MM-PBSA) method [6].

Analysis of MD trajectories for $D_{2L}R$ in complex with ligands revealed that binding of dopamine to $D_{2L}R$ stabilizes the active-state conformation of the G protein coupled receptor (GPCR) by allowing TM5 and TM6 helix structures of $D_{2L}R$ to strongly make H-bonds with the α-subunit of Gi, a finding that is also supported by MM-PBSA with a stronger enthalpy of binding. Binding of spiperone, however, stabilizes an inactive-state conformation of $D_{2L}R$, disabling H-bond formations between TM5-TM6 loop of $D_{2L}R$ and the α-subunit of Gi.

It was determined that dopamine exerts its agonist affect on D2-type dopamine receptors by anchoring the TM5-TM6 loop structure of $D_{2L}R$ to the α-subunit of Gi, which in turn inhibits its effectors. Spiperone dislodges the TM5-TM6 loop from the α-subunit of Gi, which possibly switches-on its effector.

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## OP 16. ORGANIC AND ORGANOMETALLIC TECTONES FOR SUPRAMOLECULAR GELS

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During last fourteen years we have been working on the ligand design and synthesis of new types of metal containing coordination polymers as well as synthesis of discrete coordination nano-aggregates [1-10]. We have experienced in the synthesis of new conjugated di- and tri-pyridine ligands acting as *exo*-dentate bridges in formation of anisotropic coordination polymers. More than one hundred of new crystalline supramolecular polymers have been already characterized in our laboratory (Fig. 1).

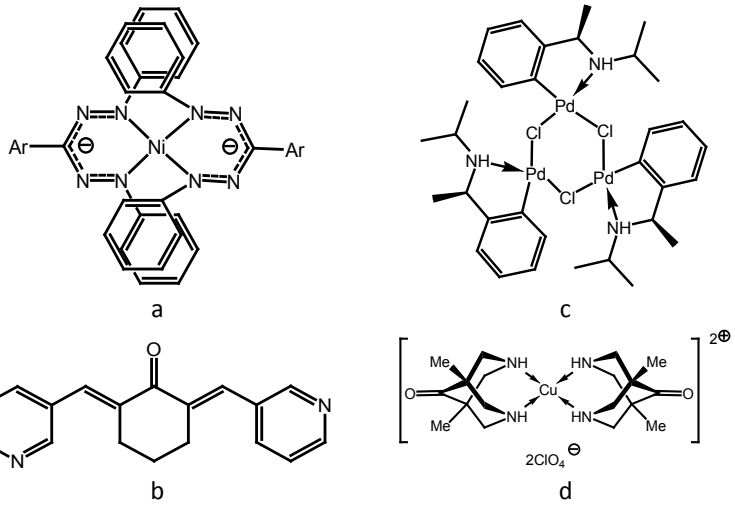
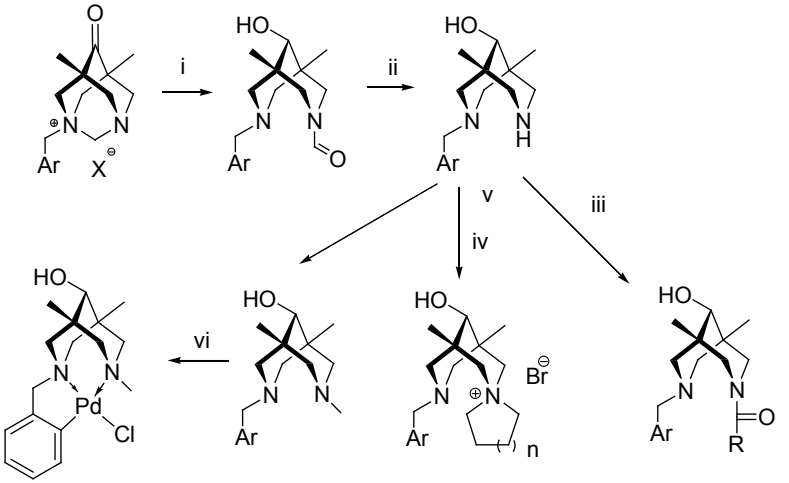



**Figure 1.** Examples of supramolecular tectons (a [5], b [1], c [9]) and supramolecular synthon (d [10]) designed in our lab

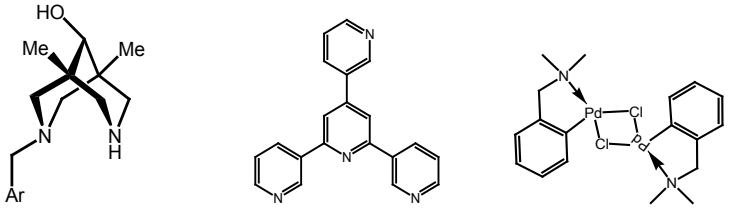
Nowadays, our group pays particular attention to the non-crystalline gel-like supramolecular/coordination polymers which are one of the most promising families of "smart materials" since they could change (sometimes reversibly) their physical and/or chemical behavior under the action of an external stimulus – light, sound, chemicals, pH, temperature, share force, redox, magnetic field etc [11]. We succeed in (serendipitous) synthesis of

supramolecular gels based on substituted bispidinol tectons (Scheme), terpyridine-like ligands and *ortho*-palladated benzylamines.



i: KOH, $H_2O$; ii: HCl, $H_2O$, t; iii: 4-$ClC_6H_4COCl$, $C_6H_6$, **BG** then NaOH, $H_2O$; iv: $Br(CH_2)_{4\text{-}5}Br$, n=1,2; v: MeI; vi: $PdCl_2(PhCN)_2$. a: Ph; b: 4-$FC_6H_4$; c: 4-$ClC_6H_4$; d: 4-$BrC_6H_4$.

All gels were studied by the combination of methods. For *molecular level* investigation IR- and NMR-spectroscopy, cyclic volt-ammetry, single crystal and powder X-ray analysis were applied. The self-organization at the *nano level* were studied by SEM, TEM, AFM and SAXS (Fig. 2). The gel *bulk properties (macro level)* were analyzed by POM, DLS, DSC and rheology study.



a b c

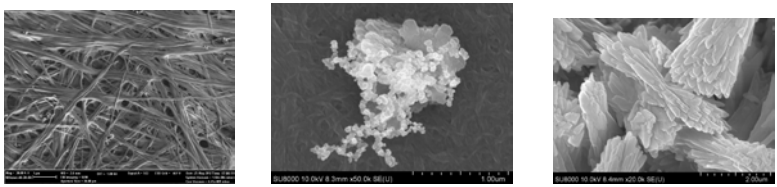
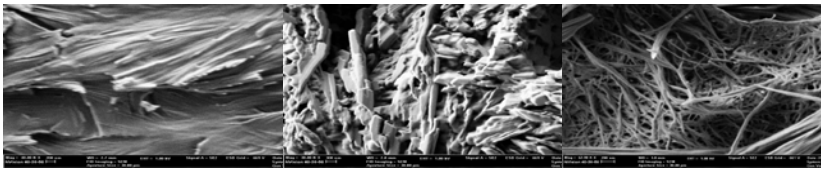


**Figure 2.** Chemical formulas of gelators studied and typical SEM images of their gels: a – bispidinols (gelled $C_6H_6$ upon amidation); b – terpyridines (gelled MeOH/MeCN upon $Ag^I$ complex formation); c – palladacycles (gelled $C_6H_6$ upon bipy addition)

Our current investigations are focused on the synthesis of supramolecular systems using non-traditional reaction media, first of all, supercritical carbon dioxide ($scCO_2$) [12]. The examples of using $scCO_2$ for aerogels preparation will be presented (Fig. 3).



a b c

**Figure 3.** SEM images of bispidinol gels formed under different drying conditions: a – xerogel from $C_6H_6$; b – xerogel from liq-$CO_2$; c - aerogel from sc-$CO_2$.

We also started a detail investigation of ferrocene-containing polymers and supramolecular materials [13]. Comprehensive achievements in the field of modern organic synthesis and nanotechnology could be find in our recent review paper [14]. The authors thank RFBR (grant № 14-03-91160) and REC M.U.S.I.C. for SCF equipment (http://www.chem.msu.ru/rus/supercritical-fluids/welcome.html).

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## OP 17. SYNTHESIS OF NOVEL CHIRAL SULFOXIDES

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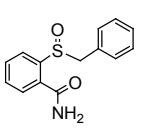
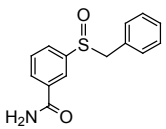
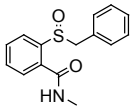
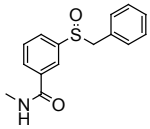
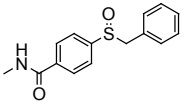
Chiral sulfoxides are widely used as valuable drug compounds (such as omeprazole, lansoprazole, pantoprazole, rabeprazole) [1, 2], pesticides (fipronil, propargit, methiocarb sulfoxide, fensulfothion, etc.) [2], chiral auxiliaries and chiral ligands to metals [3, 4], as well as have been incurporated into a variety of natural products and their synthetic derivatives. In this study novel chiral shown below were synthesized and characterized.

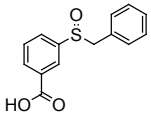

2-(Benzylsulfinyl) benzamide

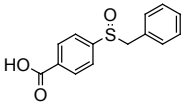

3-( Benzylsulfinyl) benzamide

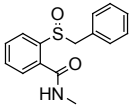

2-( Benzylsulfinyl) N-methyl benzamide


3-( Benzylsulfinyl) N-methyl benzamide

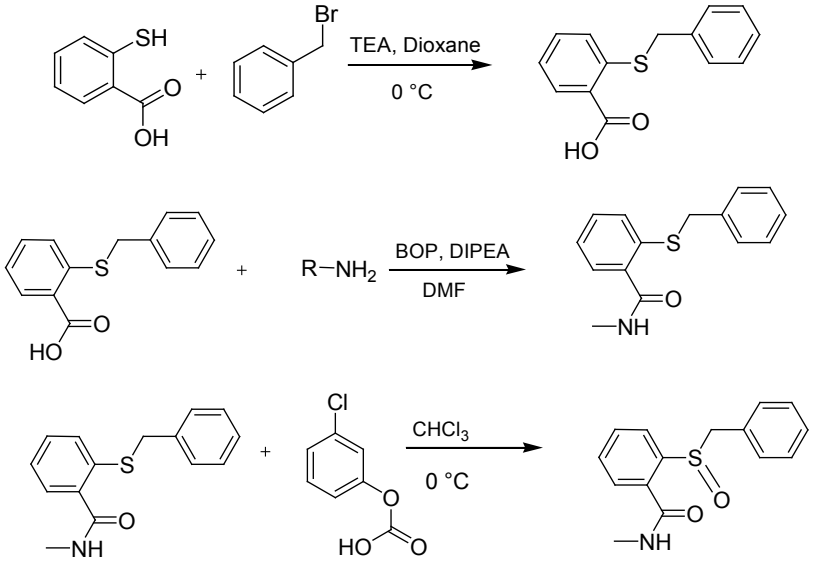

4-( Benzylsulfinyl) N-methyl benzamide


3-( Benzylsulfinyl) benzoic acid


4-(Benzylsulfinyl) benzoic acid


Methyl -2-( Benzylsulfinyl) benzoate

Synthesis of most sulfoxides were proceeded by three-step synthetic sequence, namely alkylation of commercially available thiosalicylic acid with alkyl halides affording the ortho-, meta- and para- carboxy sulfides, which were transformed into amides by coupling with different amines, and oxidized with the oxidizing agent.




The analytical methods used were: thin-layer chromatography (TLC) for monitoring the synthesis and nuclear magnetic resonance (NMR) and mass spectrometry (MS), as well as upon demand other methods for confirming the structure of synthesized compounds. Flash chromatography (FC) for purification of obtained products and TLC for monitoring of FC process.

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## OP 18. ANTIOXIDANT ACTIVITY OF ROSMARINIC ACID-RICH EXTRACTS OF SUMMER SAVORY (SATUREJA HORTENSIS L.)

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Summer savory (Satureja hortensis L., Lamiaceae) is used in several regions of the world as a spice and folk medicine. Anti-inflammatory and cytoprotective effects of S. hortensis and of its rosmarinic acid-rich phenolic fraction have been demonstrated in animal trials [1, 2]. However, previous studies of rosmarinic acid in cell models have yielded controversial results. In this study, we investigated the effects of summer savory extracts on $H_2O_2$-challenged human lymphoblastoid Jurkat T cells. LC-MS analysis confirmed the presence of rosmarinic acid and flavonoids such as hesperidin and naringin in the phenolic fraction (fig 1).

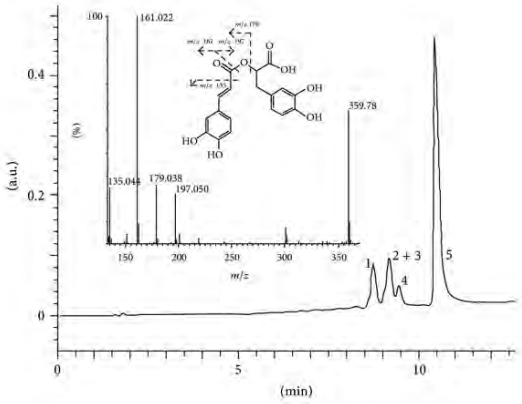


**Figure 1:** HPLC chromatogram of the S. hortensis rosmarinic acid fraction. The peak 5 represents rosmarinic acid and the peak 2 + 3 partially separated naringin and hesperidin. The peaks 1 and 4 were tentatively identified as rutin and apigenin-7-glucoside, respectively. Insert: mass-spectrum of the rosmarinic acid and its fragmentation scheme.

Adding 25 or 50 μM of $H_2O_2$ to the cell culture caused oxidative stress, manifested as generation of superoxide and peroxyl radicals, reduced cell viability, $G_0/G_1$ arrest, and enhanced apoptosis. This stress was significantly alleviated by the ethanolic and aqueous extracts of S. hortensis and by the partially purified rosmarinic acid fraction. The application of an aqueous S. hortensis extract doubled the activity of catalase and superoxide dismutase in the cells. The production of IL-2 and IL-10 interleukins was stimulated by $H_2O_2$ and was further enhanced by the addition of the S. hortensis extract or rosmarinic acid fraction. The $H_2O_2$-challenged Jurkat cells may serve as a model for investigating cellular mechanisms of cytoprotective phytonutrient effects.

The present research has demonstrated that rosmarinic acid-rich extract of S. hortensis can protect Jurkat cells from oxidative stress caused by hydrogen peroxide. These findings are in line with the antioxidant, cytoprotective, and anti-inflammatory activities of rosmarinic acid that have been observed in animals and humans. Therefore, the $H_2O_2$-challenged Jurkat cells may serve a model for investigating cellular mechanisms of cytoprotective effects of phytonutrients. It should be kept in mind, however, that these results were achieved with a rather high concentration of rosmarinic acid that supposedly could overcome the culture-associated artifacts. Further research is needed, in order to optimize the experimental system.

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## OP 19. IODINEALKOXYLATION OF LIMONENE BY PROPYNOL AND ANNILATION OF NEW CYCLE FROM ADDUCT

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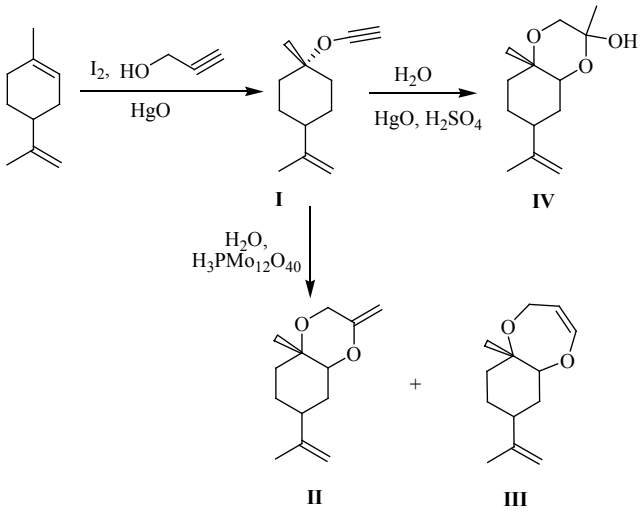
Three-component interaction of unsaturated $C_3$-alcohol, olefine and deliverer-halogen has proved oneself as a general synthesis method of corresponding β-halogen ethers [1,2].

By us it has been determined, that iodinealkoxylation of limonene by propynol and crystalline iodine is proceed regio- and stereoselectively exclusively by intracycle double bond by forming of β-iodine ether (I). By intermolecular cyclization of the last in presence of water and hetero acid transfer to mixture of isomer bicycle compounds have been realized (II, III).

Separation of isomers has been realized by column chromatography with use of hexane and hexane-benzene mixture.

Meanwhile, by hydration in condition of Kucherov reaction, along with addition of water by triple bond, a hydrolysis of iodine atom with subsequent circuit of cycle and forming of heterocycle is proceed (IV)



But in presence of natural zeolite catalyst–clinoptylolite ($(NaK)_4CaAl_6Si_{30}O_{72}\cdot 24H_2O$) process proceeds less selectively and leads to the hard separated mixtures. The basic share of this mixture consists from regioisomers, the minor part – from diastomers.

Composition and structure of compounds have been determined on base of IR and NMR spectrum and also on base of element analysis data.

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## OP 20. "SWITCH OFF/SWITCH ON" REGULATION OF DRUG CYTOTOXICITY BY CONJUGATION TO A CELL TARGETING PEPTIDE

**Y. Gilad,[1,2] M. A. Firer,[1] A. Rozovsky,[1] E. Ragozin,[1] B. Redko,[1,2] A. Albeck[2], G. Gellerman[1]**

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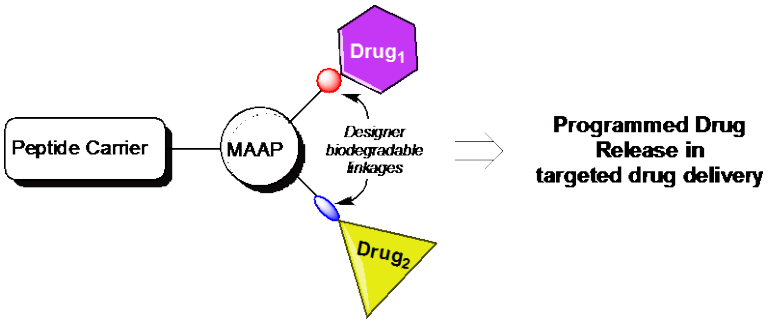
Bi-nuclear amino acid platforms loaded with various drugs for conjugation to a peptide carrier were synthesized using simple and convenient orthogonally protective solid-phase organic synthesis (SPOS). Each arm of the platform carries a different anticancer agent linked though the same or different functional group, providing discrete chemo- and bio-release profiles for each drug, and also enabling “switch off/switch on" regulation of drug cytotoxicity by conjugation to the platform and to a cell targeting peptide. The versatility of this approach enables efficient production of drug-loaded platforms and determination of favorable drug combinations/modes of linkage for subsequent conjugation to a carrier moiety for targeted cancer cell therapy. The results presented here potentiate the application of amino acid platforms for targeted drug delivery (TDD).



## OP 21. AMINO ACID-BASED BIORESORBABLE POLY(ESTER AMIDE)S: PROMISING MATERIALS FOR CONSTRUCTING DRUG-DELIVERING NANOCARRIERS

**S. Kobauri[1], V. Torchilin[2], D. Tugushi[1], R. Katsarava[1]**
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Agricultural University of Georgia, Georgia
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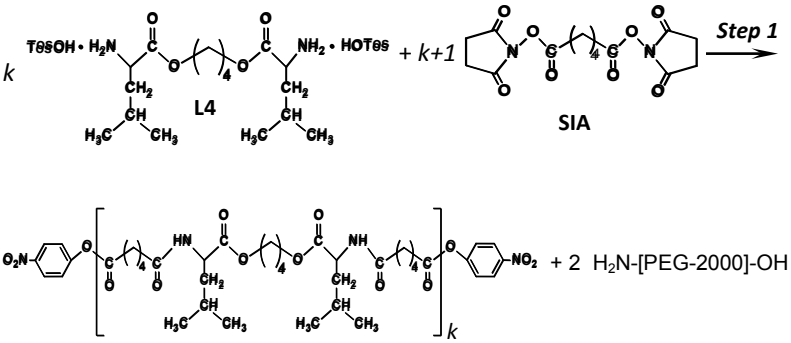
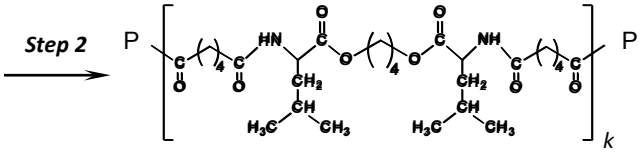
The use of various pharmaceutical nanocarriers has become one of the most important areas of nanomedicine. Polymeric micelles demonstrate a series of attractive properties as drug carriers, such as reasonable stability both *in vitro* and *in vivo*, and can be successfully used for the solubilization of various poorly soluble pharmaceuticals. These micelles can also be used as targeted drug delivery systems. It is desirable to have nano-carriers that can be cleared from the body after their function is fulfilled. The present paper deals with the synthesis of a new class of biodegradable micelle-forming polymers, namely ABA triblock-copolymer in which A-blocks represent poly(ethylene glycol) (PEG) and B-block is biodegradable amino acid-based poly(ester amide). The copolymer formed micelles of 50±2 nm size having a neutral zeta-potential [1-4].



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## OP 22. OPTIMIZATION ELECTROPHOTOCATALYTIC REMOVAL OF SULFANILAMIDE FROM AQUEOUS WATER BY TAGUCHI MODEL

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Sulfanilamide is a sulfonamide antibacterial. Chemically, it is a molecule consisting of the sulfonamide functional group attached to an aniline. As a sulfonamide antibiotic, it functions by competitively inhibiting enzymatic reactions involving para-aminobenzoic acid (PABA) [1]. PABA is needed in enzymatic reactions that produce folic acid which acts as a coenzyme in the synthesis of purine, pyrimidine and other amino acids. Sulfanilamide may result in irritation skin, allergic respiratory, and mutagenic effects. Water treatment by electrophotocatalytic (EPC) methods is widely used in the recent years [2]. These methods lead to producing hydroxyl ($OH^{\cdot}$) radical [3]. The goal of this applied- analytical research is to investigate of sulfonamide removal from water by batch EPC reactor with using zinc oxide (ZnO) nanoparticles immobilized on zinc (Zn) sheet-copper electrode, and lamp emitting dynode (LED) ultraviolet-A (UV-A) lamp. Various operating variables are tested for their effects on sulfonamide removal; these include current density, initial concentration of sulfonamide, lamp intensity, layering of ZnO nanoparticles, pH, and radiation time.

To prepare the ZnO films on the Zn electrode, dry methods are used. The sample is prepared by adding 100-300 milligrams of sulfonamide per ml of deionized water. The studied variables are pH (3-11), the sulfonamide concentration (100-300 mg $l^{-1}$), the lamp intensity (360-600 mW $cm^{-2}$), radiation time (0-45 min), the distance between lamp and electrode (1.5 cm), layering of zinc oxide nanoparticles (1-3), and current density (6-12.5 mA $cm^{-2}$). The sulfonamide concentration is measured by a high-performance liquid chromatography / mass spectrometry. Figure 1 shows a batch electrophotocatalytic reactor made of a 250 glass vessel.

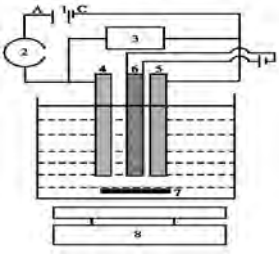

**Figure 1.** The batch EPC reactor of thin layer ZnO nanoparticles immobilized on Zn (1. Power supply, 2.Current volume, 3. Voltage volume, 4. Copper electrode, 5. Zn/ZnO electrode, 6. LED UV-A lamp, 7. Magnetic stirring bar, 8. Magnetic stirrer)

Figures 2 and 3 show the effect of the pH and current density on removal efficiency, respectively. Figure 4 shows the plots of the kinetics first and second order reaction models fitted with the sulphonamide removal experimental data in batch electrophotocatayitic reactor.

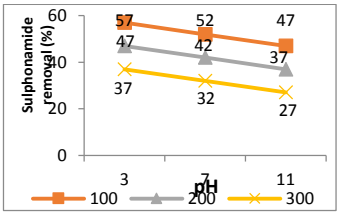


**Figure 2.** Percentage of removal efficiency of electrochemical in sulphonamide removal from contaminated water (100, 200, and 300 mg $l^{-1}$) at pH, electrolysis time 30 minute, distance between the Zn/ZnO and Cu electrode 1.5 cm, current density 6 mA $cm^{-2}$, and zinc oxide nanoparticles 10%

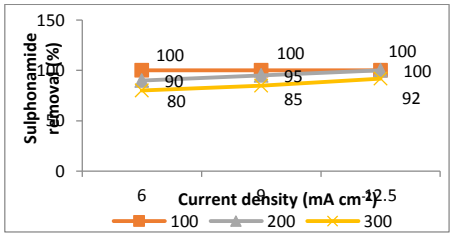


**Figure 3.** Electrophotocatalytic effect of zinc oxide nanoparticles 10% on removal percentage of sulphonamide from contaminated water (300 mg $l^{-1}$) at pH: 3, time 45 min, distance between the UV-A lamp and Zn/ZnO electrodes 1.5 cm, current density, and LED UV-A lamp power 600 mw $cm^{-2}$

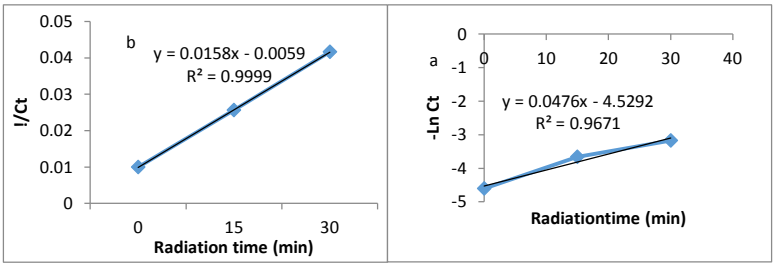


**Figure 4.** The plots of first, and second order reaction models fitted with the sulphonamide removal experimental data in batch electrophotocatalytic reactor (experimental conditions: 25 ºC, pH: 3, reaction time: 15-45 min)

The optimal removal (0) is obtained at pH 3, radiation time of 15 minutes, 2- layer of ZnO nanoparticles, lamp density 600 mw $cm^{-2}$, and current density of 9 mA $cm^{-2}$. The sulfonamide decay follows a first order reaction. The results of sulfonamide removal efficiency by Taguchi model show that the reaction time is the most important variable. The electrochemical (E) process is the least efficiency. The sulfonamide is slowly removed by $OH^{\bullet}$ radical in electrocatalytic (EC) and much more quickly photolyzed by LED UV-A lamp in EPC. The rate of decay reduces at higher concentrations. Thus, batch experiments indicate that the EPC reactor may be considered as a promising technology for treating sulfonamide-polluted water.

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## OP 23. STUDY OF ELECTRICAL PROPERTIES OF ( PVA-$BaSO_4.5H_2O$) COMPOSITES

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The study of composite materials, i.e., mixtures consisting of at least two phases of different chemical compositions, has been of great interest from both fundamental and practical standpoints. The macroscopic physical properties of such materials can be combined so as to produce materials with a desired average response. Composites have good potential for various industrial fields because of their excellent properties such as high hardness, high melting point, low density, low coefficient of thermal expansion, high thermal conductivity, good chemical stability and improved mechanical properties such as higher specific strength, better wear resistance and specific modulus. Composites are used in making solar cells, optoelectronic device elements, laser diodes and light emitting diodes (LED), industrial applications in aircraft, military and car industry [1]. Polymer-based composites are system with numerous high technological applications. These applications need a high level of composite production and manufacturing, including the chemical process, material, and structural design to suit specific purposes [2]. The advantages of PVA such of high mechanical strength and water-soluble have played as main role for this selection as compared to other polymer matrices [3] The present work deals with study the effect of $BaSO_4.5H_2O$ additive on the D.C electrical properties of poly-vinyl alcohol composite.

It has been established, that

1. The D.C electrical conductivity of the poly-vinyl alcohol increases by increasing the $BaSO_4{\cdot}5H_2O$ concentrations and the temperature.
2. The activation energy of D.C electrical conductivity decreases by increasing $BaSO_4{\cdot}5H_2O$ concentrations.

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## OP 24. EVALUATION OF ELECTRO-FENTON PROCESS PERFORMANCE FOR AN ORGANIC DYE (REACTIVE BLUE 29) REMOVAL FROM AQUEOUS SOLUTION

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The complex aromatic structure of dyes makes them more stable and difficult to be removed from water bodies. Synthetic dyes represent one of the largest groups of pollutants in wastewater of dying industries. Discharge of these wastewaters into receiving streams not only affects the aesthetic, but also reduces photosynthetic activity. Electrochemical Advanced Oxidation Processes such as the Electro-Fenton process is considered as low operational and high mineralization degree of pollutants. In this study the degradation of an anthraquinone dye, Reactive blue 29 (RB29), using an Electro-Fenton process followed was investigated. Influential factors were investigated to determine the optimum conditions for dye removal from aqueous solutions containing RB29. Synthetic samples containing Reactive Blue 29 dye were prepared and transferred into an electrochemical cell equiped with two electrodes ( anode and cathode). Electro-Fenton process was initiated by adding $Fe^{2+}$ ions to the sample while maintaining the electrical potential difference. At a certain specified time samples were analyzed for the remained dye. Based on the results obtained, the difference in electrical potential of 20 V for RB concentrations up to 100 mg/L and the electrical potential difference of 30 V for over 200 mg/L of dye concentrations were found optimum. Moreover, in this situation Maximum dye removal (100%) were observed when the reaction time, $Fe^{2+}$ concentrations and pH were 45-60 minutes, 0.7 mg/L and pH=5, respectively. In conclusion the Electro-Fenton process exhibited high potential for removal of dye in optimum condition.

## OP 25. NEW REACTIVITY OF ALIPHATIC NITRO COMPOUNDS *via* SILYLATION OF NITRONATES.

**S. L. Ioffe[1], A. Yu. Sukhorukov[1], V. O. Smirnov[1], A. A. Tabolin[1], A. A. Mikhaylov[1], Yu. A. Khomutova[1]**
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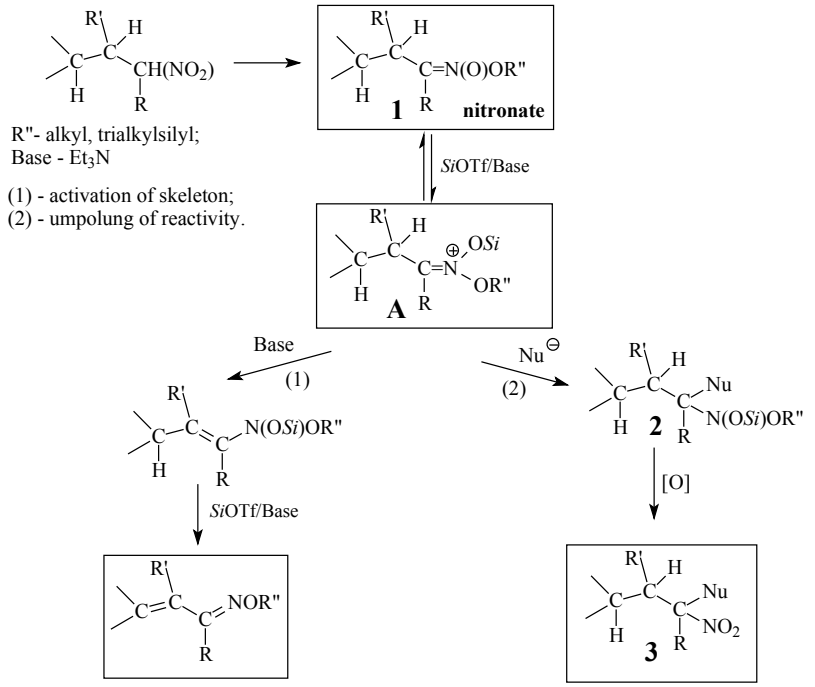
A new strategy of use in organic synthesis was developed for aliphatic nitro compounds (**AN**) [1] (Scheme 1). It consists in initial preparation of respective nitronates **1** from **AN** using a known procedures. The latter undergo a reversible silylation with power silylating agents in the presence of bases to give cations **A** that can be considered as key-intermediates.




The cationic intermediates **A** could be stabilized *via* activation of carbon skeleton of initial **AN** (the way (1)) or be coupled with various nucleophiles to give the target modified nitro compounds **3** after oxidation of

intermediate nitrosoacetals **2** (the way (2), umpolung of nitro compounds traditional reactivity).

The peculiarities of both transformations are considered as well as their using in target organic synthesis.

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## OP 26. REGIODIVERGENT SYNTHESIS OF POLYCYCLIC AROMATIC AND HETEROAROMATIC SCAFFOLDS

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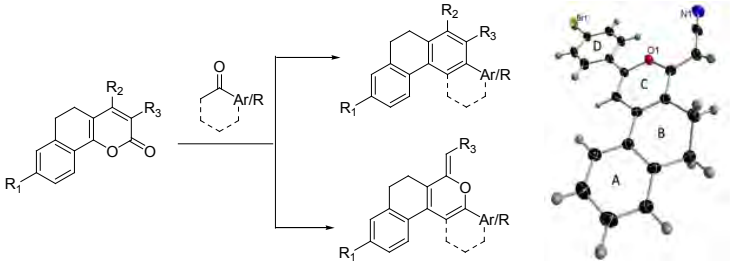
A transition metal free regiodivergent synthetic strategy has been developed for the synthesis of partially reduced polycyclic aromatic and oxygen containing heteroaromatics. The developed protocol avoids the use of expensive, moisture and air sensitive metal catalysts, organometallic reagents and ligands. Microwave irradiation played a major role to afford regioselectivity and high yields of the desired product. The reaction commences with sequential one pot process to give bridged biphenyls, chromenes and isochromenes in good to excellent yield. The structure and geometry of isochromene have been proved without any ambiguity by single crystal X-ray diffraction.

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# ⏩ POSTER PRESENTATIONS

## PP 1. SYNTHESIS OF PYRROL-2-YLPHOSPHONATES OR DIHYDROPYRIDIN-2-YLPHOSPHONATES *VIA* CYCLIZATION REACTIONS OF ACETYLENIC α-ANILINOMETHYLPHOSPHONATES

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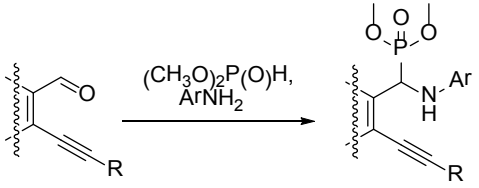
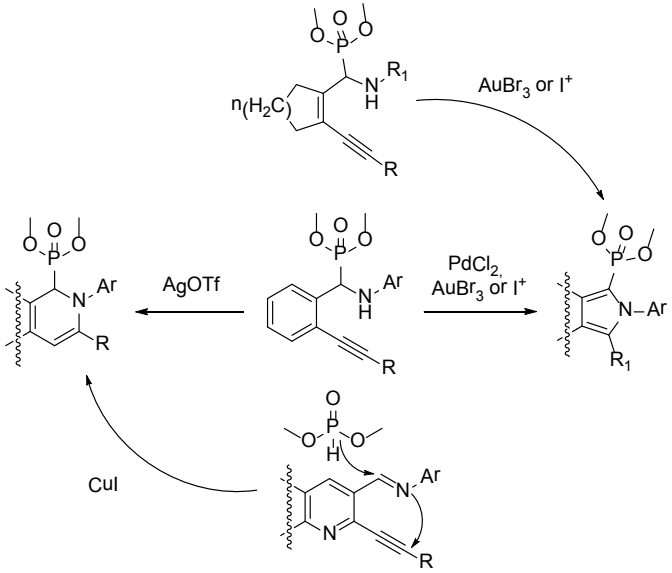
Pyrrole and 1,2-dihydropyridine framework containing systems play important role in medicinal chemistry due to their biological activities [1]. It is also known that α-aminophosphonates are interesting as the analogues of α-amino acids having broad biological applications [2]. In 2007 several reports about 5-*exo*-dig or 6-*endo*-dig cyclizations of α-amino (2- alkynylphenyl)methylphosphonates have been published [3]. To the best of our knowledge there is no information about reactivity and cyclization reactions of heteroaromatic or nonaromatic analogues of acetylenic α-anilinomethylphosphonates in the literature. Keeping in mind, that organophosphorus compounds are useful due to their biological properties, we decided to synthesize various acetylenic α-anilinomethylphosphonates and to investigate their intramolecular cyclization reactions catalyzed by Lewis acids [4].

The starting α-amino (2-alkynyl)methylphosphonates were prepared *via* three-component Kabachnik-Fields reaction between 2-alkynylcyclohex-1-enecarbaldehydes, 2-alkynylcyclopent-1-enecarbaldehydes, 2-alkynylbenzaldehydes or 1-benzyl-2-(alkynyl)-1*H*-indole-3-carbaldehydes with dimethylphosphite and aromatic amines.




Dimethyl 2,3-disubstituted 2*H*-isoindol-1-ylphosphonates were afforded by a $PdCl_2$, $AuBr_3$ catalyzed or $I^+$ mediated cyclization reaction of dimethyl (arylamino)(2-(alkynyl)phenyl)methylphosphonates, whereas dimethyl 2,3-

disubstituted 1,2-dihydroisoquinolin-1-ylphosphonates were synthesized by AgOTf promoted *6-endo*-dig cyclization reaction. It was found that nonaromatic acetylenic α-anilinomethylphosphonates undergo gold(III)-catalyzed or iodine-mediated 5-*exo*-dig cyclization to 1*H*-pyrrol-2-ylphosphonates. Unfortunately electron-donating phosphonates with indole moiety were unreactive toward Lewis acid catalyzed cyclization processes. However the Kabachnik–Fields reaction between electron-withdrawing 2-(alkynyl)nicotinaldehydes or 2-(alkynyl)quinoline-3-carbaldehydes with dimethylphosphite and arylamines gave unexpected 1,2-dihydropyridin-2-ylphosphonates. We found that three-component reaction proceeded *via* imine intermediate and in the presence of CuI, subsequent dimethylphosphite addition–6-*endo*-dig cyclization reaction took place.




During this study we have found that the outcome of cyclization reaction strongly depends on structure of starting material and used catalysts.

**Acknowledgements.** We thank Lithuanian Research Council for the financial support *(Global Grant No. VP1-3.1-SMM-07-K-01-002).*

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## PP 2. EFFECT OF HEAVY METAL ON PHYTOCHEMICAL CONSTITUENTS OF Moringa oleifera EXTRACTS

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*Moringa Oleifera* is one of the most widely cultivated species of the monogenic family Moringaceae. It posses high nutritional value and has been used in folklore medicine for treatment of various ailment related to pain and inflammation and chemical pharmacological. Lead at different concentration is introduce in to the soil where *Moringa Oleifera* were planted to know its effect on phytochemical constituent of the plant by quantitatively screening for amount of phytochemical present in *Moringa Oleifera* leaves. The phytochemical constituent concentration decreases as the concentration of lead increases, at 0ppm and 1000ppm treatment flavonoid is 2355±25 but at 2000ppm it reduces to 2155±15, 3000ppm is 1963±20 and at 4000ppm, flavonoid constituent is 1240±25.In the same vein terpenoid, saponin, and steroid follow the trend of flavonoid. At high concentration the phytochemical constituent of *Moringa Oleifera* leaves are significantly lower. The reduction in phytochemical constituent of *Moringa Oleifera* leaves is as a result of lead ($Pb(No_3)_2$) present in the soil.

A Heavy metal is a member of a loosely defined subset of element that exhibit metallic properties. It mainly includes the transition metals, some metalloids, lanthanides and actinides. Living organisms require varying amount of heavy metals, iron, cobalt, copper, Zinc are required by humans. Excessive levels of these metals can cause damage to the organism. [1] [2] Other metals such as mercury, Plutonium and lead are toxic metals and their accumulation over time in the bodies of animals can cause serious illness. Heavy metals pollution can arises from many source, most commonly arises from the purification of metals for example, the smelting of copper and the preparation of nuclear fuels. [3] To screen for amount of lead and phytochemical in plant material, several approaches can be employed to extract the

plant materials with the use of solvent of different polarities. There are many factors that determine the phytochemical constituent of a plant includes, geographical area, exposure of plant to heavy metals and so on. [5]

Pot experiment was carried out at the back of green house of the Department of crop protection and Environmental Biology, University of Ibadan. A total 20 pots were arranged in completely randomized design with four replicates, the seed used *Moringa Oleifera* and the uncontaminated soil was also collected at the same Department. The treatment includes 0ppm, 1000ppm, 2000ppm, 3000ppm and 4000ppm of lead solution. The treatment was prepared from $Pb(N0_3)_2$ salt with molecular mass 331g which contain 207g of lead (Pb). 1g of p=Pb = 331/207 x 1 =1.6g of Salt. 1000ppm was prepared by dissolving 3.2g of salt in 2 liters of distilled water. 2000ppm was prepared by dissolving 6.4g of salt in 2 liters of distilled water. 3000ppm was prepared by dissolving 9.6g of salt in 2 liters of distilled water. 4000ppm was prepared by dissolving 12.8g of salt in 2 liters of distilled water, 2 kilograms of the soil was weighed into twenty pots and the Moringa seed were sown at 2 seeds per pot. The treatment is lead at four different concentration 0ppm, 1000ppm, 2000ppm, 3000ppm and 4000ppm which were applied at four weeks after planting. The growth parameters were taken at six week and eight week after planting. Each leaf was destalked washed and air dried at average room temperature and continuous turning of the leaves was done to avert fungi growth for one week to constant weight.

**Table 1:** Vegetative parameters in $cm^3$

| Treatment | Plant Height | | Number of Leaves | |
|---|---|---|---|---|
| | 6WAP | 8WAP | 6WAP | 8WAP |
| 0ppm | 12.18 | 12.50 | 35.75 | 60.33 |
| 1000ppm | 12.87 | 12.33 | 68.87 | 61.72 |
| 2000ppm | 13.62 | 11.55 | 84.37 | 49.40 |
| 3000ppm | 12.61 | 11.20 | 50.25 | 48.50 |
| 4000ppm | 11.75 | 10.31 | 52.75 | 45.50 |

WAP= Week after planting.

They were kept away from high temperature and direct sun light to avoid destroying of active compounds. The stem and root was oven dried at 80$^{o}$C for 72 hours. 0.5g of both shoot and root were ash at 500$^{o}$C for 6hrs separately, the ash was then mixed with 10ml of 2M nitric acid and filtered, The filtrate was then make up 25ml with distilled water and the sample were taken for analysis using Atomic Absorption Spectroscopy (AAS).

**Table 2:** Effect of lead on phytochemical constituents of *Moringa Oleifera* leaves in mg/100g

| Treatment | Flavonoid | Saponin | Tannis | Terpnoids |
|---|---|---|---|---|
| 0ppm | 2355±25 | 948±17.55 | 280±8.66 | 178.00± 7.63 |
| 1000ppm | 2355±25 | 893±12.58 | 263±5.77 | 163.00±11.54 |
| 2000ppm | 2155±15 | 863± 2.88 | 240±5.00 | 156.66± 5.77 |
| 3000ppm | 1963±20 | 645±13.00 | 210±5.00 | 143.00± 2.88 |
| 4000ppm | 1240±25 | 548±10.00 | 178±5.77 | 121.66± 2.80 |

Values are mean± standard deviation of triplicate values

The number of leaves decreases with increase in lead concentration. At eight weeks the number of the leaves is very low compare to number of leaves at six weeks after planting. Whereas the number of the control leaves increases at eight weeks after planting compare to six weeks. The same thing happen to the plants height, it decreases as the concentration of lead increases. But at 1000ppm and 3000ppm there is no different between the plants heights. At eight weeks after planting the plants height decreases compare to plants height at six weeks after planting, whereas the plants height of the control increases at eight weeks after planting compare to six week after planting (Table 1). The root of *Moringa Oleifera* plant takes up lead compare to stem, the lead concentration increases in the root and stem as the concentration of lead in the soil increases. Although lead concentration in both root and stem is very low, that is *Moringa Oleifera* does not uptake much lead in the Soil? The phytochemical constituents of *Moringa Oleifera* leave decreases as the lead concentration increases, at 0ppm and 1000ppm treatment flavonoid is 2355±25 but at 2000ppm it reduces to 2155±15,3000ppm is 1963±20 and at 4000ppm, flavonoid constituent is 1240±25.In the same vein terpenoid, saponin, and steroid

follow the trend of flavonoid. Lead concentration decreases the number of leaves and plants height. Also weight of the fresh leaves decreases with increase in the concentration of lead in *Moringa Oleifera* plant and this may be as a result of disorder in normal physiological activities of the plant [6].Furthermore they also said that when lead enter the cell` of a plant even in small amount it produce a wide range of adverse effect on physiological process of the plant. The lead concentration in the roots is higher than the stems; this may be as a result of ability of the root to take up significant quantities of lead whilst simultaneously greatly restricting its translocation to above ground [4]. Phytochemical constituent of *Moringa Oleifera* leaves decreases with high concentration of lead and this may be as a result of lead affecting all metabolic activities of the plant [6].

Moringa Oleifera plant cannot withstand the stress of lead. It is concluded that reduction in phytochemical constituent of *Moringa Oleifera* is as a result of lead nitrate ($Pb(No_2)_3$ present in the soil.

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## PP 3. SYNTHESIS OF N-SUBSTITUTED (Z)-3-(2-BENZYL)-4-OXOPENT-2-YL)PYRROLE-2,5-DIONES (MALEIMIDES)

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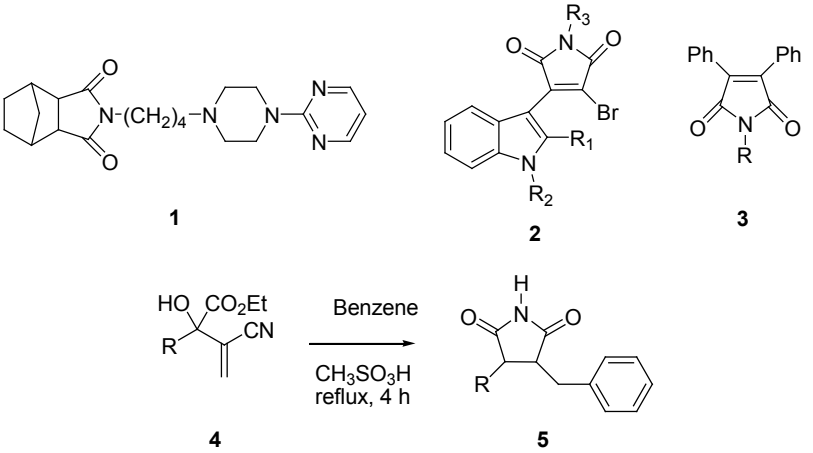
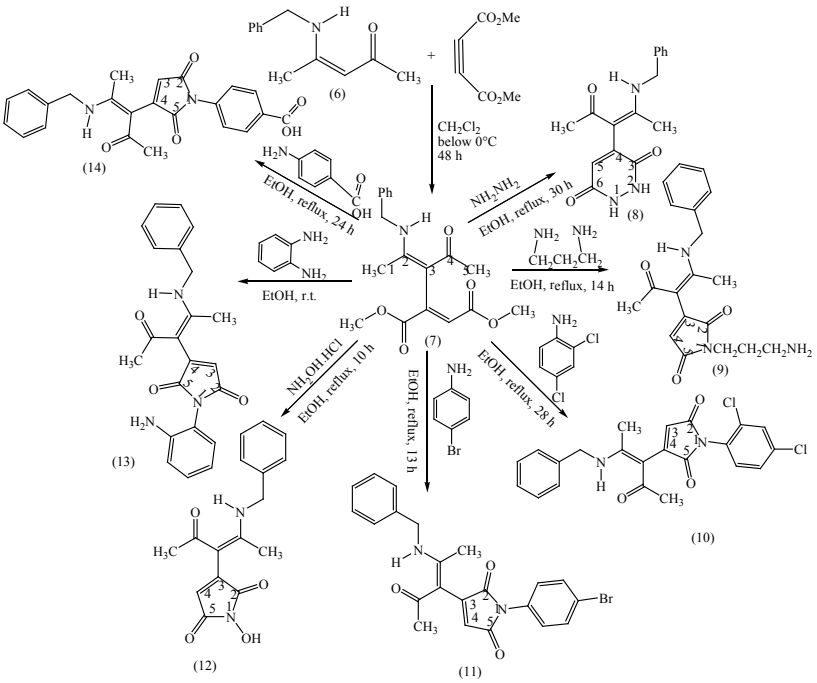
3,4-Disubstituted pyrrole-2,5-dione (maleimide) framework [1-6] represent an interesting structural organization in heterocyclic chemistry as this skeleton is present in a number of natural products such as acryriarubis A, B [1], polycitrins A, B [2] and himanimides A-D [3]. Certain compounds having this framework have also been known to exhibit various biological activities such protein kinase inhibitors [4], cell proliferation [5] and angiogenesis inhibitors [6]. Tandospiron (1) has a high affinity to the 5-HT1A receptor [7-9], while compounds containing pyrrole 2,5-dione such as (2) were found to have antibacterial activity [10]. N-Substituted 3,4-diphenyl-1H-pyrrole-2,5-dione (3) were synthesized and tested for cytostatic activity [11]. Recently, the Boylis-Hillman alcohols, 3-ethoxy carbonyl-3-hydroxy-aryl (alkyl)-2-methylene propanenitrile (4) have been conveniently transformed into 3,4-disubstituted 1H-pyrrole-2,5-dione such as (5) [12].




1 2 3 4 5

As a part of our research aims to synthesized new compounds exhabiting biological activities, several structurally interesting compounds with

substituted maleimides moieties have been synthesized. The starting material dimethyl 2-((Z)-2-(benzylamino) -4-oxopent-2-en-3-yl) fumarate (7) precursor for the of N- substituted (Z) -3- (2- benzyl) -4- oxopent-2-yl) pyrrole -2,5-diones (mateimides) was obtained by a reaction involving the enaminone (6) and dimethyl acetylenedicarboxylate in dichloromethane. The final target componds synthesized by condensation of (7) with different amines ( scheme 1) with out using any catalysts. These reactions were carried out by conventional heating method. The structures were established through IR, $^{1}$H- NMR, and $^{13}$C-NMR. IR spectra of synthesized compounds (6-14) showed bands for υNH and υC=O group, whereas $^{1}$H-NMR spectra showed similarity with starting material except some differences belong to amines moieties and $^{13}$C-NMR (DEPT-90 and DEPT-135) were used to determine type of carbon atoms.




**Scheme 1.** Reaction of compound (7) with some amines.

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## PP 4. DIPYRROLONAPHTHALENES: SYNTHESIS, RESEARCH AND BIOLOGICAL ACTIVITY

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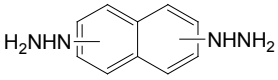
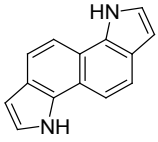
The synthesis of two unsubstituted Pyrrole rings containing new isomeric indoloindoles were carried out from isomeric heteronuclear naphthylenedihydrazines **1**, as a result, two pyrrole rings at different position are built at naphthalene nucleus and dipyrrolonaphthalenes are produced. Also we have synthesized and studied dipyrrolonaphthalene from 2,3-naphthylendihydrazine, which can be considered as benzopyrroloindole. Thus, synthesized new heterocyclic systems can be unified into one common name – isomeric dipyrrolonaphthalenes.

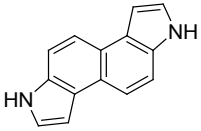



1

We synthesized Indolo[7,6-g]- (**2**) [1], Indolo[5,4-e]- (**3**) [2] and Indolo[4,5-e]indoles (**4**) [2] from 1,5-, 2,6- and 2,7- naphthylendihydrazides respecttively, and benzo[e]pyrrolo[3,2-g]indole(**5**) [3] was obtained from 2,3-naphthylendihydrazine.




**2**

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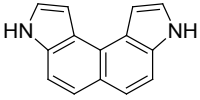
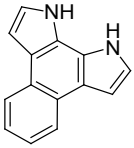



**4**




**5**

For these heterocyclic compounds were studied electrophilic substitution reactions with weak electrophilic agents. Indoloindoles more readily undergo the Vismeier-Haack reaction than indole, as indicated by the formation of α-substituted aldehydes in addition to β-substituted products. The acetylation of compound **4** at the β-position of the pyrrole ring does not take place unlike acetylation of indoloindoles **2** and **3**. This is apparently due to steric hindrance created by the closely arranged pyrrole rings in

compound **4.** In all cases, the yield of monoacetylated derivatives was substantially higher than the yield of diacetylated products. The formation of product substituted in the naphthalene nucleus upon the acetylation of compound **2** is attributable to an increase in the π-electron density and an additional activation of the naphthalene α-position due to the electron influence of the pyrrole rings.

The predominant formation of monosubstituted derivatives in azo coupling, unlike the reaction of acetylation, may be caused by low electrophilicity of the $ArN_2^+$ ion. The formation of 2-substituted derivatives from compounds **3** and **4** may be due to the steric influence of pyrrole rings and naphthalene nucleus.

The Mannich reaction readily undergoes in dipyrrolonaphthalenes with formation of gramine like bis-analogs.

The alkylation of indoloindoles were carried out using alkyl halides, under conditions of phase transfer catalysis. Predominantly were formed N,N-dialkylindoloindoles.

In order to obtain compounds with biological active properties were prepared transformation reactions of dipyrrolonaphthalenes derivatives: synthesis of heteroauxine bis-analogs, aldehydes condensation reaction with amines and CH-acids, from diether were obtained dihydrazides, diacylazides and hydrazide-hydrazones.

From benzopyrroloindole was prepared corresponding dicarboxylic acid dichloroanhydride, which then react with diamines and bisphenoles which lead to formation of indole ring containing polyamides and polyethers.

In recent years, we synthesized and studied properties of isomeric dipyrrolonaphthalene rings containing dihydroindolizines and spyropyrans type new biphotochromic systems.

Antimicrobial, biocidal and plant growth stimulation activity were studied for some Indoloindoles and benzopyrroloindoles compounds. Benzopyrroloindoles derivatives revealed high activity against *Staphylococcus aureus* and *Bacillus subtilis* bacteria, mycobacteria and fungi. It should be noted that these compounds were recommended for further enhanced biological research on corresponding infectious diseases in animals.

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## PP 5. MECHANISTIC INVESTIGATIONS OF REACTIONS BETWEEN 3-ARYLPROP-2-YNYL CARBOXYLATES AND ALDEHYDES

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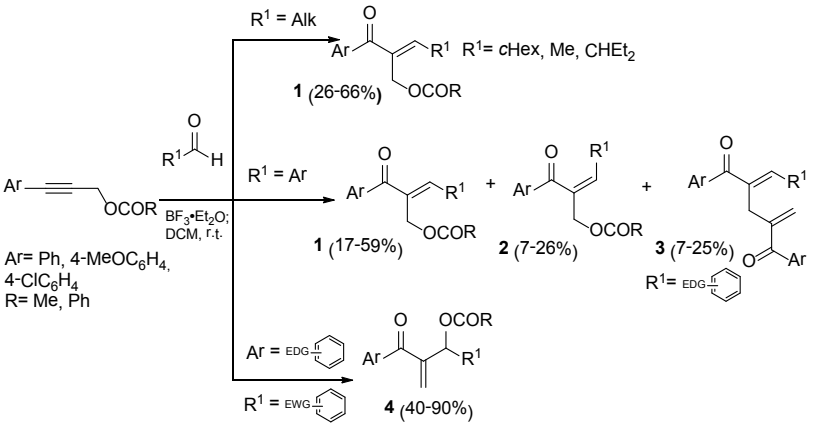
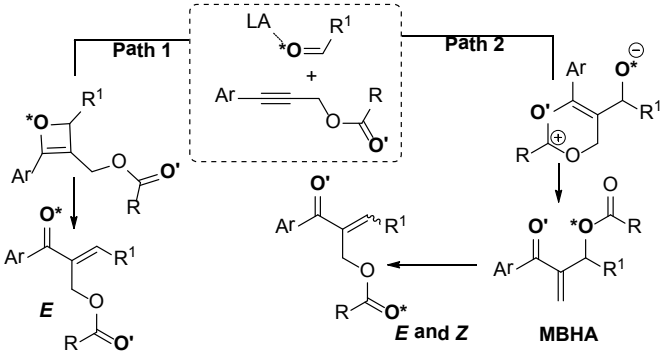
Chalcones (1,3-diaryl-2-propen-1-ones) represent a class of open chain flavonoids that are widely biosynthesized in plants. These natural products and their synthetic derivatives have shown wide spectrum of biological properties [1] including anticancer activity. It was shown that substituents in α position give potent cancer cell growth inhibition activity and selectivity. For preparation of α,β-unsaturated ketones we chose alkyne-carbonyl metathesis reaction which is an atom economic strategy of simultaneous formation of carbonyl group and double bond.

This method allows to prepare *E* configuration α,β-unsaturated ketones with various substitution patterns *via* oxete ring formation [2] in intra- [3] and intermolecular [4] reactions using strong Lewis acids. But during our previous work [5] we found that during reaction of 3-arylprop-2-ynyl carboxylates and aromatic aldehydes *E* (1) and *Z* (2) isomers were formed. Moreover 2:1 adducts (3) were detected using benzaldehydes with electron donating groups. The most interesting observations were made using 3-arylprop-2-ynyl carboxylates with donating substituents in aryl moiety and benzaldehydes with electron withdrawing groups. Having this combination it was possible to prepare Morita-Baylis-Hillman adducts (4) unavailable to synthesize by classical MBH way [6].




We also found that after prolonged stirring of MBHA **4** with Lewis acid, (*E*)- and (*Z*)-α,β-unsaturated ketones **1** and **2** were formed. Furthermore, performing reactions at lower temperatures, small amounts of MBHA **4** besides common (*E*)- and (*Z*)-enones **1** and **2** were isolated. These observations lead to the mechanistic studies on the $BF_3$•$Et_2O$ catalyzed reaction between 3-arylprop-2-ynyl carboxylates and aldehydes. The study was performed using isotopic oxygen labeling experiments, which have shown that the reactions proceed either *via* classical alkyne-carbonyl metathesis route (path 1), or *via* an unprecedented nucleophilic addition-rearrangement cascade (path 2).



Depending on the structure of the starting materials and the reaction conditions the products of alkyne-carbonyl metathesis can be MBHA, unavailable *via* traditional MBH reactions, or thermodynamically more stable (*E*)- and (*Z*)-α,β-unsaturated ketones. Therefore, some new possibilities of alkyne-carbonyl metathesis reaction with possible mechanisms, scope and limitations will be discussed.

**Acknowledgements.** We thank Lithuanian Research Council for the financial support (Doctoral academic visit No. DOC-35/2014; Global Grant No. VP1-3.1-SMM-07-K-01-002 for materials).

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## PP 6. SYNTHESIS AND GROWTH STIMULANT ACTIVITY OF (3,5-DIMETHYL-1H-PYRAZOL-1-YL)-3-METHYL-[1,2,4]TRIAZOLO[4,3-B]PYRIDAZINE DERIVATIVES

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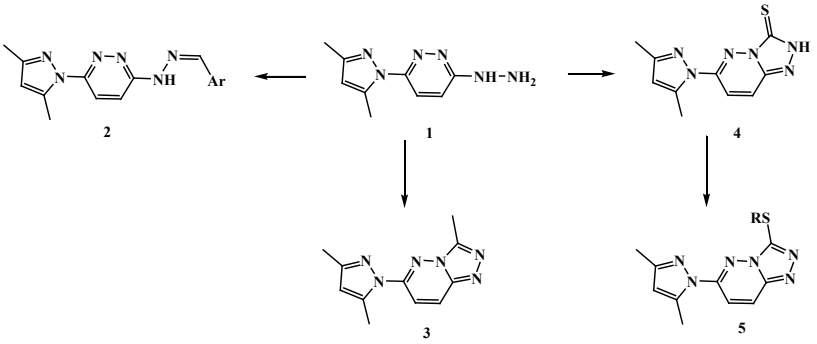
Nitrogen-containing heterocycles (pyridazine, pyrazole and triazole) derivatives exhibit a broad spectrum of biological activity. In agriculture a large series of herbicides, fungicides, insecticides, acaricides, containing these cycles are used [1]. At prolonged use of pesticides, as well as drugs the harmful organisms acquire a resistance in relation to them that requires continual updating of plant protection chemicals and pharmaceuticals arsenals. The search of new physiologically active compounds are continuing among these heterocycles derivatives. However, in literature there are only a few data on physiological properties of the compounds with combination of two mentioned heterocycles in the same molecule, exept of some triazolo-pyridazines [2-10], which show anxiolytic, antiproliferative, antifungal, antibacterial and anticonvulsant activities, affinity to GABAA and phosphodiesterase-4 receptors and also pyrazolyl-pyridazines with anti-inflammatory [11,12] and hypotensive [13] properties. At the same time there are practically no data on pesticide or growth-regulating properties of these compounds, although such heterocyclic systems may be interested in the search for new chemical means of plant protection.

The aim of the present study was the synthesis of compounds containing two or three of mentioned heterocycles in the molecules and evaluation of their pesticide and growth regulatory activity.

By reaction of 3-(3,5-dimethyl-1H-pyrazol-1-yl)-6-hydrazinylpyridazine (**1**) with arylaldehydes and acetic acid the corresponding 3-(2-arylidenehydrazinyl)-6-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazines (**2**) and 6-(3,5-dimethyl-1H-pyrazol-1-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazine (**3**) were obtainned. The interaction of the same starting compound (**1**) with carbon disulfide in an alkali alcoholic solution afforded 6-(3,5-dimethyl-1H-pyrazol-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3(2H)-thione (**4**). The alkylation of latters in DMF leads to a series of S-substituted derivatives (**5**).



Ar = 4-$OCH_3$-$C_6H_4$; 3-$NO_2$-$C_6H_4$; 3-$OCH_3$-4-OH-$C_6H_3$

R = $CH_3$; $CH_2COOCH_3$; $CH_2COOC_2H_5$; $CH_2CONH_2$; $(CH_2)_2OC_6H_5$; $(CH_3CO)_2CH$

Preliminary laboratory and vegetative tests showed that the obtained compounds don't show noticeable herbicidal or fungicide activity, however possess the expressed stimulating action on plants growth. The greatest activity was 85% in comparison with widely used heteroauxin. Data of biological screening testify that synthesized hitherto unexplored heterocyclic systems can be perspective for search of new growth stimulators.

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## PP 7. SYNTHESIS OF TRICYCLO[6.2.2.0$^{2,7}$]DODECANE-3,6,9,10-TETROL

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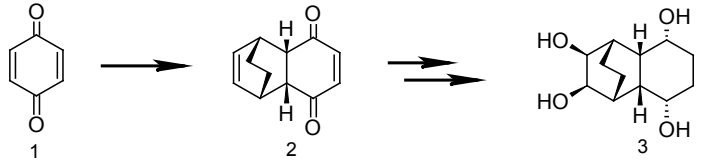
Cyclitols, highly hydroxylated cycloalkanes, are important compounds as they can be potentially used as glycosidase inhibitors as well as in the chemotherapeutic applications against diabetes, cancer, and viral infections [1]. Polyhydroxy cyclohexanes such as inositols, quercitols, carbasugars, dihydroconduritols (toxocarols), and polyhydroxy cyclohexenes including conduritols belong to the family of cyclitols [1,2]. Interest in conduritols and their analogues have been amplified due to synthetic challenge and presence of a variety of biological activities such as antifeedant, antibiotics, antileukemics and growth-regulation [2]. Recently, considerable interest has been shown in the design of new-generation cyclitol mimetics containing multiple hydroxy groups because of the fundamental importance of cyclitols.




Stereoselective synthesis of tricyclo[6.2.2.0$^{2,7}$]dodecane-3,6,9,10-tetrol was developed starting from *p*-benzoquinone **1**. The *endo* selective Diels-Alder cycloaddition of *p*-benzoquinone and 1,3-cyclohexadiene afforded the corresponding bicyclic diketone **2**. The synthesis of title compound was based on the cycloadduct by selective reduction with $NaBH_4$, acetylation with AcCl and hydroxylation with $OsO_4$-NMO. Hydrolysis of the acetate groups furnished the desired tetrol **3**.[3] The structures of all of compounds obtained were identified by NMR spectra.

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## PP 8. SORPTION OF GOLD BY POLYMER SORBENT MODIFIED WITH DITHIZONE

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A new chelating polymer sorbent in the result of chemically modification of phosphochlorylated polybutadiene with dithizone has been synthesized. Sorbent has cross-linked structure and shows complexing property [1]. The synthesized sorbent has been investigated by IR spectroscopy and its sorption properties towards gold were studied. The results of the spectra analysis before and after gold sorption showed that the interaction of the sorbent to gold ions results in little change in the spectrum. The appearance of new frequence band or shifting of the absorption maxima is not observed. This is explained by the fact that the Au (III) ions are not restored to Au (I) in the sorption process.

Study of sorption of gold from hydrochloric acid solutions of different concentrations onto polymeric sorbent shows that the new chelating polymer sorbent in the result of chemically modification of phosphochlorylated polybutadiene with dithizone can be used in 1M acid concentration. Rate extraction of trace gold is characterized by high value: the equilibrium time does not exceed from 30 minutes.

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## PP 9. UNUSUAL TRANSFORMATIONS OF 2-THIOHYDANTOINS AND THEIR DERIVATIVES IN COMPLEXATION REACTIONS

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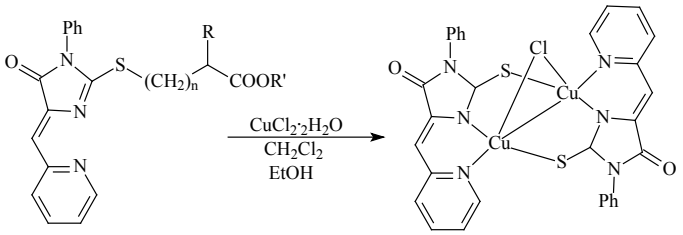
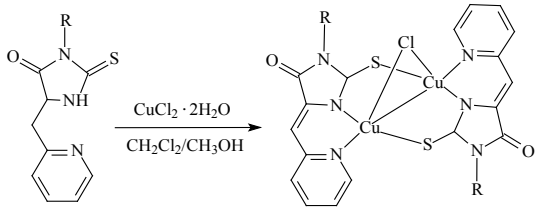
2-Thiohydantoins (4-oxoimidazolidine-2-thiones) and their S-alkylated derivatives (2-alkylthio-3,5-dihydro-4H-imidazol-4-ones) have attracted the attention of researchers for more than a century, but investigations into the chemistry of thiohydantoins have not yet been exhausted. The current interest is very much related to the biphilic reactivity and broad spectrum of pharmacological properties (anticonvulsant, antibacterial, antiviral, antihypertensive, antidiabetic activity) of these compounds [see, for example, 1,2]. Complexes of 2-thiohydantoins and their derivatives with transition metals can serve as effective models of the active centers in some metalloenzymes [3] and effective catalysts of redox reactions, for example, epoxidation under the action of nitric oxide [4].

In recent years, we have developed synthetic approaches to 5-pyridyl- or 5-imidazolyl-substituted 2-thiohydantoins and 2-alkylthio-3,5-dihydro-4H-imidazol-4-ones and their complexes with Ni(II), Co(II), Cu(II) and Cu(I). The corresponding mono and dinuclear coordination compounds have been synthesized and their redox properties and catalytical and biological activities have been investigated [5-9]. The present report summarizes the data from our laboratory studies on unusual transformations of thiohydantoin or 2-alkylthio-3,5-dihydro-4H-imidazol-4-one moieties in the processes of complexation reactions with copper(II) salts:

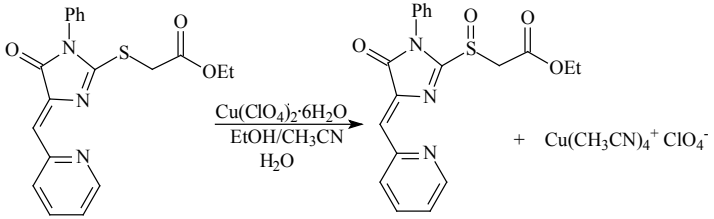
1. C-S Bond cleavage within the ligand molecules with the formation mixed-valence copper complexes of 2-thiolato-3-phenyl-5-(pyridine-2-ylmethylene)-3,5-dihydro-4H-imidazole-4-on [9]:



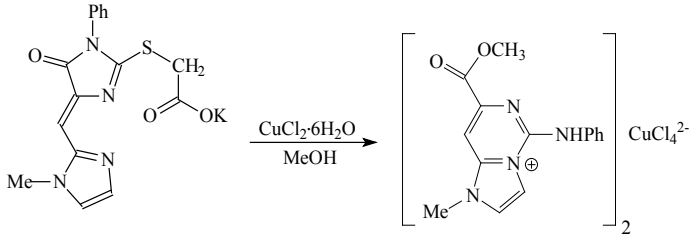

2. Dehydrogenation of ligand with the double C=C bond formation:




3. Oxidation of ligand on sulfur atom with the formation of sulfoxide and copper(I) salt [10]:




4. ANRORC reaction with the formation imidazo[1,2-*c*]pyrimidin-4-ium salt [11]:



5. Conversion of 2-thiohydantoins and their derivatives to corresponding hydantoins [12].

The proposed mechanisms of the presented ligand transformationswill be discussed.

**Acknowledgments**. The authors gratefully acknowledge the financial support of the Ministry of Education and Science of the Russian Federation in the framework of Increase Competitiveness Program of NUST «MISiS» (Grant # К1-2014-022) and financial support of Russian Foundation for Basic Research (Grants ## 12-03-33148, 12-04-00988, 13-03-00399).

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## PP 10. SYNTHESIS OF A BASIC MONOMERIC MOIETY OF NATURAL POLYETHER FROM COMFREY AND THEIR COMPARATIVE BIOLOGICAL ACTIVITY

**M. Merlani, V. Barbakadze, K. Mulkijanyan, L. Gogilashvili, L. Amiranashvili, M. Moistsrafishvili, N. Mushkiasvili, Zh. Novikova, M. Sulakvelidze, M. Moistsrafishvili, N. Mushkiasvili**
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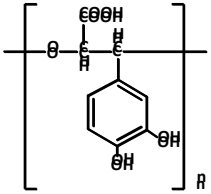
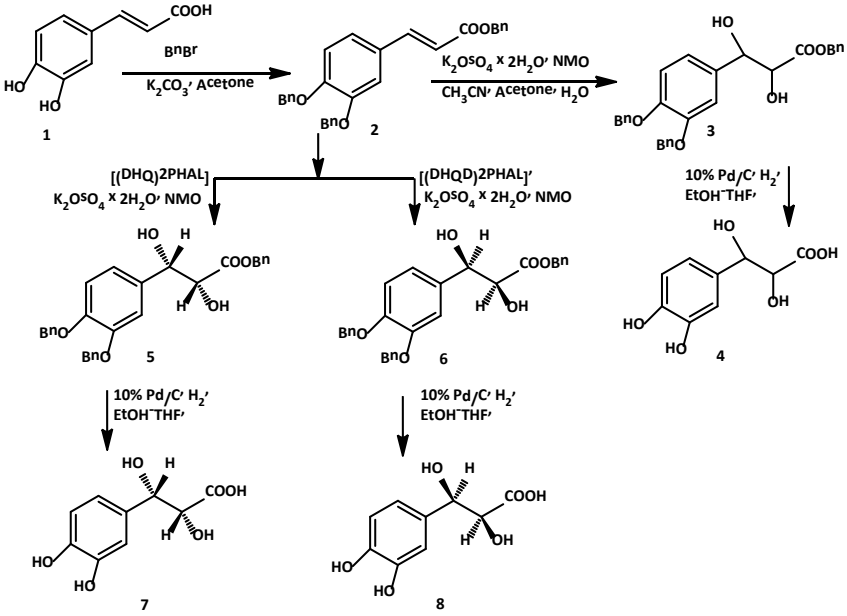
In order to clarify the biologically active principle of natural polyether from Comfrey (**NPC**) poly-[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)-ethylene] (fig.1) the racemic and enantioselective synthesis of its monomer - 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propionic acid (4) **(SM)** has been carried out starting from caffeic acid (1) according the scheme (1). The comparative biological activity of natural polymer and synthetic monomer was evaluated in several in-vitro and in-vivo experiments. The racemate (4) as well as its enantiomers (7 and 8) exhibited strong antioxidant activity against hypochlorite and N,N-diphenyl-N-picryl-hydrazyl (DPPH) free radical that appeared about 40-fold higher than that of the corresponding natural polyether [1].



Haematopoietic efficacy of NPC and corresponding monomer has been studied also in mice drug-induced leukopenia caused by cytostatic drug cyclophosphan (350 mg / kg, ip). leucopoiesis in experimental animals (165% and 81% correspondingly, $p < 0,01$) [2].




Intraperitoneal administration (1 mg/kg) of both the NPC and SM caused significant increase of NPC and SM were studied as well to appraise pharmacological efficacy in in vivo experiments (mouse excisional wound model). Ointments, containing 2.5% NPC was found to have pronounced wound-healing properties and by efficacy it does not yield to 2.5 % allantoin ointment. SM also exhibited wound healing activity, but appeared less effective than NPC [3].

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## PP 11. SYNTHESIS OF 16β-AMINO, 17-HYDROXY DERIVATIVES OF 5α-STEROIDS

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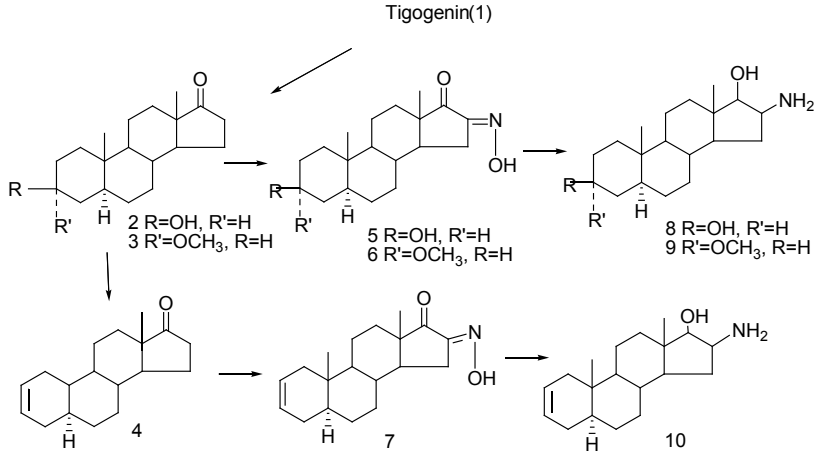
Amino steroids are claimed to be used for treatment of cardiovascular disorders [1]. The aim of present work was the synthesis of some 16β-amino steroids on the basis of steroidal sapogenin - tigogenin (I) isolated from *Yucca gloriosa.* Previously described scheme [2] was used for the conversion of (I) into epiandrosterone (2). Ketons (3) and (4) were obtained on the basis of (2) and transformed into corresponding 16-oximes (5-7) [3]. Subsequent stereoselective reduction of 16-oxime and 17-keto- groups with $LiAlH_4$ in THF resulted in obtaining preferably of 16 β- amino-17β-ol derivatives (8-10) (Scheme 1). Because of the stereo specificity of the mentioned process pure product of reaction was isolated by the treatment with D(+)-tartaric acid. Crystallization of obtained salts from absolute ethanol and subsequent treatment with aqueous solution 10% NaOH gave amines (8-10).




**Scheme 1.**

The structure of synthesized compounds was established by IR, $^{1}H$, $^{13}C$ NMR spectroscopy, mass-spectrometry and elemental analysis. Absolute

configuration of 16β-amino, 17β-hydroxy derivatives (8-10) was determined on the basis of X-ray analysis of 3,16, 17-triacetate derivative of amine (8) (Fig.1).

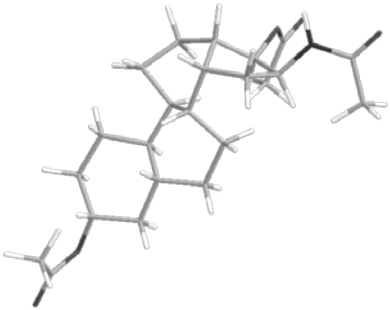


**Figure 1**

Clarification of biological activity of synthesized compounds is in process.

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## PP 12. THE DESIGN OF ORGANOHYBRID STRUCTURES

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One of the most actual problem in the field of informational nanotechnology is the development of photochromic recording media for three-dimensional optical memory with high information capacity. Usually these light-sensitive materials are developed by employment of thermally irreversible photochromic compounds, particularly 1,2-diarylethenes, in polymer binders [1]. Unfortunately, the information capacity (resolution) of these recording media is limited by diffusion and low content (up to 5 mass %) of photochromic compounds in a polymer matrix.

The present report on the synthesis and the spectral-kinetic study of photochromic three-dimensional silicone polymers (coatings) based on 1,2-dihetarylethenes with N-hydroxyethyl and N-allyl groups, polysiloxanes and polysilazanes. The polymers prepared contain photochromic moieties linked to the polymer chain by covalent bonds that allow achieving high concentration of photochromic units (up to 40%).

This work was supported by the Russian Foundation for Basic Research (Project 14-03-00204).

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## PP 13. FLAVONOIDS FROM THE LEAVES OF PHELLODENDRON LAVALLEI DODE, INTRODUCED IN GEORGIA

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From ancient times leaves of Phellodendron Lavallei Dode is used in folk medicine for treatment of dysentery, neurodermatitis, pneumonia, tuberculosis, plevritis, hepatitis and other diseases. The leaves are claimed to have antitumor, fungicidal, anti-inflammatory, antiseptic, bactericidal, diuretic, wound healing and other activities [1].

Medicine "Flacoside" that is active against herpes virus, is prepared from the P.Lavallei leaves, moreover the leaves are offered as a raw material of alkaloid berberin.

Chemical investigation of leaves of the P. Lavallei Dode introduced in Georgian coast of the Black Sea is carried out. It is established that leaves contain significant amounts (10%) of phenolic compounds. 4 individual compounds were isolated from the ethyl acetate sum and identified as (2R,3R)-3,5-dihydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)-7-[O-β-D-glucopyranosyl] oxy-2,3-dihydroxychromen-4-one(phellamurin), hyperin, trifolin and (2R, 3R)-3,5-dihydroxy-2-(4-hydroxyphenyl)-8-(3-metylbut-2-enyl)-7-[O-β-D-xylopyranosyl(1→3)-O-β-D-glucopyranosyl]-oxy-2,3-dihydro-chromen-4-one [2,3].

These phenolics are isolated from P. Lavallei Dode for the first time and represent, to our knowledge, new organic compound.

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# PP 14. SOME DERIVATIVES OF 3β-PHENYLACETOXY-5α-ANDROSTAN-17-ONE AND ASSESSMENT OF THEIR BIOLOGICAL ACTIVITY

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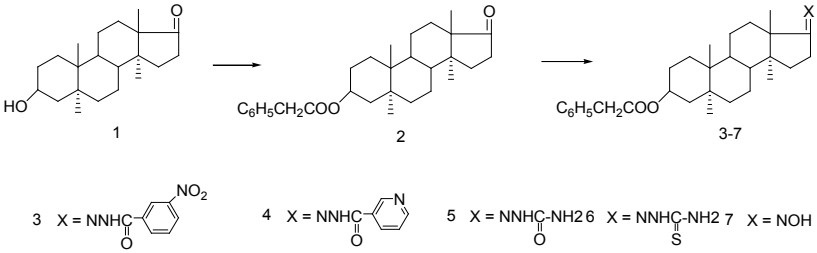
The known hydrazones, thio- and semicarbazones of various structure are mentioned amongs effective medicinal drugs used for treatment of viral and microbial diseases. Some representatives of 5α-steroidal hydrazones are also characterized with high antitubercular and antiviral activities.

In order to receive new bioactive structures we carried out modify of 5α-androstan-3β-ol-17-one **1** by chloranhydride of phenylacetic acid. By condensation of synthesized 3β-phenylacetoxy-5α-androstan-17-one **2** with hydrazides of acids, thio-, semicarbazides and hydroxylamine were received corresponding derivatives **3-7** and were studied their biological activity. The structures of the compounds **3-7** were confirmed by spectral analyses.




Antiviral activity of steroids **3-7** were studied at Utah State University National Institute of Allergy and Infectious Diseases (NIAID) (USA). Screening results on the Vero 76 cell line revealed, that m-nitrobenzoylhydrazone of 3β-phenylacetoxy-5α-androstan-17-one **3** is highly active and nicotinylhydrazone of 3β-phenylacetoxy-5α-androstan-17-one **4** -moderately active towards Polio virus (strain WM-3). On the same cell line compounds **3, 4** exhibit minor activity towards Sars coronavirus (strain Urban), but only hydrazone **4** appeared to have slight activity towards Rift Valley fever and Tacaribe viruses (strains MP-12 and TRVL 11573, corespondingly). Semicarbazone **5**, thiosemicarbazone **6** and hydroximinosteroide **7** were inactive towards all mentioned strains.

## PP 15. THE ALKALOIDS OF PANCRATIUM MARITIMUM L. GROWN IN GEORGIA

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Pancratium maritimum L. (Amaryllidaceae family) is widely spread in Georgia on the Black sea beach.

We researched vegetative organs of plants for the alkaloid composition, which was collected in the period of fructification in area of Kobuleti in 2012.

We were getting the sum of alkaloids from preliminarily alkalized air-dry pounding bulbs and overground parts. We were extracting with chloroform. After organic solvent evaporation, acid-base processing and extraction with chloroform for the second time, we were getting the sum of alkaloids: from the overground part – 0.20%, from the bulbs – 0.24%. We got individual alkaloids from fraction the sum of alkaloids on the silicagel column (L 100/160μ) with chromatographic method and elution was performed with chloroform-methanol mixture. We were making qualitative analysis of the sum and individual substances in the solvent mixture: chloroform:methanol 6:1 (1), chloroform:methanol: 25% ammonia (86:13:1) (2). The separated spots were detected with Dragendorff reagent.

From the study for alkaloids composition of Pancratium maritimum L., we established that this plant contains: lycorine, galanthamine, tazettine, gemanthamine and galanthine. Galanthine is isolated from Pancratium at first.

From the study of the sum of alkaloids and dynamics of galanthamine accumulation according to phases of vegetation in the bulbs, we established that the sum of alkaloids and maximal content of galanthamine is at the end of phase of vegetation, therefore it is advisable to collect bulbs in this period.

**Dynamics of accumulation of alkaloids in the bulbs of Pancratium maritimum L.**

| phase of vegetation | The content of the sum of alkaloids on the air-dry raw materilas (%) | The content of galanthamine on the air-dry raw materilas (%) |
|---|---|---|
| beginning of vegetation | 0.035 | 0.014 |
| budding and beginning of fruiting | 0.070 | 0.022 |
| fruiting | 0.184 | 0.043 |
| fructification | 0.240 | 0.072 |
| the end of vegetation | 0.255 | 0.086 |

According conducting researches Pancratium maritimum L. can be recommended as valuable raw materials for receiving galanthamine and lycorine.

## PP 16. OBTAINING AND RESEARCHING OF PLANT BIOLOGICALLY ACTIVE AGENTS BY USING OF ENDOPHYTIC FUNGI

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Natural biologically active agents are even more often used in agriculture, medicine and food industry. Endophytic fungi are relatively novel source of natural bioactive compounds [1, 2]. Plant endophytic fungi spend the whole or part of their lifecycle colonizing inter- and/or intra-cellularly in the healthy tissues of the host plants, typically causing no apparent symptoms of disease. They are important components of plant micro-ecosystems [3, 4]. Endophytic fungi are found in many plants and more than one million species of endophytic fungi exist in the nature [5]. During the long period of co-evolution the useful relations have been formed between each endophytic fungi and its host plant. Some endophytic fungi have an ability to produce the same or similar biologically active agents as their host plant. After discovery of bioactive compound paclitaxel (taxol) in endophytic fungus *Taxomyces andreanae,* interests of scientists in research of endophytic fungi have been increased [6]. It is valuable bioactive compound, on its basis preparation of multifunctional, almost useful biologically active compounds with antimicrobial, insecticidal, cytotoxic and anticancer activities is possible. Compounds obtained from endophytic fungi could be classified as alkaloids, terpenoids, steroids, quinones, lignans, phenols and lactones [7].

Application of endophytic fungi of European yew (*Taxus baccata*) for obtaining antimicrobial compounds is possible in Georgia, this plant is widespread in Batsara nature reserve. Antimicrobial metabolites could be obtained from endophytic fungus *Pichia guilliermondii,* which grows in the plant *Paris polyphylla var. Yunnanensis,* as well as from endophytic fungi *Clusia spp.(Clusiaceae).* Many important compounds as paclitaxel and its analoguess which represent tetracyclic diterpenoids, are received from the endophytic fungus. Podophyllotoxin is a well-known lignin, together with anticancer effect it has antibacterial, immunostimulating and antirheumatic properties.

Bioactive agents obtained from endophytic fungus are actually the same compounds as existing ones in host plant. Thus application of endophytic fungus for obtaining bioactive agents is perspective and promotes further development of their use. Podophyllotoxin (PDT) known aryltetralin lignin also should be noted. It has potent antibacterial, antineoplastic, antiviral, antioxidant, immunostimulation and anti-rheumatic properties. PDT has been used as a precursor for chemical synthesis of the anticancer preparations like etoposide, teniposide and others [8].

Camptothecin (CPT), a pentacyclic quinoline alkaloid, for the first time was isolated from the wood of *Camptotheca acuminata* in 1966 and is an effect-tive means against cancer [9]. Vinblastine and vincristine, the terpenoid indole alkaloids derived from the coupling of vindoline and Catharan-thine monomers, are two of the well-known antineoplastic agents [10].

After collecting of biomass, isolation of biologically active agents by means of the original method developed by us - stimulated natural extraction by use of plant precipitators will be carried out. Separation of some fractions and checking at the biological test-objects should be done. Selected narrow fractions will be investigated on GC/MS and by other chemical methods, their further modification for efficiency increase is possible.

Plant endophytic fungi, as an important micro biological source for producing bioactive compounds originally from their host plants, have attracted attention of many scientists. Their theoretical research as well as potential applications is studied, but there are still many issues that need to be defined and resolved.

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## PP 17. Nano-$MoO_3$ AS A CATALYST FOR ONE-POT GREEN AND EFFICIENT SYNTHESIS OF NEW TETRAHYDROPYRIMIDINE DERIVATIVES

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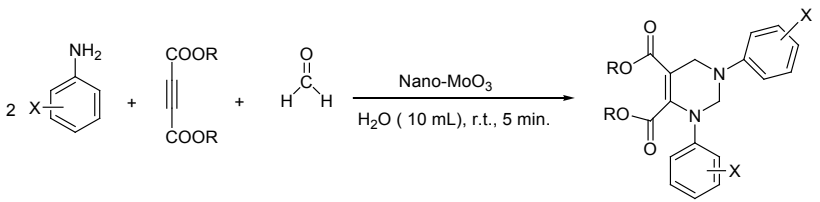
Poly functionalized heterocyclic compounds play important roles in drug discovery process [1]. Therefore, it is not surprising that research on the synthesis of poly functionalized heterocyclic compounds has received the considerable attention in recent years [2]. Pyrimidine derivatives comprise a diverse and interesting group of heterocyclic drugs which are extremely important for their biological activities specially as a significant part in construction of DNA and/or RNA scaffold [3]. As a part of our ongoing research on the development of new routes to synthesize the new tetrahydropyrimidine derivatives; hereby, we report green and highly efficient one-pot process to 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines derivatives, using a three-component reaction involving anilines, formaldehyde and dialkylacetylenedicarboxylate was developed in aqueous media using nano-$MoO_3$(Scheme1). In this protocol, nano-$MoO_3$ efficiently catalyzes the reaction in water to afford the corresponding products in high yields.




X:OH, $NO_2$, $CH_3$, Cl,...
R:Et,Me

89-95%

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## PP 18. A GREEN PROTOCOL FOR THE SYNTHESIS OF QUINOXALINE AND QUINOLINE DERIVATIVES AND EVALUATION OF THEIR ANTIBACTERIAL ACTIVITIES

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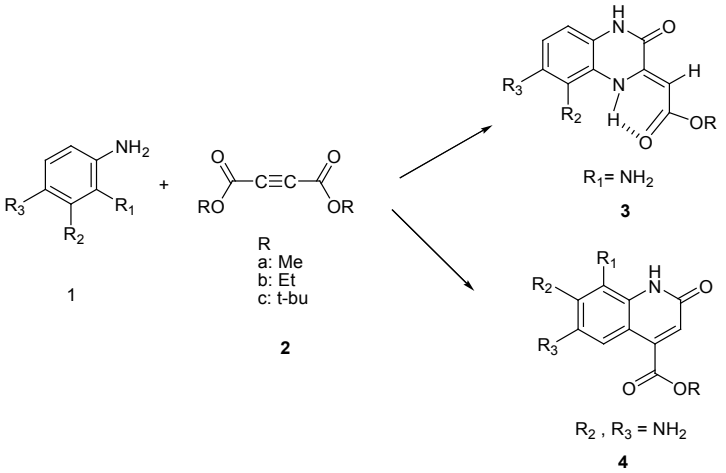
Heterocycle compounds containing nitrogen hetroatome are common in nature. Since these derivatives have a core constituent of many pharmaceuticals as well as agrochemicals [1]. The presence of nitrogen hetrocyclic nucleus in the framework of various pharmacologically active compounds with antimalarial, antitumor, anthelmintic, antibacterial, antiasthmatic, and antiplatelet activities continue to promote their synthetic efforts [2]. Due to these useful pharmacophoric properties, they have been extensively studied [3]. In view of the emerging importance of *N*-heterocycle compounds and our general interest in solventless chemical process [4], we envisioned expediting the synthesis quinoxalin and quinolin derivatives from the reaction of phenylenediamines, and dialkylacetylene dicarboxylates under catalyst and solvent free condition. All the synthesized compounds have been evaluated for their antibacterial activity towards two Gram positive and two Gram negative bacteria activity. Hereby, we report herein, an efficient and fast method for the preparation of quinoxalines and quinolin derivatives that involves grinding of phenylenediamine derivative and appropriate dialkylacetylene dicarboxylates using pestle and mortar (scheme 1). This solvent free approach requires only a few minutes of reaction time. This type of reaction is expected to be the most economical method since neither catalyst nor solvent is used.




**Scheme 1**

As shown in table 1**,** in most cases, the MCR afforded quinoxalines and quinolin products with high yield (>85%).

**Table 1.** Synthesis of quinoxalines and quinolin derivatives

| Entry | R | $R_1$ | $R_2$ | $R_3$ | Product | Time(Min) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | Me | $NH_2$ | H | H | 3a | 2 | 97 |
| 2 | Et | $NH_2$ | H | H | 3b | 2 | 94 |
| 3 | t-Bu | $NH_2$ | H | H | 3c | 2 | 96 |
| 4 | Me | H | $NH_2$ | H | 4a | 10 | 90 |
| 5 | Et | H | $NH_2$ | H | 4b | 10 | 91 |
| 6 | t-Bu | H | $NH_2$ | H | 4c | 10 | 86 |
| 7 | Me | H | H | $NH_2$ | 4d | 20 | 85 |
| 8 | Et | H | H | $NH_2$ | 4e | 20 | 86 |
| 9 | t-Bu | H | H | $NH_2$ | 4f | 20 | 89 |

Finally, all synthesized compounds were screened for antimicrobial activity against tow Gram-positive bacteria (Pseudomonas aeruginosa **PTCC 1077**,

Escherichia coli **PTCC 1330**) and tow Gram-negative bacteria (Staphylococcus areus **PTCC 1133**, Bacillus cereus **PTCC 1015**) and compare their activity with Gentamycin and Ampicillin as reference drugs for Gram-negative and Gram-positive bacteria. Table 2. The minimum inhibitory concentration (MIC) of the synthesized compounds and reference drugs determined by microdillution method [5]. As can be seen from table 2, compounds **4f**, antibacterial activity was observed against all species of Gram-positive and Gram-negative bacteria used in the study (MIC = 6.25-12,5 mg/ml), and the compounds **3a-c** was observed good antibacterial activity against tow Gram-positive bacteria. Compound **3a** was found to be same Ampicillin activity against S.areus (MIC=3.25 mg/ml) and compounds **3b-c**, **4f** was found same Ampicillin activity against B.cereus (MIC=12.5 mg/ml)

**Table 2.** MIC (lg/ml) values of products 3 and 4

| Compound | MIC [mg/ml] | | | |
|---|---|---|---|---|
| | P. aeroginosa | E. coli | B. cereus | S. areus |
| 3a | >100 | >50 | >25 | >3.125 |
| 3b | >100 | >50 | >12.5 | >6.5 |
| 3c | >50 | >25 | >12.5 | >6.5 |
| 4a | >50 | >100 | >100 | >50 |
| 4b | >25 | >100 | >50 | >25 |
| 4c | >50 | >50 | >100 | >50 |
| 4d | >25 | >50 | >25 | >25 |
| 4e | >25 | >12/5 | >50 | >25 |

In summary, we have described a simple, and one-pot, two-component reaction between dialkyl acetylene dicarboxylate and phenylenediamines derivatives for the preparation of nitrogen heterocycles in good yields. The advantages of the reported method are simple available starting materials, short reaction time, simple work-up, neutral reaction conditions and high yields.

Almost most of the compounds exhibited moderate to good antibacterial activity against all the tested strains.

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## PP 19. QUANTUM-CHEMICAL MODELING OF THE TERT-BUTYL-3-(3,4-DIBENZOXYPHENYL)-OXIRANE-2-GLYCIDATE SYNTHESIS REACTION

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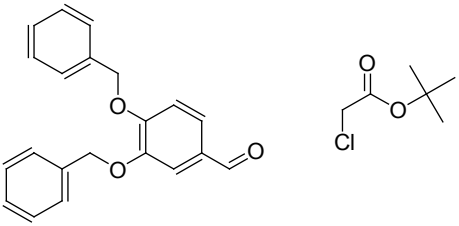
Since ancient times, the plants was used as a main treatment for various diseases. However, along with accumulation of the knowledge and development of the technology a large number of synthetic chemical emerged on the pharmaceutical market. Nowadays, particular attention is paid for appropriate optical purity of the synthetic medicines. Compound can be exist in the form of racemates.

Synthesis of the tert-butyl-3-(3,4-dibenzoxyphenyl)-oxirane-2 glycidate can be accomplished by the mechanism of the Darzens reaction (Darzens condensation or glycidic ester condensation).

We choice the 3,4-dibenzoxyphenyl and tert-butyl 2-chloroacetates as a initial substance.




In present study we calculated the geometrical and electronic characters of the intermediate products of the synthesis reaction of the tert-butyl-3-(3,4-dibenzoxyphenyl)- oxirane-2 glycidate, such as the heat of formation (ΔHf), the ionization potential (I), the dipole momentum (μ), the net atomic charge (qi) and the bond order (Pij) using quantum-chemical non-empirical Density functional theory (DFT) method.

## PP 20. SYNTHESIS OF A NEW TYPES OF N-GLYCOSILAMINES

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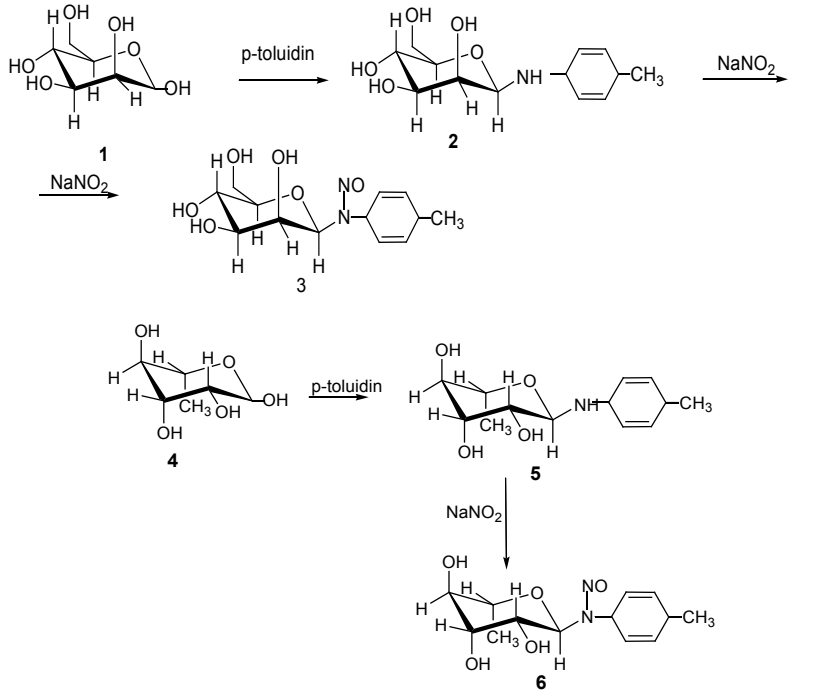
Among the drugs offered in recently years for therapy of tumor-bearing patients, appeared as one of the most perspective derivatives of nitrosourea [1,2]. In this respect it seems important the synthesis of its new structural analogues with attraction of various amino acids, biogenic amines, some alkaloids and other biologically and pharmacologically active compounds.

Well known nitrosoalkylurea (NAU) possess polarity and can be used as an acceptor at formation of hydrogen bonds, nevertheless it is not enough hydrophilous to provide good solubility in water. In this respect typical NAU with low-polarity substituent are characterized with small solubility in water and good solubility in most of organic solvents. As most legible instance in this regard can be considered antibiotic streptozotocin (possessing high solubility in water and in low-polarity organic solvents), the derivative of nitrosometylurea (NMU) and 2-deoxy-D-glucose. Expressed antineoplastic efficiency of this preparation in respect of some experimental tumoral and cellular culture and Its specific diabetogenic action have formed the basis for application of streptozotocin in treatment of patients with metastasizing insuloma [3,4].

Recently the growing attention is attracted to the synthesis of the derivatives of nitrosourea. However, the opportunities of all structural modifications of this class of compounds are still not exhausted.

The goal of present investigation consist in synthesis of N-glycosides containing in a molecule nitrosogroup (N=O). As an initial substance in the given work has been used the products of condensation of D-mannose (1) and L-rhamnose (4) - cN-*p*-tolyl -β-D-mannopyranoze (2) and N-*p*-tolyl -β-L-rhamnopyranoze (5). By interaction of compounds (2,5) with sodium nitrite corresponding nitrosoderivatives (3,6) has been received. Reaction proceeds according to the following scheme:




1 2 3 4 5 6

The structures of obtained compounds were established by physical-chemical methods of analysis. PMR spectra were recorded in $CDCl_3$ on a Bruker WM-250 spectrometer (250 MHz) with TMS internal standart. $^{13}C$ NMR spectra were recorded on a Bruker AM-300 ( 75,5 MHz) in $CDCl_3$. The optical rotation was measured on an SU-3 universal saccharimeter at 20±2°C. IR spectra were obtained in KBr disk on a UR-20 spectrometer. The purity of products and $R_f$ values were determined on Silufol UV-254.

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## PP 21. REGIOSELECTIVE SYNTHESIS OF BROMOINDOLES

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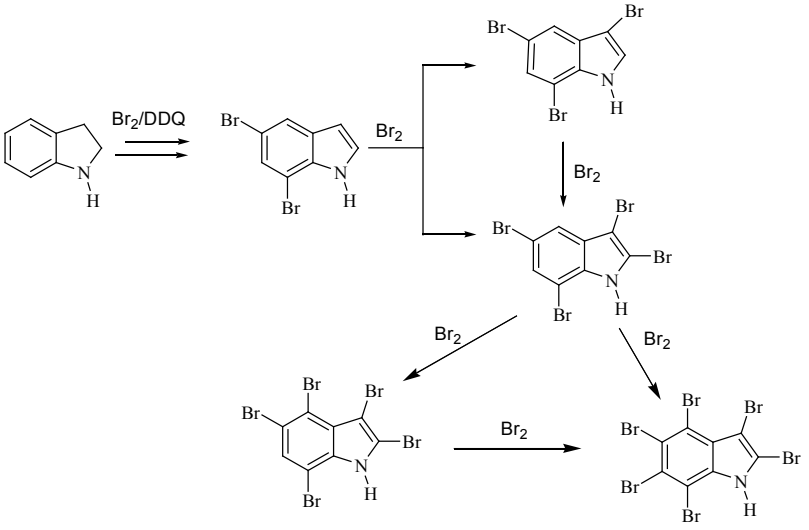
Indole and indole derivatives are an important class of compounds of particular interest due to biologically activities [1]. Many brominated indole derivatives have been isolated from marine sources and shown to exhibit interesting biological activities as antifungal and antibacterial. In addition to this, synthesis of bromoindoles has received considerable attention because of regioselectivity [2].

In this work, we interested in bromination of indole nucleus. We report a simple and regioselective route for preparation of bromoindoles [3].




This study is supported by TUBITAK (Project No:112T403 ).

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## PP 22. NEW TRIAZATRUXENES

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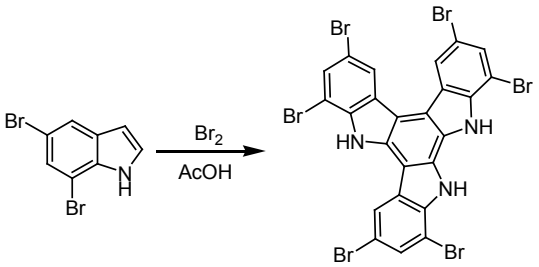
The synthesis of triazatruxene derivatives is significant because of their wide aromatic surface [1]. Their good planar structures, extend conjugation and strong electron donating ability, which can be very easily substituted by functional groups, make them promising material [2].

In this study we synthesized new triazatruksen derivatives via trimerization of 5,7-dibromo-1*H*-indole that can be easily substituted by functional groups [3].

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## PP 23. PHOSPHOLIPIDS FROM THE SEEDS OF *AMARANTHUS* GENUS GROWING IN GEORGIA

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Revealing and identification of biologically active compounds (BAC) including phytogenous lipids and their further application for medicinal purposes is considered amongst topical issues of phytochemistry.

Genus *Amaranthus* (Fam. *Amaranthaceae*) belongs to worldwide spread genera, however its 9 representatives wild growing in Georgia yet are not studied profoundly.

The aim of present work was the investigation of lipid compositions of the roots of cultivated decorative *A. cruentus* and wild growing *A. retroflexus* and *A. blitoides* S. Wats.

Crude neutral lipids (NL) were obtained from air-dried grinded seeds by 4-fold cold extraction with hexane. The brownish oily transparent liquid has been obtained containing NLs in following amounts: *A. cruentus* 7%, *A. retroflexus* 6.7% and *A. blitoides* 6.1%. The residue was additionally processed to obtain polar lipids using Folch method. In brief the raw was extracted 4 fold with chloroform : methanol (2:1) at room temperature and the obtained extract vacuum-dried yielding brownish oily mass *A. cruentus* 1.6%, *A. retroflexus* 1.4% and *A. blitoides* 1.1%.

Polar lipids obtained from seeds were subsequently treated with hexane, chloroform and water to remove residual NLs, amino acids and other admixtures. Qualitative analysis of polar lipids was carried by bidirectional chromatography using the following eluent systems: 1) chloroform: methanol : ammonia (60:30:5); 2) chloroform : methanol : glacial acetic acid : water (170:25:25:6). The plates were processed with iodine vapor and Vaskovski's reagent.

6 spots with one and the same Rf-s that correspond to known phospholipids lysophosphatidylcholine, phosphatidylinosite, phosphatidylcholine, phos-

phatidyl-ethanolamine, N-acyllysophosphatidylcholine, N-acyllysophosphatidylethanolamine were detected on all chromatograms; 1 unidentified phospholipid was detected on *A. cruentus* chromatogram.

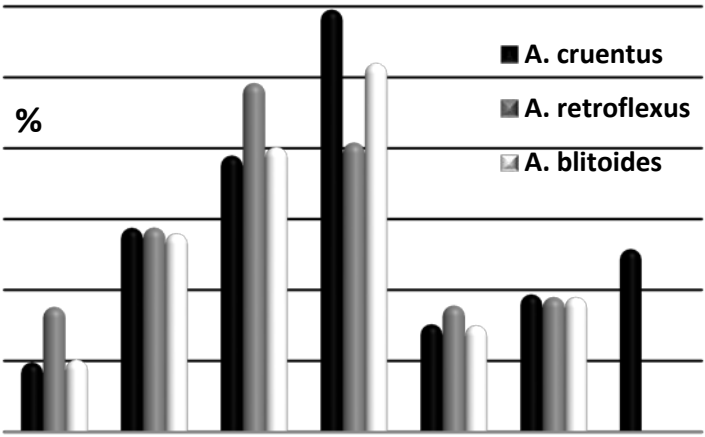


**Fig.1.** Phospholipidic spectra of different species of *Amaranthus* genus

Quantitative analysis (based on inorganic phosphorous) was carried out spectrophotometrically at 354 nm. The results are given in Fig.1.

It may be concluded that *A. cruentus , A. retroflexus* and *A. blitoides* polar lipids have identical phospholipidic spectra, but differ slightly in quantities of particular phospholipids.

## PP 24. NHERENTLY CHIRAL CALIX[4]ARENES: SYNTHESIS, OPTICAL RESOLUTION AND ABSOLUTE CONFIGURATION

**O. A. Yesypenko[1], M. A. Klyachina[1], V. I. Boyko[1], S. V. Shishkina[2] , O. V. Shishkin[2], A. M. Yesypenko[1], V. I. Kalchenko[1]**
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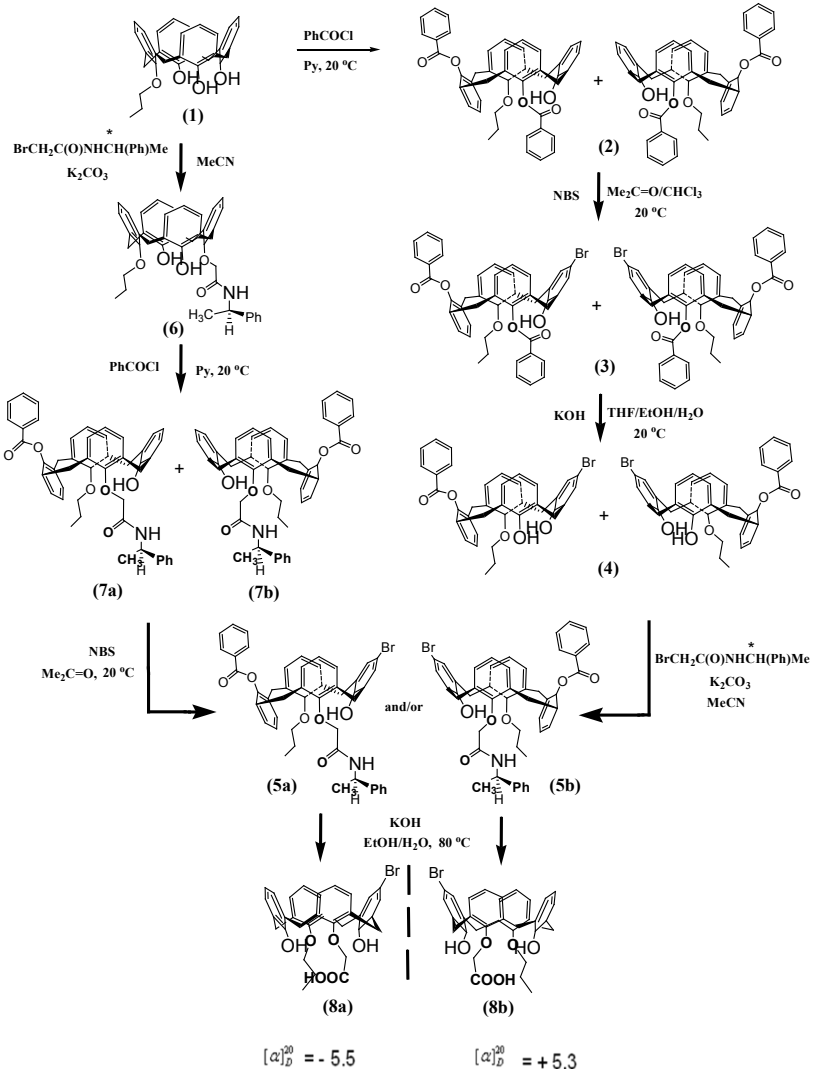
Stereoselective synthesis of optically active compounds is an important task of modern organic chemistry. A unique three-dimensional structure of calix[4]arene allows to create inherently chiral compounds wherein chirality is provided by asymmetric arrangement of achiral substituents on the platform of the macrocycle. Chiral calixarenes can serve as a basis for the creation of chiral catalysts, shifting agents in NMR spectroscopy, chiral stationary phases for chromatography and enantioselective sensors [1].

In this work we proposed two simple synthesis of optically pure inherently chiral calix[4]arene carboxylic acids (8a) and (8b) from available monopropoxy-calix[4]arene (1). In the first method we protect two hydroxyl groups by treating compound (1) with benzoyl chloride in pyridine and obtain the 1-propoxy-2,3-dibenzoate (2) as enantiomeric pair. Bromination of such calixarene occurs quantitatively in the *para*-position of unsubstituted phenol ring. Basic hydrolysis of the product (3) at 20°C allows us to selectively remove only one benzoate-protecting group. We obtain the 1-propoxy-2-benzoate (4) in 88% yield. The reaction with chiral (*R*)-N-(1-phenylethyl)bromoacetamide in the presence of $K_2CO_3$ converts enantiomeric pair (4) into diastereomeric pair (5a,5b), which was separated by column chromatography.

The second method [2] starts with regioselectively alkylation of compound (1) by (*R*)-N-(1-phenylethyl)bromoacetamide in the presence of $K_2CO_3$. We obtain the 1,3-disubstituted calixarene (6) in 98% yield. The next benzoylation of one hydroxyl group of molecule (6) in pyridine leads to the mixture of diastereomers (7a) and (7b) in a 55:45 ratio. Diastereomers were separated by column chromatography and recrystallization. The regioselective bromination of optically pure (7a) or (7b) with NBS in acetone gave amide (5a) or (5b) in 97% and 94% yields respectively. The phenylethylamide and benzoyl residues of calixarenes (5a) and (5b) were removed by refluxing with 150-fold excess of KOH in ethanol/water medium.




Structure and absolute configuration of the obtained compounds has been proved by NMR spectroscopy and X-ray analysis. All benzoates (2)-(5), (7) adopt the *partial cone* conformation and the *anti*-oriented is benzoate-protecting benzene ring adjacent to the propoxy-substituted ring. Acids (8a)

and (8b) have the *cone* conformation. They are enantiomers and have equal but opposite angles of polarized light rotation plane.

Carboxylic acids (8) are useful reagents for the synthesis of inherently chiral derivatives of calix[4]arene. They are also promising as organic catalysts for asymmetric synthesis, as enantioselective sorbents and sensors.

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## PP 25. NEW HETEROCYCLIC SYSTEMS CONTAINING THIAZOLO[3,2-*a*]-PYRIMIDINE AND PYRIMIDO[2,1-*b*]THIAZINE MOIETY

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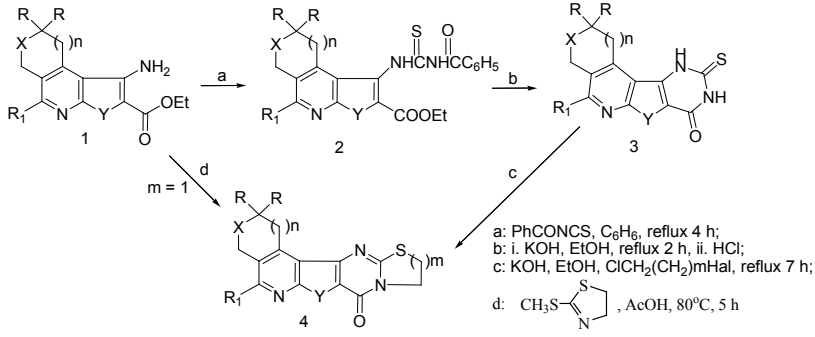
Sulfur- and nitrogen-containing heterocycles occupy an important place in the field of condensed heterocyclic compounds due to their wide application in organic synthesis and various fields of industry, medicine, and agriculture [1, 2].

The present work is the continuation of our previous studies on synthesis of condensed derivatives of furo(thieno)[2,3-*b*]pyridines [3, 4]. Herein, we report some our data on synthesis of new heterocyclic systems as potential biologically active compounds. For this purpose fused ethyl 3-aminofuro(thieno)[2,3-*b*]pyridine-2-carboxylates **1** were used as starting materials. These compounds **1** by condensation with benzoylisothiocyanate, gave the relevant thioureido derivatives **2**, whose cyclization under the action of potassium hydroxide in ethanol led to the formation of 2-thioxo-2,3-dihydropyrido[3',2':4,5]furo(thieno)[3,2-*d*]pyrimidin-4(1*H*)-ones **3**.




R = H, Me; $R_1$ = alkyl, aryl; X = $CH_2$, O; Y = O, S; n = 0, 1; m = 1, 2

In order to synthesize new pentacyclic systems condensed on the [*b*] side of the pyrimidine ring, the pyrimidinethiones 3 were reacted with dihalogenides to afford the aimed thiazolo[3,2-*a*]pyrimidines and pyrimido[2,1-*b*][1,3]thiazines 4.

The structure of thiazolo[3,2-*a*]pyrimidines 4 (m = 1) has been confirmed both by physico-chemical methods and by counter-synthesis starting from the corresponding furo(thieno)[2,3-*b*]pyridines 1. Thus, the reaction of compounds 1 with 2-(methylthio)-4,5-dihydro-1,3-thiazole led to the formation of compounds 4 (m = 1). However, the yield of the target products 4 in this “one-pot” reaction is markedly lower.

Therefore, the synthesis of new heterocyclic systems opens up new horizons for preparation of new promising pharmacologically active compounds.

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## PP 26. AN EFFICIENT AND OPERATIVE METHOD FOR THE ONE-POT TANDEM SYNTHESIS OF 3,5-DISUBSTITUTED-1,2,4-OXADIAZOLES FROM BENZYL HALIDS

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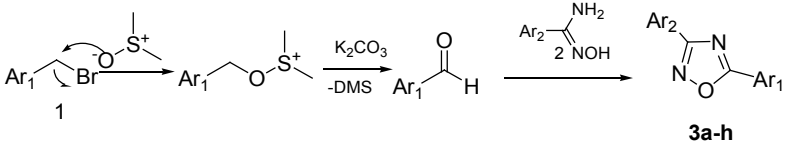
This study is the first example of one-pot tandem approach for the synthesis of 3,5-disubstituted-1,2,4-oxadiazole derivatives from benzyl halides and amidoxime. Various derivatives of 3,5-disubstituted 1,2,4-oxadiazole were obtained in excellent yields under mild conditions using DMSO in the absence of an additional oxidant. Benzyl bromides bearing a range of substituent proved to be suitable substrates for this protocol.This method offers a very efficient and convenient application of Kornblum oxidation.

1,2,4-Oxadiazole derivatives are important pharmacophore with different pharmacological activities including antitumor, antibacterial, analgesic, anti-inflammatory, anticancer, monoamine oxidase inhibition, tyrosine kinase inhibition, muscarinic agonism, and histamine $H_3$ antagonism [1-6].

Based on our knowledge there are no report about the using of aryl halides as starting materials in the synthesis of 1,2,4-oxadiazole synthesis in a one-pot manner. On the other hand, the introduction of the new methodologies providing for ease of synthesis from readily available chemical reagents, purification, and convenient isolation of the products lead to improve the existing scientific literature. Therefore, we have evaluated the feasibility of synthesizing 1,2,4-oxadiazoles from amidoximes and commercially available benzyl halides under mild condition.

Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles derivatives **3a-h**: A mixture of benzyl bromide **1** (1 mmol) and $K_2CO_3$ (1.5 mmol) in dimethyl sulfoxide (DMSO) (1 mL) was stirred for 4 h at 110 °C. Then, benzamidoxime **2** (1mmol) were added to the reaction mixture and stirring was continued at 110 °C for 4 h. The reaction mixture was cooled to room temperature and $H_2O$ (3 mL) was added.The precipitate was filtered, washed with $H_2O$ (2 mL), then it was dried. Crude products were purified by column chromatography using diethyl ether/ethyl acetate (5:1) as an eluent to give pure 3,5-diphenyl-1,2,4-oxadiazole **3(a-h)**.

Here, in the first step a series of benzyl bromides, under mild Kornblum oxidation conditions, was reacted with DMSO in the presence of $K_2CO_3$ as basic catalyst. The reaction was studied both under microwave irradiation as well as conventional heating. The striking observation was that the reaction under heating at 110° was considerably accelerated as compared to that under classical conditions using microwaves irradiation.




**Scheme 1.** The one pot synthesis of 3,5-disubstituted-1,2,4-oxadiazole derivatives 3(a-h) from amidoximes and benzyl bromides

Thus, under modified Kornblum oxidation conditions, benzylic bromide substrates **1** in DMSO in the presence of $K_2CO_3$ at 110 °C was converted into the corresponding aldehydes (Scheme **1**).The benzyl halides were efficiently oxidized to the corresponding aldehydes in excellent yields. Subsequently the in situ prepared aldehydes without further purification, was condensed with different amidoximes at 110 °C to achieve the corresponding 3,5-disubstituted 1,2,4-oxadiazole derivatives **3a-h** in acceptable yields 73–82% (table **1**).

**Table 1:** Synthesis of 3,5-disubstituted-1,2,4-oxadiazole derivatives 3a-h.

| Entry | $Ar_1$ | $Ar_2$ | Yield (%) [a] |
|---|---|---|---|
| 1 | Ph | Ph | 80 |
| 2 | 4-$CH_3$-$C_6H_4$ | 4-$CH_3$-$C_6H_4$ | 77 |
| 3 | 4-Cl-$C_6H_4$ | Ph | 75 |
| 4 | 2-Cl-$C_6H_4$ | 3-$NO_2$-C6H4 | 73 |
| 5 | 4-$CH_3$-$C_6H_4$ | 4-Cl-$C_6H_4$ | 82 |
| 6 | 4-Cl-$C_6H_4$ | 4-Cl-$C_6H_4$ | 78 |
| 7 | 2,4-$Cl_2C_6H_4$ | 4-$CH_3$-$C_6H_4$ | 80 |
| 8 | 4-Br | 4-F-$C_6H_4$ | 76 |

[a] Isolated yield after recrystallization.

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## PP 27. SYNTHETIC STUDIES IN THE FIELD OF 5-PHENYLTHIOINDOLE

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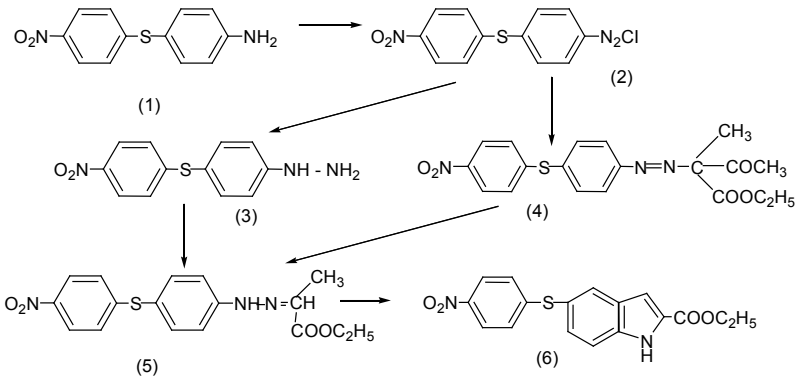
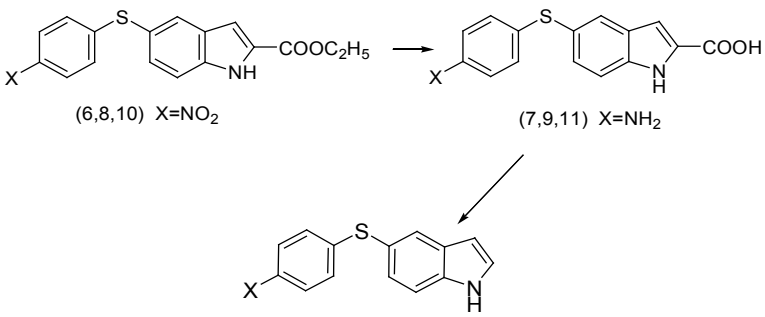
Nev derivatives of 5-phenylthio indole were synthesized according E.Fisher reaction.The initial 2-ethoxycarbonyl-5(p-nitrophenyl thio)indole(6) were obtained by cyclization 4-p-nitrophenyl thio phenyl hydrazone of ethyl ester of pirograpе acid (5) with the 56% rezult. Hydrazone (5) was produced by the method of Jack Kligerman and the classical scheme of Fischer. Diazotation of 4-amino-4[I]-nitrophenyl-sulfide(1) proceeds at 35-40°C, corresponding diazonium salt (2)precipitates from the solution at 60-65°C in the form of stable pale-green, needle-like crystals.




We are studied ester and nitro groups recombination of 2-ethoxycarbonyl-5(p-nitrophenylthio)indole(6). Revive of nitrogroup was impossible in $Zn/CaCl_2/H_2O$. 2-ethoxycarbonyl-5(p-aminophenylthio)indole(7) efficiency totals is 55%. Hydrolysis of 6 and 7 esters, gave the relevant nitro and amino acids (8.9) and decarboxilation of these acids was conducted in boiling quinolin while presence of the copper chromite.




The report examines the characteristics of these transformations. The structure and the composition of the obtained compounds were established using modern physical-chemical methods of research.

## PP 28. OXIDATIVE RING D EXPANSION DURING THERMAL CYCLIZATION HYDRAZONES 3β-ACETOXYPREGNA-5,6-DIEN-20-ONE. SYNTHESIS OF DODECAHYDRO-13H-PHENANTHRENE[1,2,5,6]-PYRANO[2,3-d]-PYRAZOLE

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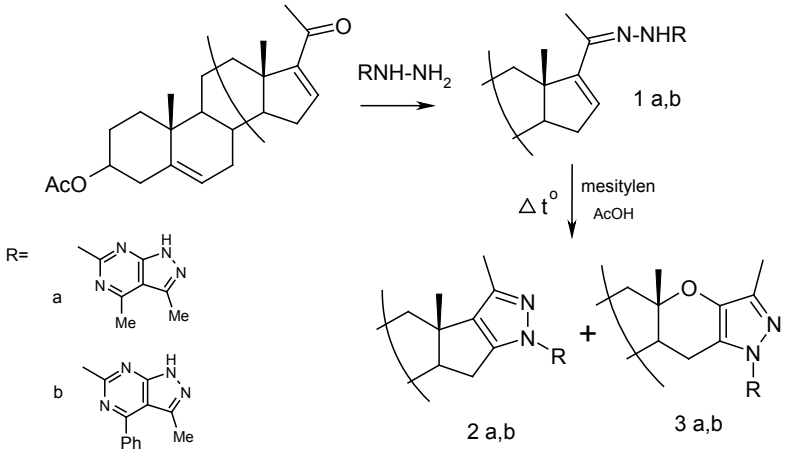
It is known that hydrazone derivatives of dehydropregnenolone are cyclise to pyrazolines [1,2] that simultaneously can turn under heating into appropriate pyrazoles [3]. We have found that cyclization reaction of dehydropregnenolone hydrazones **1a,b** over reflux in mesitylene in the presence of acetic acid led to formation along with expected pyrazoles **2a,b** also products of the steroid D oxidative ring expansion - previously unknown derivatives dodecahydro-13H-phenanthrene[1,2,5,6]-pyrano[2,3-d]-pyrazoles **3a,b.**




The structure of obtained compounds was identified using NMR spectroscopy $^{1}H$, $^{13}C$ two-dimensional methods of $^{1}H$ COSY, TOCSY, ROESY and the $^{1}H$, $^{13}C$ HSQC, HMBC and spectra of mass and high resolution (ESI).

## References

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## PP 29. 2-ARYL-4-BENZOYLIMIDAZOLONES - NOVEL STRUCTURAL ANALOGUES OF COMBRETASTATINE DERIVATIVES

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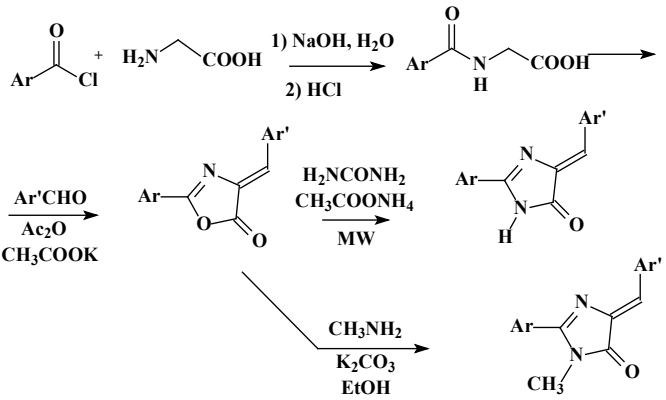
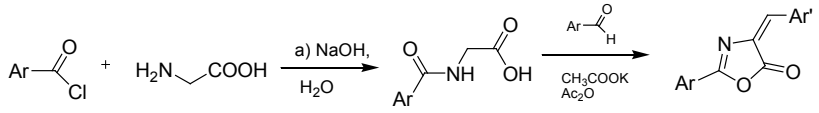
Currently, in medical chemistry a great attention is paid to the searching for compounds, exhibiting high antitumor activity. One of the most important molecular targets of anticancer agents is a cellular protein tubulin. This protein is capable of polymerizing to form microtubules, which play an important role in mitotic division and formation of the cytoskeleton of living organism cells.

Combretastatin A (CA-4) - compound isolated from a plant Compretum caffrum, - hit-compound, which give rise to many structural classes of ligands of the colchicine site of tubulin due to its relatively simple structure and a very high anticancer activity. Combretastatin A4 binds to tubulin with the so-called "the colchicine site", which prevents the binding of the protein dimer transition in a curved conformation to the "direct", which is important for the formation of microtubules [1] However, CA-4 has not very good pharmacokinetic properties because of its lipophilicity and correspondingly low solubility in water. Furthermore, this compound has a low chemical stability and able to isomerize the double bond with the formation of the thermodynamically more stable trans-isomer. Therefore, the creation of combretastatin analogues as potential anticancer agents is still an actual problem and has attracted the attention of many researchers.

The aim of this work was the creation of new structural types of potential ligands of the tubulin protein, which are the analogues of combretastatin A-4 on the basis of 2,4-substituted 1,3-imidazol-5 (4*H*) -ones. For their synthesis, a three-step sequence involving: 1) in the first step the synthesis of substituted hippuric acids from the available halogenides of aromatic carboxylic acids and glycine; 2) following condensation the obtained N-acylglycines with aromatic aldehydes and 3) the final substitution of the oxygen atoms formed azalactone NH or $NCH_3$ group by the action appropriate nitrogen-containing nucleophile was chosen.




As a result of this work oxazolones and imidazolones containing in ring A fluorine, methyl and methoxy groups were synthesized with different outputs. All synthesized oxazolones and imidazolones are isolated as a single geometrical isomer. The inhibitory effect of the synthesized compounds on proliferation of human lung carcinoma A549 cells was evaluated using MTT test.[2] All imidazolones containing at para-position fluorine atom in ring A, showed cytotoxicity to A549 cells with an IC50 in the micromolar concentration range (IC50 colchicine using as positive control is 0.03 mM).



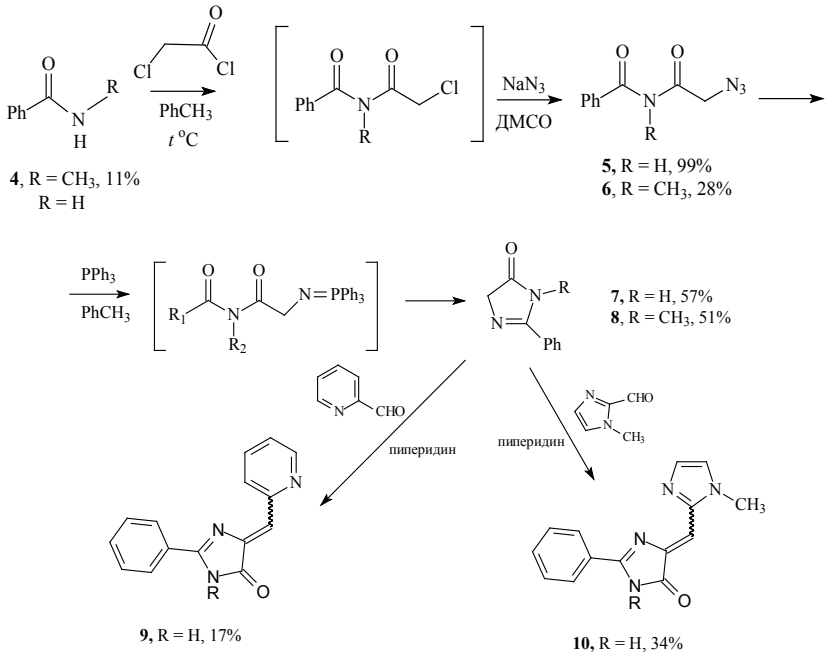

1a Ar = Ph
1b Ar = 4-F-$C_6H_4$
1c Ar = 4-$CH_3$-$C_6H_4$
1d Ar = 4-$CH_3O$-$C_6H_4$

2a Ar = Ph, 86%
2b Ar = 4-F-$C_6H_4$, 75%
2c Ar = 4-$CH_3$-$C_6H_4$, 57%
2d Ar = 4-$CH_3O$-$C_6H_4$, 71%

3a Ar = Ph, Ar' = Ph, 99%
3b Ar = Ph, Ar' = 4F-$C_6H_4$, 30%
3c Ar = 4F-$C_6H_4$, Ar' = 4-$CH_3O$-$C_6H_4$, 22%
3d Ar = 4-F-$C_6H_4$, Ar' = 4-F-$C_6H_4$, 69%
3e Ar = 4-F-$C_6H_4$, Ar' = 2,3,4-$(CH_3O)_3$-$C_6H_2$, 22%
3f Ar = 4-F-$C_6H_4$, Ar' = 3,4-$(CH_3O)_2$-$C_6H_3$, 21%
3g Ar = 4-F-$C_6H_4$, Ar' = 2,4,5-$(CH_3O)_3$-$C_6H_2$, 35%
3h Ar = 4-F-$C_6H$

For the synthesis of hetaryl-substituted compounds was used an alternative procedure based on the three-step sequence. In the first step benzamide was refluxed with chloroacetyl chloride, then evaporated and added to sodium azide Next, the azide was reacted with triphenylphosphine for Staudinger reaction; the product is cyclized by reaction of aza-Wittig. The resulting imidazolone 7 is condensed with 2-pyridinecarbaldehyde and N-

methylimidazole-2-carbaldehyde. Target compounds 9, 10 were isolated as a mixtures of geometric isomers, as evidenced by the presence of the vinyl protons of the two signals in their 1H NMR spectra. The ratio of isomers Z / E ratio is 1: 3 for compound 9, and 1: 1 for compound 10.




**4**, R = $CH_3$, 11%
R = H

**5,** R = H, 99%
**6**, R = $CH_3$, 28%

**7,** R = H, 57%
**8**, R = $CH_3$, 51%

**9,** R = H, 17%

**10,** R = H, 34%

The authors gratefully acknowledge the assistance of Nicolay Kuznetsov for MTT cytotoxicity assay and the financial support of Russian Foundation for Basic Research (Grants ## 12-03-33148, 12-04-00988, 13-03-00399).

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## PP 30. THERMAL AND Sc(OTf)$_3$ CATALYZED 1,3-DIPOLAR CYCLOADDITION OF CHIRAL CYCLIC NITRONES TO α,β-UNSATURATED LACTONES: EXPERIMENTAL STUDIES

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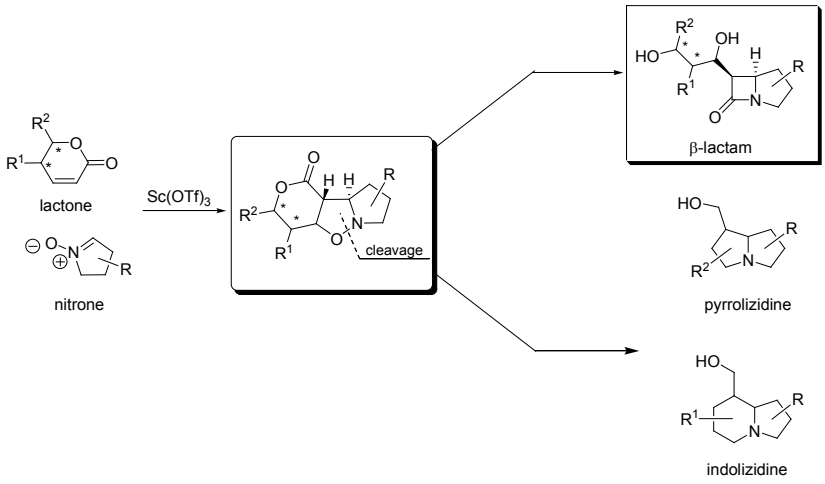
1,3-Dipolar cycloaddition reactions (1,3-DCA) are powerful tool for the synthesis of heterocyclic compounds. Their advantage is fact that, the cycloaddition of 1,3-dipole, such as a nitrone, to double bond, results in formation of up to three continuous stereogenic centers in single step.[1] Previously, we had demonstrated that cyclic dipolarophiles, such as sugar-derived δ-lactones, are attractive reagents for the thermally induced 1,3-DCA. Obtained adducts can be transformed into selected iminosugars [2], or be attractive entry to the basic skeleton of thienamycin [3].

Herein, we present our recent studies on 1,3-dipolar cycloaddition reactions under thermal and catalytic conditions as well as the strategies for the transformation of cycloadducts into selected bioactive compounds.

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## PP 31. SUGAR-DERIVED CYCLIC IMINES: ONE-POT SYNTHESIS AND DIRECT FUNCTIONALIZATION

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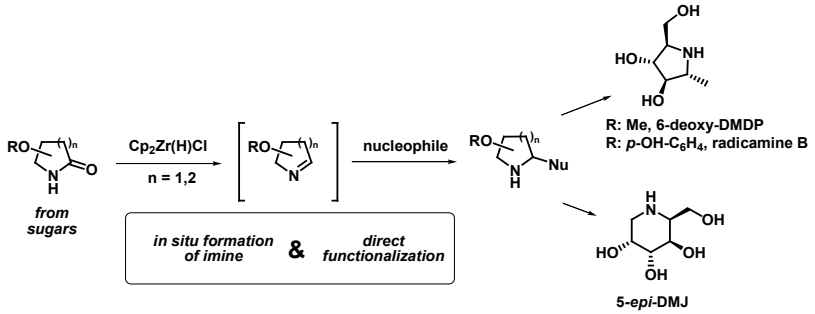
A simple method of synthesis sugar-derived imines[1] by Schwartz's reagent reduction of easily available sugar lactams [2] has been described. A direct addition of nucleophiles to the generated *in situ* cyclic imines and subsequent deprotection of hydroxyl function allows to convert sugar lactams in polyhydroxylated pyrolidines and piperidines [3].




This project is financed by the European Union within the European Regional Development Fund, Project POIG.01.01.02.-14-102/09. Authors are also grateful for The Regional Council of Mazovia and European Union within European Regional Development Fund for PhD student scholarship for P. Szcześniak.

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# ACID CATALYZED REARRANGEMENT OF VINYL AND KETENE ACETALS – STEREOSELECTIVE SYNTHESIS OF *C*-GLYCOSIDES AND RELATED COMPOUNDS

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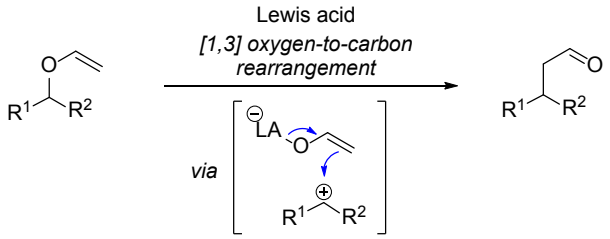
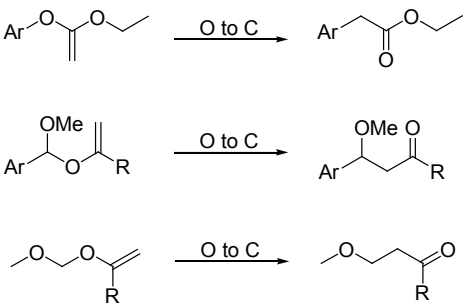
The reaction [1,3] rearrangements of vinyl ethers represent powerful method of construction of a new carbon-carbon bond by the breaking carbon-oxygen one.[1]




This transformation involves the rearrangement of molecules bearing latent electrophilic and nucleophilic moieties, the *in situ* molecular fragmentation of which results in the concomitant formation of a stabilized positive charged species and an activated nucleophile. These species re-combine to generate the product by formation of a new carbon–carbon bond. The most prevalent oxygen-to-carbon rearrangements are those whereby the stabilization of positive charge is mediated by an oxygen atom.

Recently, we initiated studies aimed at basic aspects of oxygen-to-carbon rearrangement. We demonstrated that simple, substituted vinyl and ketene acetals undergo smooth oxygen-to-carbon rearrangement with catalytic amount of TMSOTf (1 mol%) to afford chain-extended ketones or esters, respectively.[2]




This transformation can also be applied to the sugar-derived anomeric vinyl ethers to produce *C*-glycosides.[2]

The scope of applicability of this method will be presented.

This project was financed by the European Union within the European Regional Development Fund, Project POIG.01.01.02.-14-102/09.

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## PP 32. DIASTEREOSELECTIVE SYNTHESIS OF β-LACTAMS *VIA* KINUGASA REACTION WITH CHIRAL ACYCLIC NITRONES

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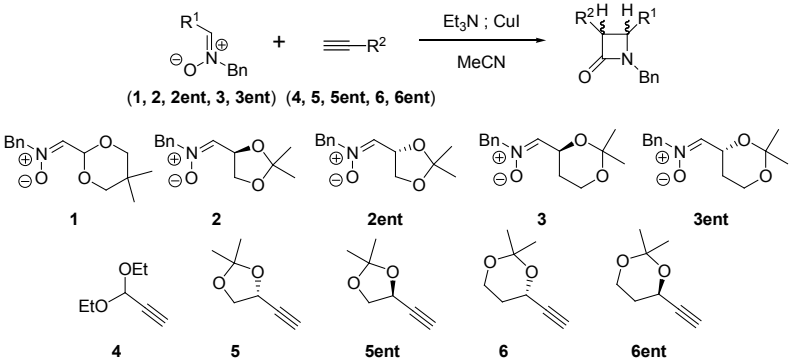
An approach to β-lactams *via* Kinugasa reaction [1] between chiral terminal copper acetylides and chiral open-chain nitrones bearing either 1,3-dioxane or 1,3-dioxolane moieties will be reported. Stereochemical preferences observed in these reactions will be discussed. The reaction provides an access to a variety of interesting β-lactam structures. Electronic circular dichroism (ECD) in combination with NMR spectroscopy was shown as useful and effective method for reliable determination of the absolute configuration of all components of a complex mixtures of azetidinones.




This project is financed by the European Union within the European Regional Development Fund, Project POIG.01.01.02.-14-102/09. Authors are also grateful for The Regional Council of Mazovia and European Union within European Regional Development Fund for PhD student scholarship for L. Mucha.

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## PP 33. THE KINUGASA REACTION AS A USEFUL METHOD FOR THE SYNTHESIS OF β-LACTAMS FROM BASIC RESEARCH TO PRACTICAL APPLICATIONS

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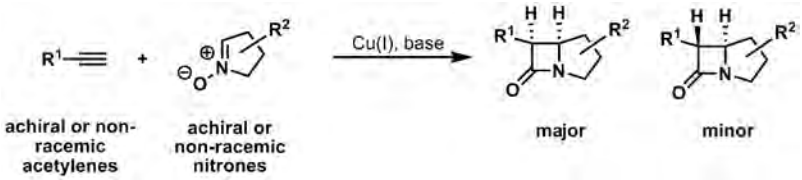
The copper(I) mediated reaction of nitrones and terminal acetylenes, known as Kinugasa reaction, represents an attractive method of direct formation of the β-lactam ring.[1,2] Herein, we present our studies on Kinugasa reaction involving cyclic nitrones readily available from hydroxy acids or amino acids and terminal acetylenes either achiral or bearing a stereogenic center. The stereochemical pathway of the reaction its scope and limitations and practical applications will be discussed.[3-9]




This project was financed by the European Union within the European Regional Development Fund, Project POIG.01.01.02.-14-102/09.

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## PP 34. SYNTHESIS OF POLYHYDROXYLATED QUINOLIZIDINE AND INDOLIZIDINE SCAFFOLD FROM SUGAR-DERIVED LACTAMS VIA ONE-POT REDUCTION/MANNICH/MICHAEL SEQUENCE

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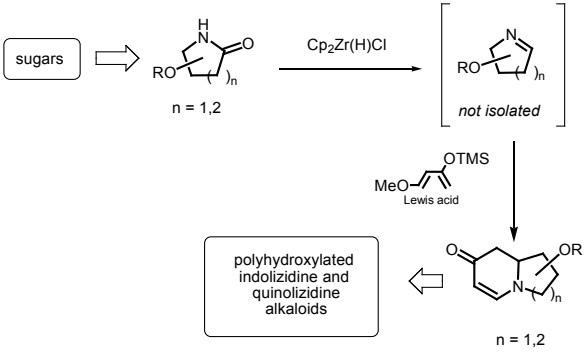
A direct approach to synthesis of indolizidine and quinolizidine scaffolds of iminosugars is described. Presented strategy is based on one-pot sugar lactam reduction with Schwartz's reagent [1] followed by a diastereoselective Mannich/Michael tandem reaction of the resulting sugar imine with Danishefsky's diene [2]. The obtained bicyclic products are attractive building blocks for the synthesis of various naturally occurring polyhydroxylated alkaloids and their derivatives.




This project is financed by the European Union within the European Regional Development Fund, Project POIG.01.01.02.-14-102/09. Authors are also grateful for The Regional Council of Mazovia and European Union within European Regional Development Fund for PhD student scholarship for P. Szcześniak.

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## PP 35. AN ENTRY TO ENANTIOSELECTIVE SYNTHESIS OF β-LACTAMS

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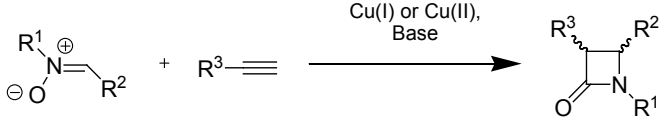
β-Lactams are very important class of organic compounds due to their biological activity (antibiotics, such as penicillins and cephalosporins,[1] anticancer agents [2], and cholesterol absorbance inhibitors [3]). They have also been used as attractive building blocks in the stereocontrolled synthesis of complex organic compounds [4]. The importance of β-lactam compounds maintains a high level of interest in methods of their synthesis at academic and industrial laboratories.

Among the numerous method of synthesis of chiral β-lactams, the copper-mediated reaction of nitrones **1** with terminal alkynes **2,** described in the 1970's (known as Kinugasa reaction, Scheme 1) is particularly interesting method for direct formation of 2-azetidinone ring [5].



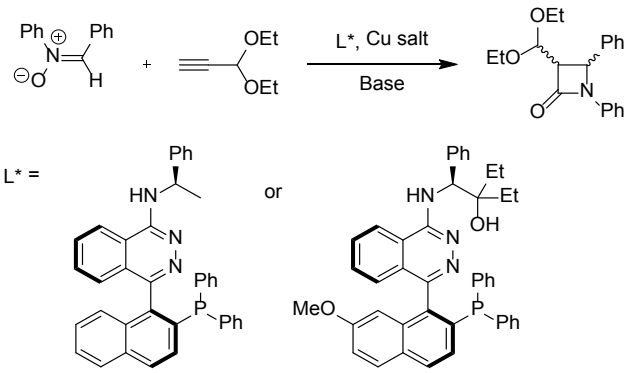

**1** **2** **3**

**Scheme 1.** Kinugasa reaction

Unfortunately, the number of reports related to diastereo- and enantioselective formation of β-lactams *via* Kinugasa reaction is still limited. Moreover, in most of the known cases only *C*,*N*-diarylnitrones have been applied. Reports of reactions involving aliphatic nitrones are scarce.

Herein, we report catalytic enantioselective Kinugasa reaction of aliphatic alkynes using complexes of Cu salts with readily available biaryl *N*,*P*-ligands described by Carreira as catalysts (Scheme 2) [6,7].

During our research we examined various solvents, bases and copper sources. β-Lactams were obtained in moderate to good enantioselectivity and good yields.




**Scheme 2.** Catalytic enantioselective Kinugasa reaction

This project is financed by Polish National Science Centre, Grant “Fuga” No. 2013/08/S/ST5/00569.

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## PP 36. NEW DATA REGARDING MECHANISM OF INDOLIZATION REACTION OF ARYLHYDRAZONES

**Sh. Samsoniya[1], N. Chikvaidze[2], J. Kereselidze[1], Z. Pachulia[2], N. Iashvili[1]**
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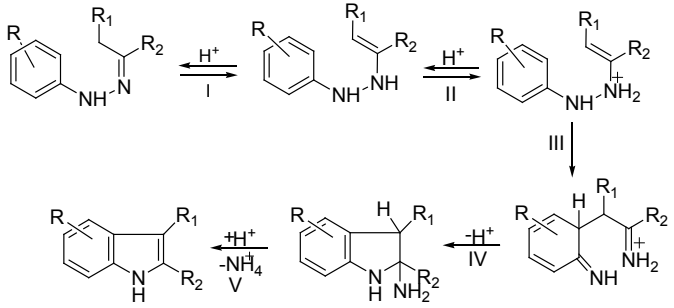
niniko2211@gmail.com

Among several known methods for synthesis of Indole rings, the most popular one is the classical reaction of E.Fischer Indolization reaction of Arylhydrazones in the presence of acid catalyst. Several articles regarding this mechanism are present among them are synoptic articles. Nowadays accepted mechanism is the one shown on the scheme. For a while, one of the step in Fischer's reaction (III) – formation of new C-C bond was subject of discussion: To count it as [2,3']-sigmatropic rearrangement, as intermolecular nucleophilic reaction, as process where N-protonated N-hydrazine electrocyclic reaction goes through or as something else.



Authors of the article published in 2011, are confirming the argument regarding the importance of electric factors of this step. In particular, electron donors present in carbonyl fragment suspend the formation of indole ring [1]. Results of our observations are corresponding well with these data. Correspondence of optimal temperatures with the electronic nature of a substituent during the indolization of aryl hydrazones became clear. We conducted comparative analysis of these temperatures. We generalized literature and our experimental data [2,3], as well as the results of quantum-chemical calculations.

In the report, obtained data, on an example of acetophenone derivatives ad some oxo compounds is discussed. In particular, peculiarity of influence from groups R, $R_1$, and $R_2$.

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## PP 37. DEPHORMYLATION REACTION OF INDOLE ALDEHIDES AND BIS-INDOLE ALDEHIDES

**Sh. Samsoniya[1], G. Basharuli[2], Z. Pachulia[2], N. Targamadze[1], L. Kvirikadze[1]**

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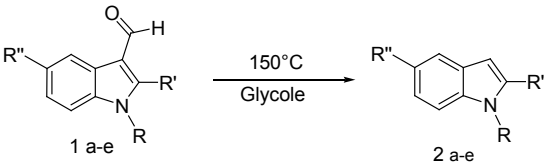
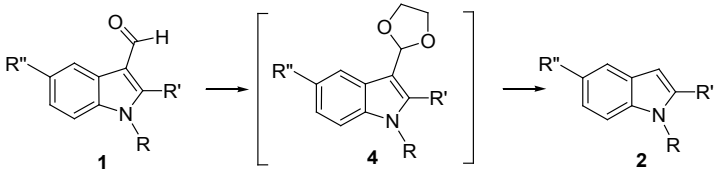
[2] Sokhumi State University
g_basharuli@yahoo.com

Unusual dephormylation reaction of indole-3-yl Aldehide derivatives have been described [1,2]. These reactions nearly have quantitative yield. Later, it was discovered that this reaction proceeds in the derivatives of symmetric 3,3'-diphormyl-5,5'-bisindoles. Also it turned out that the reaction yield does not depend on the electronic nature of the substitute.




**a** R = Me, R' = Ph, R" = H;
**b** R = H, R' = Ph, R" = H;
**c** R = H, R' = $C_6H_4CH_2Ph$, R" = H;
**d** R= H, R' = $C_6H_4CH_2CH_2Ph$, R" = H;
**e** R =H, R' = $CO_2Et$, R" = Me

It should be noted, that the reaction does not take place in monohydric alcohols or in other high boiling solvents. In our opinion, these reactions proceed by elimination of Doxolane ring from intermediate Cyclic Acetales generated on the first step, or by other types of destruction.

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## PP 38. NEW DATA REGARDING UNUSUAL CHLORINATION REACTION OF INDOLE RING

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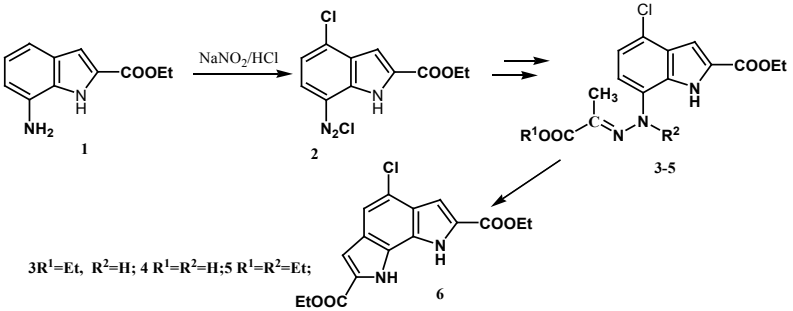
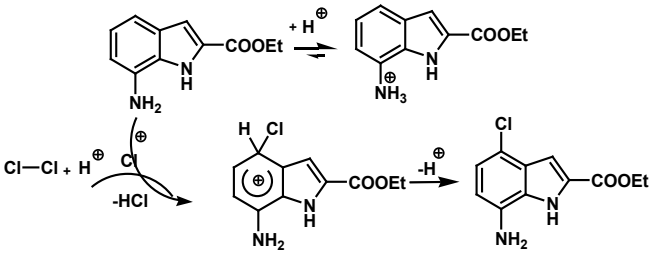
Previously, we described Unusual chlorination reaction of [1] indole rings during diazoniation reaction of 7-amino-2-ethoxycarbonilindole (2).




Later, we conducted the study of quantum-chemical mechanism of this reaction. Calculations were conducted on basic and protonated amines of isolated molecule, as well as on hydrated forms in a solution. In every case, it was affirmed that this is electrophilic substitution, which follows the following scheme:




In the report, experimental and quantum-chemical parameters are discussed.

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## PP 39. SYNTHESIS AND TRANSFORMATIONS OF SOME SYMMETRICAL BIS-PYRIDAZINOINDOLES

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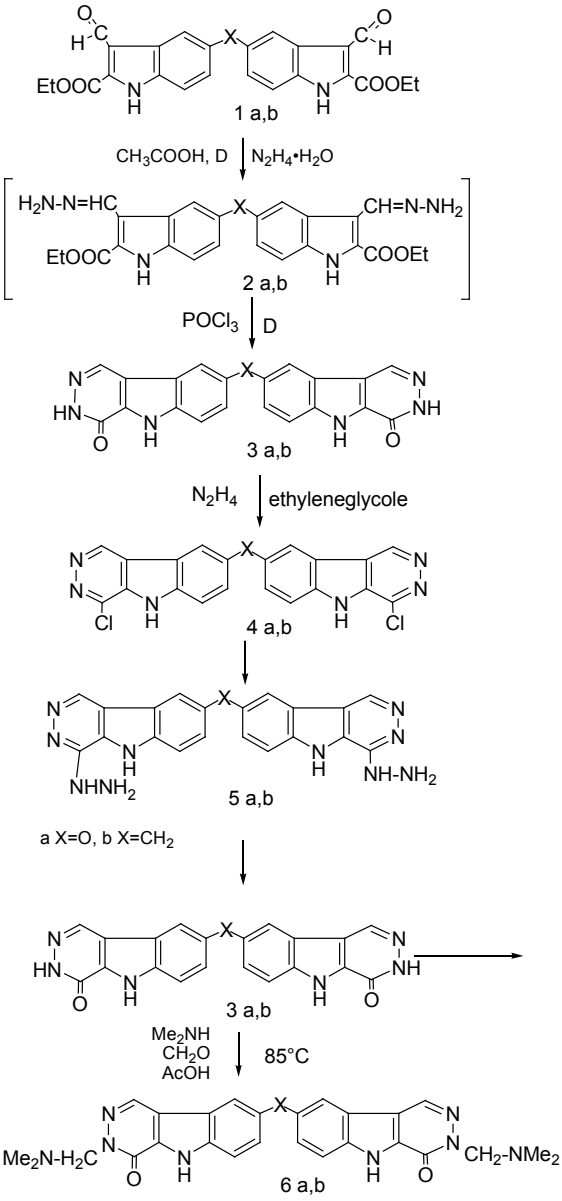
On the basis of 2,2'-diethoxycarbonyl-bis(indol-5-yl) oxide(1a) and 3,3'-diphormyl derivatives of 2,2'-diethoxycarbonyl-bis(indol-5-yl) methane (1b), corresponding, 4,4'-dioxo-8,8'-bispyridazinoindoles (3a,b) with symmetric structures were synthesized. Reaction was conducted by boiling the mixture of dialdehyde and hydrazine hydrate in glacial acetic acid.

Obtained bis(3,5-dihydro-4H-pyridazino[4,5-b] indol-4-on-8-yl) oxide (3a) and bis(3,5-dihydro-4H-pyridazino[4,5-b] indol-4-on-8-yl) methane (3b) are cyclic hydrazides. Aromatization was conducted by boiling compounds in excess $POCl_3$. Obtained intermediate chloro organic compounds 4 a,b are more reactive then initial pyridazinones (3 a,b), which raises the possibility to introduce new functional groups in the heterocycle, using nucleophilic substitution on halogen atoms. Using this, several interesting compounds like diamines, dihydrazines, dihydrazones and their derivatives can be obta-inned.

Substitution reaction of chlorine atoms proceeds fully in harsh conditions – by heating up the mixture of dichlorine derivatives and hydrazine hydrate in ethylene glycol up to 120 °C. Corresponding dihydrazines are obtained in high yield. It should be noted, that raw products of the reaction also contain traces of some more compounds, which, probably, are obtained by the interaction of initial dichlorine derivatives, or reaction products (4a, b) (or some intermediate products) with the solvent. Obtained dihydrazines (5a,b) are bisindolic analogues of the effective antihypertensive drug – Apresoline. As, they contain hydrazine fragments, these compounds can be used as intermediates for synthesizing other interesting compounds.

bis(3,5-dihydro-4H-pyridazino[4,5-b] indol-4-on-8-yl) oxide (3a) and bis(3,5-dihydro-4H-pyridazino[4,5-b] indol-4-on-8-yl) methane (3b) participate in Mannich reaction, in conditions representative of 2,2'-diethoxycarbonyl-bisindoles (85 °C). Substitution goes through in hydrazide NH- group. Corresponding bis-dimethylaminomethyl derivatives (6 a,b) have high yield.


1 a,b
CH3COOH, D
N2H4•H2O
2 a,b
POCl3
D
3 a,b
N2H4
ethyleneglycole
4 a,b
5 a,b
a X=O, b X=CH2
3 a,b
Me2NH
CH2O
AcOH
85°C
6 a,b

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## PP 40. DOUBLE QUENCHED MOLECULAR BEACONS IN REAL-TIME PCR ASSAY

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Optimization of fluorogenic properties of DNA-probes is a way to successful PCR. Molecular beacons [1,2] provide more opportunities to influence the fluorescence during real-time PCR assay. Our experiments show that fluorogenic properties of molecular beacons depend on the linker structure used for fluorophores or quenchers attachment.

We synthesized a new material for 3'-modification of DNA-probes. This is modified control pore glass (CPG), which contains two alkyne functions and one dimethoxytrityl-protected hydroxyl. We assume that the flexible structure of the linker is likely to bring the fluorophore and the quencher into close proximity. Terminal alkyne is used as an efficient function for [3+2] azide-alkyne cycloaddition. Thus, this reagent is useful to introduce double modifications into 3'-position of oligonucleotides.

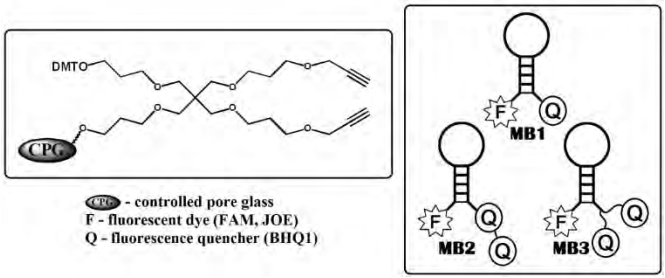


**Figure 1**

Six molecular beacons containing a probe sequence (a part of *Fusarium avenaceum* elongation factor 1α, GeneBank accession number JF278604, underlined) 5'-FAM (or JOE)-gcggggtcattcgaaacgcattcattaccccgc-BHQ1 (or BHQ1-BHQ1, or $(BHQ1)_2$)-3' (MB1, MB2, MB3 in fig.1 respectively) were prepared. Linear pair of BHQ1 was attached by the use of BHQ1 phosphoramidite reagent for the first condensation step on BHQ-CPG.

Parallel pair of BHQ1 was introduced with two-alkyne branched CPG (fig. 1) followed by [3+2] azide-alkyne cycloaddition with BHQ1-azide.

Two quenchers in the structure of molecular beacons compared to single quencher-probes reduce background fluorescence up to 2 times, thus increasing the fluorescence signal/background ratio up to about 2 for FAM-BHQ1-BHQ1 and JOE-BHQ1-BHQ1 molecular beacons (MB2 structure compared to MB1). Molecular beacons with parallel pair of BHQ1 (MB3) behave similar to single-labelled molecular beacons (MB1). Probably, the flexible linker does not provide necessary conformation for effective quenching.

Thus, we propose new structure design of molecular beacons to enhance fluorogenic properties of DNA probes applied in diagnostic tools.

## References

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## PP 41. IN SITU FORMATION OF SALICYLIC ALDEHYDE VIA INTERACTION OF O-CARBOXYBENZENEDIAZONIUM TOSYLATES WITH ZN(OTF)$_2$ IN DMF

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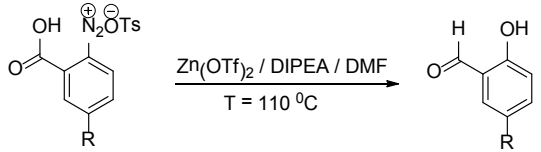
The aromatic diazonium salts are one of the most important reagents in organic chemistry. Also they are the most significant building blocks in the classical organic synthesis, due to its high reactivity in a wide range of reactions [1-3].

Research group of prof. V. D. Filimonov has earlier developed the method of obtaining the new class of arenediazonium salts - arenediazonium tosylates (ADT) [4]. It is known that they have a unique stability unless other aromatic diazonium salts. Moreover arenediazonium tosylates are non-explosive substances. It is shown that the ADT demonstrate high activity in typical "diazonium" reactions of iodo-dediazoniation and azocoupling. Arenediazonium tosylates are effective arylating agents in Pd-catalyzed reaction in alcohol solutions [4] and reactive N-electrophiles in reactions of triazenes and formazans preparation [5]. Also they appear as unique substrates for covalent modification of carbon-containing nano- and macrosurfaces [6]. At this point the reactive ability of arenediazonium tosylates is insufficiently examined. So the aim of our work was to study the behavior of aromatic diazonium salts in DMF with presence of zinc triflate and N,N-diisopropylethylamine in stoichiometric amounts following by the general scheme:




R = -H (1), - Br (2), - I (3)

We have found that o-carboxybenzenediazonium tosylates smoothly react with Zn(OTf)$_2$/DIPEA with formation of salicylaldehyde derivatives.

Reaction takes about 45-50 minutes in DMF solution at 110 °C. The salicylaldehyde derivatives was isolated and characterized as hydrazones

from 2,4-dinitrophenylhydrazine because corresponding aldehydes have a good solubility in water.

Formation of o-hydroxyaldehydes in this reaction associated with ortho position of two groups: diazogroup and carboxyl group. This fact has been proven by a series of experiments with the o-nitrobenzoic acid, benzoic acid, m-carboxybenzenediazonium tosylate, p- carboxybenzenediazonium tosylate under the same conditions. In all these cases, the formation of the aldehyde was not detected. The mechanism of this reaction is not fully investigated, but we suggested, that it associated with migration of carboxylic hydroxyl to the o-position of benzene ring via decomposition of diazo-group.

The developed interaction is relatively simple and quick way for obtaining of salicylaldehyde and its derivatives.

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## PP 42. THE SYNTHESIS OF NEW FLUORESENT FORMAZANS AND ITS METAL COMPLEXES

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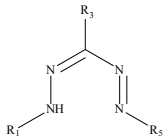
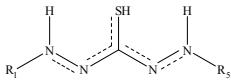
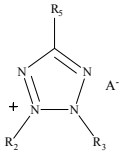
Formazans **1** and their derivatives such as thiocarbazones **2** or tetrazolium salts **3** are key compounds in analytical chemistry, histochemistry and cell biology [1-3]. One of the most applicable formazans is 3-nitroformazans, which possess a good synthetic applicability and can be used as nitrogen-rich analogues of β-diketimine ligands [4]. Moreover, 3-nitroformazans are applied for simple thiocarbazones synthesis, which possible to use as reagents for trace metal analysis.




**1**




**2**

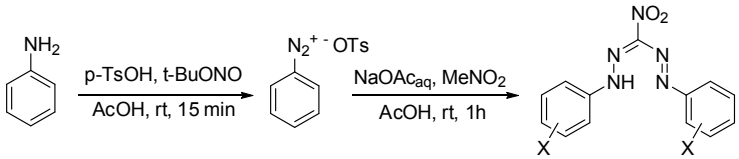



**3**

The common method of express quantitative analysis is UV-vis spectroscopy. However, this method has many limitations due to mutual superposition of substances spectra in a mixture. The luminescence spectroscopy almost hasn't this drawback, therefore simple and effective fluorescent formazans, thiocarbazones and tetrazolium salts synthesis is actual aim.

3-nitroformazans are most handy for thiocarbazones synthesis, and the most common method of 3-nitroformazans synthesis is the interaction of diazonium salts with nitromethane in alkaline solutions [4–6]. It should be noted that the usages of arenediazonium chlorides and tetrafluoroborates are often dangerous and inconvenient due to high explosibility and low stability. Recently it has been shown that p-toluenesulfonic acid as a counter-ion in diazonium salts allows decreasing the traditional hazards associated with high explosibility and low stability, and increasing their reactivity significantly in convenient reaction [7,8].

We have found out that 3-nitroformazans containing electron-donating and electron-withdrawing groups can be synthesized from anilines via modified Pel'kis et.al. method using arenediazonium tosylates (ADT) with high yields (Scheme 1).




**Scheme 1.** One-pot preparation of 3-nitroformazans from aromatic amines

The resulting 3-nitroformazans were formed as colored microcrystalline solids and removed by simple filtration without further purification.

Following that, obtained potential fluorescent 3-nitroformazans were reacted with $Ni^{2+}$ source with formation of bidentant complex Ni(formazan)$_2$ **4** by previously reported method [9]. Moreover, the obtained formazans were used as substrates for synthesis of corresponding thiocarbazones [3]. Next, thiocarbazones were reacted [10] with $Zn^{2+}$, $Cu^{2+}$ and $Ni^{2+}$ for synthesis of complexes (**5**) (Scheme 2).

The obtained complexes of 3-nitroformazans and thiocarbazones have good fluorescent characteristics, and at this time, we investigate possibility of using their in analytical chemistry.

## PP 43. EFFECT OF ASCORBIC ACID (VITAMIN C) ON THE ESR SPECTRA OF THE RED AND BLACK HAIR

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High incidence of melanoma in the individuals with red hair is due to the syntesis of pheomelanin pigments in the human tissue and its phototoxic properties. Recently, synthesis of pheomelanin has also been monitored in UV-independent pathways of oxidative stress.

Therefore, first of all it is important to evaluate melanoma risk in different individuals, which can be accomplished by analyzing ESR spectras of their hairs, but at the same time to find an effective antioxidant, capable to minimize damage of pheumelanin.

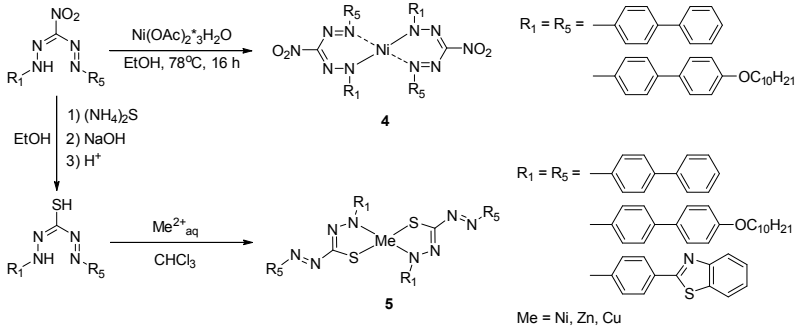
In our laboratory works we have shown, that ascorbic acid (Vitamin C) is an effective antioxidant for neutralization of pheumelanin free radicals. During our research work we have defined presumable optimal concentration of ascorbic acid, which neutralizes free radicals in the human hair very effectively – 10mmole.

It is also important to mention, that ascorbic acid has an influence not only on the free radicals of pheumelanin, but also on the free radicals of eumelanin. Although the optimal dose concentration for both is the same.

Chemical mechanism of influence of ascorbic acid on free radicals of eumelanin and pheumelanin is also shown.

According to changes of ESR signal we have considered, that ascorbic acid doublet (in terms of 0.188 mtesla hyperfine coupling g=2.0037) is overlapped with spectras of red and black hair.

Finally, it can be said, that presumable optimal dose of ascorbic acid, to be used in the creams for skin protection, as well as for prevention of different skin disorders, including melanoma, has been defined in vitro.




**Scheme 2.** Preparation of formazans and thiocarbazones metal complex

Analytical band of luminescence spectra of formazans and thiocarbazones complexes with various metals tend to overlap lesser than in the UV-vis spectra. This property will allow analyzing metals or their compounds in the mixture.

Unfortunately, formazans complex formed over time, which limits their using for express determination of metal traces. But it should be noted, that complexes **4** and **5** have potential electroluminescent activity and they can be used for electrochemical studies.

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## PP 44. 2-(PYRIDIN-2-YL)-1,3-BENZOTHIAZOLES: ALTERNATIVE SYNTHETIC APPROACHES AND STUDY OF COMPLEXATION REACTIONS

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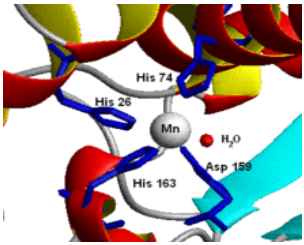
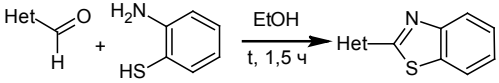
It is known that the interaction of the bidentate organic N,N-ligand 2-(pyridin-2-yl)-1,3-benzothiazole with hexahydrate perchlorate copper leads to the formation of a coordination compound with the square-pyramidal geometry of the coordination environment of copper, which is a low molecular weight analogue of the natural metalloenzymes superoxide dismutase (SOD).




Previously, we have studied the reaction of a series of heteroaromatic aldehydes with 2-aminothiophenol, giving products as the corresponding 2-hetaryl-benzothiazoles. The resulting 2-hetarilbenzothiazoles were studied in complex formation reactions perchlorate copper (II) and cobalt (II). According to X-ray data obtained coordination compounds have similar geometry to the geometry of the active site of SOD. However, the resulting complex compounds had a very low solubility in water.

To obtain low molecular weight analogues of SOD, has good solubility in water, benzothiazole ring must enter various hydrophilic substituents. For this purpose, an example of a 6-methoxy-2-pyridin-2-yl-1.3-benzothiazole we have developed two approaches.

Products of steps obtained in high yields, the composition and structure of the obtained compounds were confirmed by NMR and IR spectroscopy, and elemental analysis.

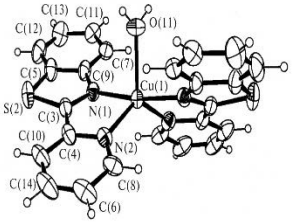


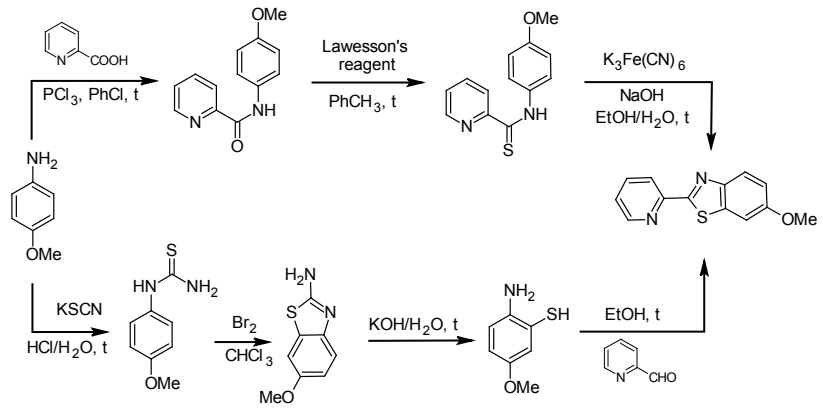

1, Het = 93%

3, Het = 47%

2, Het = 52%

4, Het = 39%




**Acknowledgment**.
This work was supported by RFBR (grant №13-03-00399-a).

## PP 45. NEW DERIVATIVES OF INDOCYANINE DYES AND USING THEREOF AS FLUORESCENT LABELS

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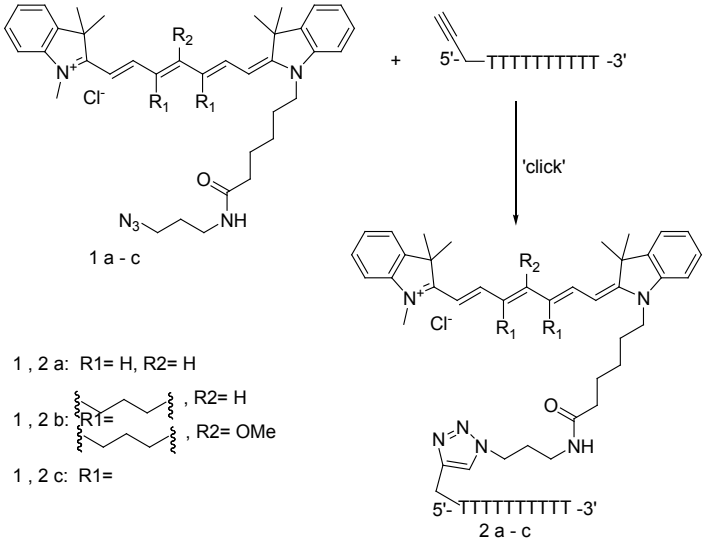
Polymethine cyanine dyes are widely used as fluorescent tags in genetic analysis, DNA sequencing, in vivo imaging, and proteomics. The advantages of polymethine dyes in bioanalytical methods include their strong spectral properties in the longer wavelength region (700 - 900 nm) with minimal background from biomolecules [1].

However, poor chemical stability of those dyes restrains their use as fluorescent markers in site-specific biolabeling strategies, especially those requiring additional purification steps by RP-HPLC. To overcome this limitation, numerous studies have been performed, to reveal that incorporating a rigid cycloalkyl ring into the polymethine chain increases stability of the resulting analogues [2] and improves the quantum yields of their conjugates with DNA.



In the present paper, we report the synthesis of three heptamethine azide derivatives 1a-c with flexible (1a) and rigid cyclohexenyl fragment (1b and 1c). These three dyes were used for [3+2]-cycloaddition to the synthetic alkyne-modified oligonucleotide 5'-(Alkyne)-TTTTTTTTTT-3'. The resulting DNA conjugates 2a-c were purified with RP HPLC and their spectral properties were studied.

Absorption and emission maxima of conjugates 2a-c depend on the dye structure and correlate with the strength of electron donor groups of the substituents. The basic conjugate 2a has abs/em maxima 750/777 nm. Rigid cyclohexenyl fragment in 2b shifts maxima to 756/780 nm, and additional MeO-group in 2c results in 763/784 nm. The influence of the rigid cyclohexenyl fragment in 2b,c on the spectral properties was also studied. Quantum yield of conjugates 2b,c is about 20% higher compared with basic conjugate 2a.

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## PP 46. 1,4-ADDITION REACTIONS TO 3-SUBSTITUTED COUMARINS

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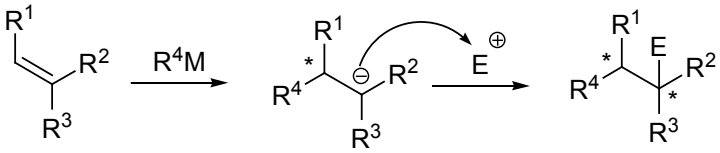
One of the most effective methods for C-C single bond formation is the 1,4-conjugated addition or also known as Michael reaction. This method is widely used in organic synthesis because of the vast variety of Michael's acceptors and organometallic compounds. By using this reaction it is possible to form multiple stereocenters in a single synthetic procedure.

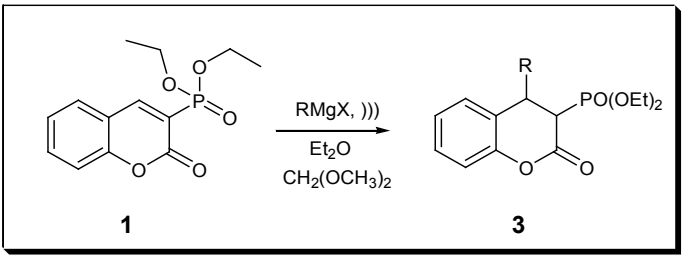
The Michael addition involves the addition of a nucleophile, also called a "Michael donor", to an activated electrophilic olefin, the 'Michael acceptor', resulting in a 'Michael adduct',[1] as shown in Fig. 1.




$R^3$ = COR, COOR, $CONR_3$, $NO_2$ ,$PO(OR)_2$
$R^4$ = alkyl, aryl, alkenyl, alkynyl

**Figure 1.**

Although, the Michael addition is generally considered the addition of enolate nucleophiles to activated olefins, a wide range of functional groups possess sufficient nucleophilicity to perform as Michael donors. Reactions involving non-enolate nucleophiles such as amines, thiols, and phosphines are typically referred to as 'Michael-type additions'. The Michael acceptor possesses an electron withdrawing and resonance stabilizing activating group, which stabilizes the anionic intermediate [1].




**Scheme 1.**

In our previous studies on the chemical behavior of substituted in third position 2-oxo-2H-1-benzopyrans (coumarins) against nucleophile reagents, we observed that these compounds are good acceptors in 1,4-conjugate addition reactions (for example reactions with – phosphites, azo compounds etc.).

Here in we present our study on the chemical behavior of 3-etoxycarbonyl and 3-phosphonocoumarin with series of preformed organomagnesium compounds. Grignard, Reformatsky and Ivanov's reagents were used as nucleophiles too.

The group noticed that when ultrasound is used the desired products are isolated with better yields for shorter reaction time and this method has better reproducibility then the typical condition for the Michael reaction. *Syn*-addition to the C3-C4 bond of the 2-oxopyran ring is observed which leads to *anti*-disposal of the incorporated group and the substituent in third position.

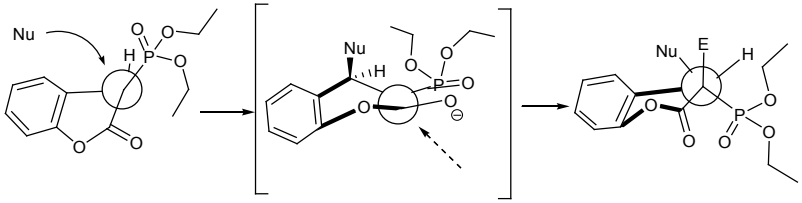



**Figure 2**.

The proposed mechanism of the reaction is confirmed by the NMR-spectra data of the products. The observed values for spin-spin interaction between

protons H3-H4 range from 0.3 to 1Hz and by using Carlplus equation we can assume that the angle between those protons is near 90$^{o}$.

**Acknowledgment.** This work was supported by the European Social Fund and Republic of Bulgaria, Operational Programme “Human Resources Development”, 2007-2013 framework, Grant № БG051PO001-3.3.06-0027 from July 2013.

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## PP 47. SYNTHES AZODERIVATIVES OF 4-AMINOANTYIPIRINA AND INVESTIIGATION OF COMPLEXFORMATION WITH NICKEL(II)

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β-diketones and their derivatives are widely applied for photometric and extraction-photometric determination of metals. Therefore, the synthesis of new organic reagents on the basis of 4- aminoantyipirina- 1-phenyl-2,3-dimetyilpirazalone-5-azo-4-pirohallol. The reagent has been synthesized by a known method.The composition and structure of this reagent installed by elemental analysis, IR and NMR spectroscopy.Spectroscopically determined tautomeric forms and study of their analytical capabilities is the analytical task. The reagent is readily soluble in ethanol and acetone. It is established that these reagents form colored compounds with the ions $Ni^{2+}$, $Fe^{3+}$.

The complex formation of nickel(II) with 1-phenyl-2,3-dimetylpirazalone-5-azo-4-pirohallol (R) in the presence of cation surface active substances (CSAS) cetylpyridinium chloride (SPCl), cetylpyridinium bromide (SPBr), cetyltrimethylammonium bromide (SPMABr) has been investigated. It has been studiedthat the R ethanolic solution at pH 6 has a maximum absorption band (λ=580 nm). In these conditions, it forms a complex with nickel(II) (maximum absorption at 510 nm).Study of the complex obtained in the presence of KSAS in a wide pH range revealed that under the influence of the KSAS complexes formed triple complex Ni(II)-R-SPCl, Ni(II)-R-SPBr, Ni(II)-R-SPMABr light absorption maximum 537 nm 541 nm and 563 nm, respectively.optimum conditions of complexformation medium of the given complexes.

It has been learndthe dependence of the optical density from the pH of the solution showed that the optimal complexformation conditions in the presence of CSAS shifts to the acidic medium of pH 3, 4, 5 respectively.

Yield of the complex Ni(II)-R is maximal at a concentration of $8\cdot10^{-3}$ M R, Ni(II)-R- SPCl while $8\cdot10^{-5}$ MR and$10^{-4}$ M SPCl, Ni(II)-R-SPBr while $8\cdot10^{-5}$ M R and $4{,}6\cdot10^{-4}$SPBr, Ni(II)-R-SPMABr $8\cdot10^{-5}$ M R and $4{,}8\cdot10^{-4}$ M SPMABr. Different physico-chemical methods established for identification the ratio

of the components in the complexes that are formed. The ratio of components ofbinary system is as 1:2 (Ni(II)-R) and the ratio of components of triple complexes is as 1:2:2 (N(II)-R-КПАВ) (table).

The effect of interfering ions and masking agents has been learned. The determination of nickel(II) is not interfered by alkali metals and ions of Ca(II), Ba(II), Mn(II), Cr(III), Sn(IV), Ga(III), In(III), Zr(IV) is not interfere. These methods is highly sensitive and selective. It is a very rapid and a simple technique.

**Table.** Main characteristics of the nickel(II) complexes

| Complexes | pH opt | $\lambda_{max}$, nm | ε | M: R | Liney.grad interval. schedule, ug/ml |
|---|---|---|---|---|---|
| Ni-R | 6 | 510 | 10000 | 1:2 | 0.12-2.32 |
| Ni(II)R-SPCl | 3 | 537 | 18600 | 1:2:2 | 0.07-2.32 |
| Ni(II)R-SPBr | 4 | 541 | 17250 | 1:2:2 | 0.07-2.32 |
| Ni(II)R-SPMABr | 5 | 563 | 15000 | 1:2:2 | 0.12-2.32 |

## PP 48. DEVELOPMENT OF PHOTOCATALYTIC $TiO_2$ NANOFIBERS BY ELECTROSPINNING AND ITS APPLICATION TO DEGRADATION OF ANILINE IN AQUEOUS SOLUTION

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Aniline is a priority pollutant, that is known as a toxic organic pollutants released as effluents from several industries. Several physicochemical methods have been used for degradation of this pollutant. In this study, $TiO_2$ nanofibers for the treatment of aniline from synthetic wastewater by using electrospinning method was considered. The $TiO_2$ nanofibers was characterized utilizing FT-IR and X-ray diffraction measurements. The effects of different variables, such as irradiation time, the amount of photocatalyst, initial pH values and initial concentration of pollutant on the photodegradation of aniline were investigated to find the optimum condition. A laboratory-scale batch photocatalytic reactor with a low pressure UV lamp in the center of it was used. Results showed that the photocatalytic system was highly efficient for degrading anilinein reasonable time. The maximum degradation efficiency of aniline was 99.9% in 0.5 g/L of $TiO_2$ nanofibers and alkaline pH. The experimental adsorption isotherm of aniline, complied with Langmuir type, From the results of various kinetic models, pseudo-second-order fit well with the aniline sorption kinetics conducted at different initial aniline concentrations. As a conclusion, The photocatalytic process by using $TiO_2$ nanofibers has great potential for aniline degradation in wastewaters.

## PP 49. REGIOSELECTIVE SYNTHESIS OF BROMOINDOLES

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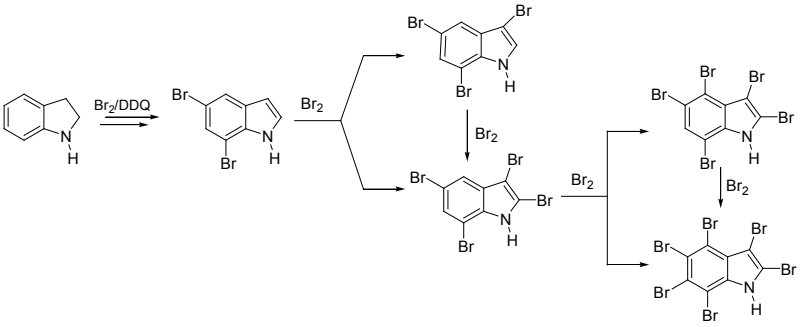
Indole and indole derivatives are an important class of compounds of particular interest due to biologically activities [1]. Many brominated indole derivatives have been isolated from marine sources and shown to exhibit interesting biological activities as antifungal and antibacterial. In addition to this, synthesis of bromoindoles has received considerable attention because of regioselectivity [2]. In this work, we interested in bromination of indole nucleus. We report a simple and regioselective route for preparation of bromoindoles [3].




This study is supported by TUBITAK (Project No:112T403 ).

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## PP 50. INVESTIGATION OF CONSTITUENT PARAFFINS IN PRECIPITATED RESIDUAL IN OIL PIPES

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Residual petroleum in pipes is peculiar type of product, which mainly consists of paraffins and ceresin. In the world, the production of cerein consists of several thousand tons, which, considering increased demand, is not enough. Practical usage of residual petroleum is also highly relevant, as it will lead to the manufacture of different compositions of small tonnage scarce, expensive products paraffins (m.p. 50-65 °C, carbon number $C_{25}$-$C_{35}$) and ceresin (m.p. 65-90 °C, carbon number $C_{36}$-$C_{53}$). This is also significant in terms of ecological standpoint, because in case it is burned, pollution of the atmosphere will be evaded.

It was affirmed by scientific calculations that the usage of residual petroleum is cost effective, only when the componential composition of the residue has more than 30% of petroleum in it. In our case, residue is completely presented in terms of its components.

Previously, we conducted fractional investigation [1,2] of diesel in Samgori high paraffin petroleum, for its use as diesel in engines, and for the use of extracted paraffins as washing utensils after they are oxidized to fatty acids.

High content of paraffins in residual petroleum, which is approximately 60 percent, is interesting.

The especially interesting fraction is 180°-350°C, which contains small amounts of sulfur. Another thing to consider, is the possibility of obtaining winter diesel component with high cetane number and appropriate melting point [1,3], by deparaffinization of this fraction.

Low cost of this product is notable, which is derived from the price of raw material, which by itself is residual petroleum. This is also significant in terms of ecological value, since this residue will not be used as boiler fuel.

In the report, some aspects of method worked out by us, for recycling residual petroleum, is described.

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## PP 51. SYNTHESIS OF 5-TRIAZINYL-SULFANYLALKYL-3*H*-[1,3,4]-OXADIAZOL-2-THIONE DERIVATIVES

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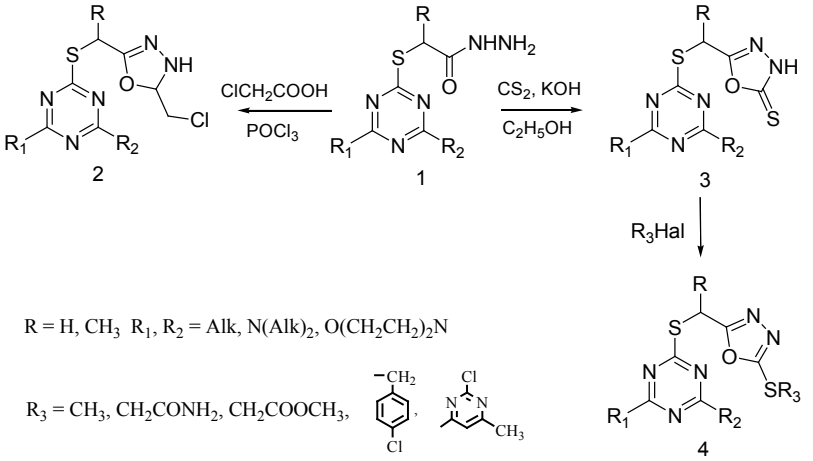
The pesticides, synthesized on the base of 1,3,5-triazine, have been known for several decades. In agriculture the most widely used are the herbicides of chlorotriazine, fluoroalkyltriazine, methoxytriazine, methylthiotriazine and triazinone derivatives [1]. In the late 80s a new effective and low-toxic herbicides of triazinylsulfonylurea series was discovered [1]. Five-membered heterocyclic derivatives (oxadiazole, thiadiazole, etc) are more active in relation to plants than insects and mites, so they are mainly used as herbicides, fungicides and plant growth regulators. Arsenal of crop protection chemicals used in agriculture on the basis of [1,3,4]-oxadiazole is quite limited. Among them can be identified selective herbicide (3,4-dichlorophenyl)-4-methyl-[1,2,4]-oxazolidin-2,5-dione (methazole-2) herbicides dimefuron, oxadiargyl, oxadiazon and insecticide metoxadiazone [1]. However, considerable interest have virtually unexplored heterocyclic systems with combination of [1,3,4]oxadiazole and [1,3,5]triazine rings in the same molecules, against which the harmful pests and diseases had not yet acquired any resistance. Therefore, the aim of the present study was the synthesis of new derivatives of heterocyclic systems containing in the molecule both of two mentioned heterocycles and their biological evaluation.

By interaction of of 4,6-disubstituted 2-thio-acetohydrazides or propanehydrazides (**1**) with chloro-acetic acid in $POCl_3$ the corresponding 5-(chloromethyl)-4,5-dihydro-[1,3,4]-oxadiazol-2-yl-methylthio derivatives (**2**) were obtained. The reaction of the same starting compound with carbon disulfide in an alkali alcoholic solution and further alkylation leads to [1,3,4]-oxadiazole-2(3H)-thiones (**3**) and their S-alkylated products (**4**), respectively.




At preliminary laboratory and vegetative tests the obtained compounds showed the expressed stimulating action on plants growth. The greatest activity was 98% in comparison with widely used heteroauxin. Data of biological screening testify that synthesized hitherto unexplored heterocyclic systems can be of interest for search of new growth stimulators.

## PP 52. STUDY ON ELECTROPHILE-MEDIATED CYCLIZATION OF PROPARGYLIC AMIDES

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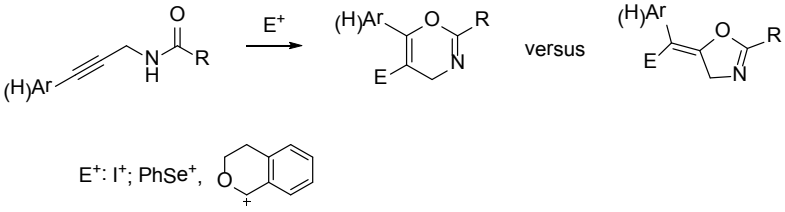
1,3-Oxazine, oxazoline and oxazole rings bearing substrates are important classes of heterocyclic compounds in material and medicinal chemistry due to their diverse physical and biological properties [1]. It is known that these heterocyclic rings can be formed during cyclizations of propargylic amides. Usually 5-*exo*-dig or 6-*endo*-dig cyclizations of propargylic amides are induced by strong bases or catalyzed by palladium, copper, silver and gold salts [2].

In the present investigation, we report on catalyst-free electrophile-mediated cyclizations of propargylic amides for the synthesis of functionalized oxazine and oxazoline derivatives.




In this study, we tested the reactivity of propargylic amides with some electrophilic reagents. The mechanistic aspects of the reactions together with scope and limitations will be discussed.

**Acknowledgments**. The research was funded by the European Social Fund under the Global Grant measure *(Grant Nr. VP-3.1-SMM-07-K-01-002)*

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## PP 53. SYNTHESIS OF SOME CYCLOSUBSTITUTED THIOPHENE CONTAINING ETHYLAMINES, ALCOHOLS AND BIHETEROCYCLES

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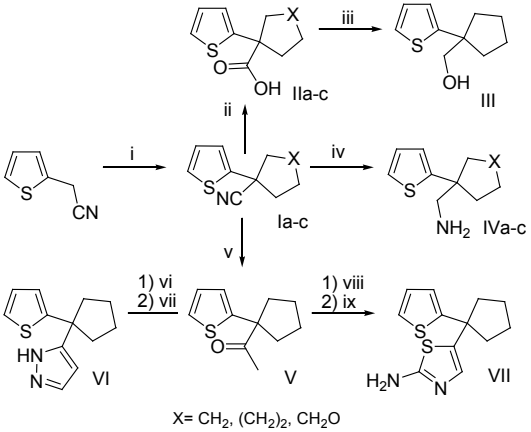
Thiophenes are not common in nature - their derivatives with a side chain were isolated from fungus *Daedelia junperina* and roots of *Echinops spaerocephalus.* Some of their derivatives are featured in literature sources as biologically active compounds and drugs. Thiophene is a moiety of such modern drugs, as ticlopidine, clopidogrel and tinopidine. Functionalized thiophene derivatives exhibit diverse biological activities and can be used in therapy as anti-bacterial agents, for treatment of hyperproliferative disorders [1a], as allosteric enhancers of agonist activity at adenosine $A_1$ receptors [1b], in the treatment of diseases associated with inappropriate angiogenesis and hPPAR mediated disease or condition [1c]. Possibilities of thiophene derivatives as competitive inhibitors of protein tyrosine phosphatase 1B inhibitors and up regulating HLA-DM activity [1d] were evaluated as well.

We have previously shown, that aromatic systems containing α,α-disubstituted cycles in the side chain, exhibit diverse biological activities [2] and investigations in this area are promising. Also according to some preliminary results, some of the derivatives of the mentioned compounds possess good proteasome inhibiting activities.

Started from 2-thiopheneacetonitrile interaction with dihalides: 1,4-dibromobutan, 1,5-dibromopentane or 2-chloroethyl ether, we obtained corresponding cyclopentane, cyclohexane and tetrahydropyran derivatives I(a-c) [3] which were the initial compounds for the preparation of various ethylthiophene derivatives, containing open functionalities such as amino, hydroxy groups. By the basic hydrolysis of the initial compounds, corresponding acids III (a-c) were obtained with yields of up to 75%. The reduction of carboxyl group in IIa was carried out with 80% yield resulting in the alcohol III, which is also interesting as a building-block agent.

The desired amines IV (a-c) were obtained by the reduction of the nitrile group in compounds I (a-c).




***Scheme 1.*** Synthesis of new derivatives of thiophene. Reagents and conditions: *(i)* NaOH, dihalide (1,4-dibromobutan; 1,5-dibromopentan or 2-chloroethyl ether), 50°C, 50-60% yield; *(ii)* KOH, ethylene glycol, reflux 12h, 68-74% yield; *(iii)* benzene, $LiAlH_4$/DEE, reflux 5h., 81% yield, *(iv)* $LiAlH_4$, DEE, reflux, 70-71% yield, (v) MeMgX, $C_6H_6$, reflux, (vi) DMF/DMA, Xy, reflux, (vii) $NH_2NH_2 \cdot H_2O$, reflux, 20-30 min, (viii) $Br_2$, $CHCl_3$, 30-32 °C, (ix) thiourea, EtOH, reflux, 6 h.

The interaction of nitrile with Grignard reagent in benzene leads to obtaining of corresponding acetyl compound V, which represents interest by itself as a building block for construction of various heterocyclic systems, as well as introduction of different functionalities. As an example, the obtaining of pyrazole and aminothiazole rings were performed by the appropriate procedures.

**Acknowledgmnents.** This work was supported by State Committee Science MES RA, in frame of the research project No SCS 13-1D330.

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## PP 54. SPECTROSCOPIC (FT-IR, FT-RAMAN, $^{1}H$ AND $^{13}C$ NMR), THEORETICAL AND MICROBIOLOGICAL STUDY OF *TRANS o*-COUMARIC ACID AND ALKALI METAL *o*-COUMARATES

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The aim of this work is research continuate of a correlation between the molecular structure and electronic charge distribution of phenolic compounds and their biological activity [1-4]. In this paper we investigated molecular structure and the electronic charge distribution of derivatives of cinnamic acids and their metal salts.

The influence of lithium, sodium, potassium, rubidium and cesium cations on the electronic system of *trans o*-coumaric (2-hydroxycinnamic) acid was studied. We investigated relationship between molecular structure of the tested compounds and antimicrobial activity. For research we used complementary molecular spectroscopic techniques such as infrared (FT-IR), Raman (FT-Raman) and nuclear magnetic resonance ($^{1}H$ and $^{13}C$ NMR).

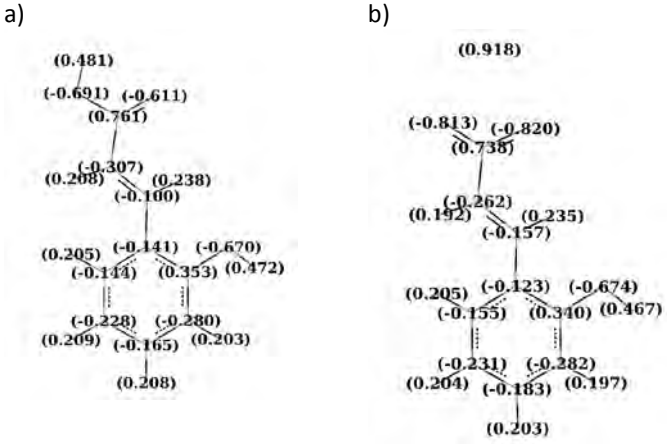


**Fig. 1.** Electronic charge distribution (NBO method) calculated for molecules of *trans o*-coumaric acid (a) and its sodium salt (b).

Structure of the molecules were optimized and the structural characteristics were calculated by density functional theory (DFT) using B3LYP method with 6-311++G(d, p) as basis set. Geometric and magnetic aromaticity indices, atomic charges, dipole moments and energies were also calculated. Theoretical parameters were compared to the experimental characteristics of investigated compounds. Correlations between some bands and some metal parameters, such as electronegativity, ionization energy, atomic and ionic radius, have been noticed. The microbial activity of studied compounds was tested against *Escherichia coli*, *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus, Proteus vulgaris* and *Candida albicans*.

**Acknowledgment**

This work was supported by Bialystok University of Technology (theme No S/WBiIŚ/1/2012)

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## PP 55. SPECTROSCOPIC (IR, RAMAN, UV-NIR) AND SPECTROFLUORIMETRIC STUDY OF LANTHANIDE PICOLINATES AND ISONICOTINATES

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In the previous papers, we investigated influence of metals on the electronic system of biological important ligands, such as benzoic, salicylic and nicotinic acid [1-3]. The aim of this paper is:

- Spectroscopic study (absorption, emission, transition energy scheme) of light lanthanide picolinates and isonicotinates,
- Examining the influence of lanthanides on the electron system of picolinic and isonicotinic acid
- Comparing the influence of different metals on the range of disturbution or the stabilization of the electron system of picolinic, isonicotinic and benzoic acids.

In this study we applied following methods: IR, Raman, UV-NIR, spectrofluorimetric and theoretical calculated (DFT). The obtained results were compared with results previously published studies on the influence of alkali metal, alkaline earth metal, 3d-transitional metal on the electron system of pyridinecarboxylic and benzoic acid. Discussion the effect of metals on electronic system of pyridinecarboxylic acid depending on position of nitrogen in aromatic ring.

### Acknowledgment

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## PP 56. 5-CAFFEOYLQUINIC ACID (CHLOROGENIC ACID, 5-CQA): FT-IR, FT-RAMAN, 1H, 13C AND 2D NMR, UV/VIS, THEORETICAL (AT B3LYP/6-311++G** LEVEL) AS WELL AS ANTIMICROBIAL AND ANTICANCER STUDIES

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Chlorogenic acids (CGA) are a family of esters formed between mono- and di-acyl quinic acids (QA) and cinnamic acid derivatives such as caffeic, ferulic or *p*-coumaric acids. Thirty different types of CGA have been recognized in green coffee beans. The vast majority of these compounds belong to three classes: caffeoylquinic acids (CQA), di-caffeoylquinic acids (diCQA) and feruloylquinic acids (FQA). Among the caffeoylquinic acids three isomers may be distinguished: 5-*O*-caffeoylquinic acid (chlorogenic acid), 3-*O*-caffeoylquinic acid (noechlorogenic acid) and 4-*O*-caffeoylquinic acid (cryptochlorogenic acid). 5-CQA is the major CGA presents in brewed coffee and many fruits (e.g. apples, artichokes, prunes, hawthorn). 5-CQA is a scavenger for reactive species of oxygen and nitrogen [1]. Cytotoxic activity of chlorogenic acid against human oral squamous cell carcinoma (HSC-2) and salivary gland tumor (HSG) cell lines was studied and it was revealed that 5-CQA induced apoptotic cell death characterized by DNA fragmentation and activation of caspase activity [2]. 5-CQA lowered triglyceride and cholesterol concentrations, significantly inhibited fatty acid synthase and exhibited a potential anti-obesity effect in high-fat diet-induced mice [3]. 5-CQA regulates glucose and lipid metabolism via the activation of AMP-dependent kinase (AMPK). This suggest that 5-CQA may contribute to mitigating type 2 diabetes [4]. In this work spectroscopic: FT-IR, FT-IR, FT-Raman, $^{1}$H (400.15 MHz), $^{13}$C (100.63 MHz) and 2D (COSY, HSQC, HMBC) NMR and theoretical (in B3LYP/6-311++G** level) study of 5-*O*-caffeoylquinic acid was done. Moreover antimicrobial activity of 5-CQA toward *Escherichia coli, Staphylococcus aureus, Enterococcus faecium, Proteus vulgaris, Pseudomonas aeruginosa, Klebsiella pneumoniae, Candida albicans* and *Saccharomyces*

*cerevisiae* as well as anticancer properties of 5-CQA against SK-MEL-5, MCF-7, HeLa, PC-3 and U-87 cell lines were established.

## Acknowledgement

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## PP 57. AQUEOUS MEDIATED [3+2]-CYCLOADDITION OF NITRILES WITH SODIUM AZIDE USING CYANURIC CHLORIDE: A HIGHLY EFFICIENT PROTOCOL FOR SYNTHESIS OF 5-SUBSTITUTED 1*H*-TETRAZOLES

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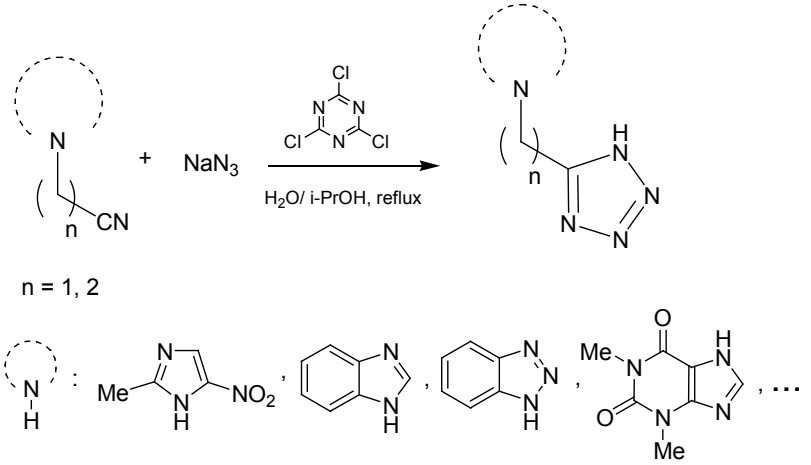
Tetrazole cores represent an important class of heterocycles which exhibit a wide range of applications as organocatalysis and transition metal catalysis, propellants, explosives, and perhaps most commonly, as bioisosteres for carboxylic acids [1,2]. Tetrazole derivatives display diverse pharmacological activities such as anti-inflammatory, anticonvulsant, anti-allergic, antibacterial, and antifungal properties [3]. In particular, well established drugs including losartan, candesartan, zolarsartan, and valsartan have 5-substituted tetrazole cores in their structures [3]. The most common rout to access 5-substituted 1*H*-tetrazoles is [3+2]-cycloaddition of hydrazoic acid and/or trimethyl silyl azide with nitriles [4]. However, these azide ion precursors are highly toxic, volatile and explosive which limit the applicability of these methods especially in large scale synthesis. Recently, Sharpless and coworkers reported that $ZnBr_2$ can catalyze the cycloaddition of nitriles with sodium azide to afford 5-substituted 1*H*-tetrazoles; however, this method suffers from an inconvenience drawback which is formation of zinc-tetrazole complex [5]. Since a few protocols for efficient synthesis of 5-substituted 1*H*-tetrazoles have been established so far; therefore, there is still a necessity to extend and improve the convenient and efficient methods for easy and confident access to 5-substituted 1*H*-tetrazoles.

Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) is a stable, nonvolatile, inexpensive, and safe reagent which has been extensively used in various organic transformations [6]. Recently, we have reported the application of cyanuric chloride as a useful and efficient reagent for several important organic transformations [7-9]. Herein, we report the application of cyanuric chloride as a highly efficient catalyst for [3+2]-cycloaddition of nitriles with sodium azide in refluxing $H_2O$/*i*-PrOH to afford the novel 5-substituted 1*H*-tetrazoles with potential biological activities (Scheme 1).




**Scheme 1.** Synthesis of 5-substituted 1*H*-tetrazoles using cyanuric chloride

To established the optimize condition, firstly we chose the [3+2]-cycloaddition of 2-(1*H*-benzo[d]imidazol-1-yl) acetonitrile with sodium azide in the presence of cyanuric chloride to afford 1-((1*H*-tetrazol-5-yl)methyl)-1*H*-benzo[d]imidazole. The effect of various solvents and temperatures was studied on the cycloaddition of model substrates. According to the obtained results, the sample reaction was efficiently achieved in a solution mixture of $H_2O$/*i*-PrOH (1:1, V/V) at reflux condition. Beside cyanuric chloride, the influences of many Brønsted and Lewis acids were tested on sample reaction and it was proved that the catalytic performance of cyanuric chloride is superior to other tested acids. The generality and applicability of the present protocol were confirmed by its application to a wide range of structurally diverse nitriles. The several representative structures of synthesized 5-substituted 1*H*-tetrazoles are shown in Figure 1. The results have demonstrated that cyanuric chloride is a suitable and highly efficient organocatalyst for [3+2]-cycloaddion between various nitriles and sodium azide affording the corresponding 5-substituted 1*H*-tetrazoles in good to excellent yields. As it is indicated in Figure 1, nitriles bearing various *N*-heterocycles with different functional groups can tolerate the reaction condition. In this research, the N-heterocyclic scaffolds as significant pharmacophoric residue found in the structure of many important drugs

have been designated. The biological studies of synthesized compounds are currently under investigation and will be reported due course.

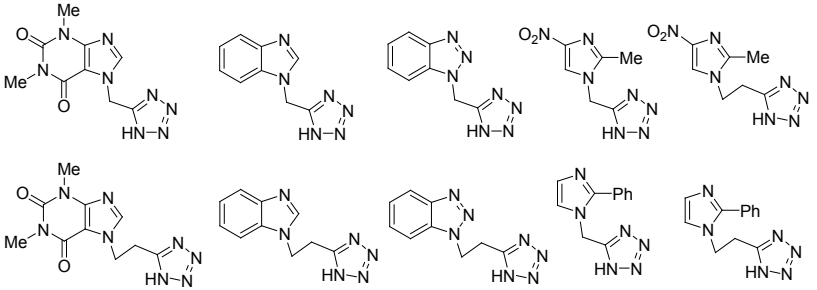


**Figure 1.** Representative structures of synthesized 5-substituted 1*H*-tetrazoles

In summary, a novel and highly efficient protocol has been established for [3+2]-cycloaddion between various nitriles and sodium azide. Using this method, various structurally diverse nitriles underwent the reaction with sodium azide in the presence of cyanuric chloride to afford the corresponding 5-substituted 1H-tetrazoles in good to excellent yields.

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## PP 58. TETRABUTYLAMMONIUM SILICA SULFATE AS A NOVEL AND EFFICIENT NEUTRAL CATALYST FOR THE CHEMOSELECTIVE RING OPENING OF EPOXIDES WITH CARBOXYLIC ACIDS

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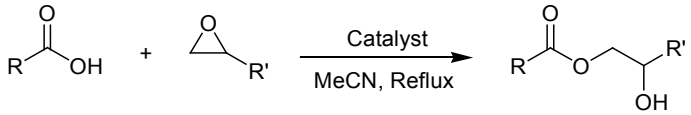
Epoxides are well-known and fully established carbon electrophiles capable of reacting with various nucleophiles. Their ability to undergo regioselective ring opening reactions contributes largely to their synthetic value [1]. Among various nucleophiles, the reaction of carboxylic acids with epoxides has attracted particular attention from a practical standpoint. This reaction is a model for the study of the metabolism of oxirane compounds in living organisms [2], and is of great economic importance in the coating and polymer industry [3]. Additionally, the ring opening of epoxides with carboxylic acids provides a suitable and attractive strategy for the protection of 1,2-diols, which in turn leads to the formation of 1,2-diol mono-esters as precursors for many organic syntheses [4].

The reactions of epoxides with carboxylic acids are generally carried out using various reagents and conditions, especially by the use of protic/Lewis acids and bases [5]. Previously, we have reported the use of tetrabutylammonium bromide (TBAB) [5] and [bmim]Br [6] as promoters for the selective ring opening of epoxides with structurally diverse carboxylic acids to afford the corresponding 1,2-diol mono-esters in neutral condition. In this context, we now report a simple and highly efficient protocol for the regio- and chemoselective synthesis of 1,2-diol mono-esters via ring opening of epoxides with structurally diverse carboxylic acids using tetrabutylammonium silica sulfate as a novel and highly efficient catalyst in neutral condition (Scheme 1).




R= aryl, alkenyl, alkyl, ... R'= alkyl, aryl, alkyloxy, aryloxy,...
Catalyst: Tetrabutylammonium Silica Sulfate

**Scheme 1.** Ring opening of epoxides with carboxylic acids using tetrabutylammonium silica sulfate

To optimize the reaction condition, we selected the ring opening of 2-(phenoxy-methyl)oxirane with benzoic acid in the presence of tetrabutyl-ammonium silica sulfate as a model reaction to afford 2-hydroxy-3-phenoxypropyl benzoate. Initially, we tested the effect of various solvents on the reaction time and yield. Among the examined solvents, anhydrous MeCN was found to be the most appropriate solvent and it was used for all subsequent reactions. We also found that in the absence of catalyst, no reaction was achieved even if the reaction was prolonged for 48 h.

In a series of other experiments, we examined the effect of temperature on the model reaction. The results have demonstrated that the ring opening of 2-(phenoxymethyl)oxirane with benzoic acid were efficiently achieved in refluxing MeCN.

To explore the scope of this method, the optimized reaction conditions were extended to the reaction of a variety of structurally diverse epoxides and carboxylic acids. The several representative structures of synthesized 1,2-diol mono-esters are shown in Figure 1. As shown in Figure 1, this method is highly efficient and suitable for ring opening of various epoxides with different carboxylic acids.

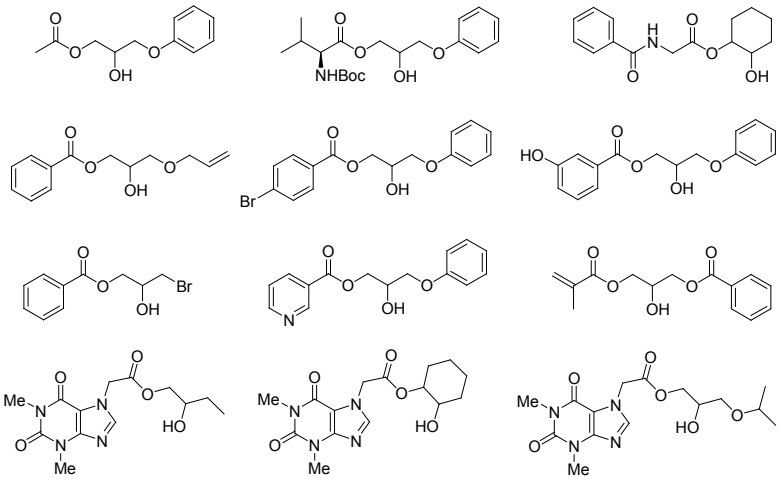



**Figure 1.** Representative structures of synthesized 1,2-diol mono-esters

It is clear that this protocol is highly efficient and useful for aromatic, heteroaromatic, vinylic, and aliphatic carboxylic acids. This method is highly

chemoselective for hydroxy benzoic acid derivatives, as the hydroxyl group does not contribute in ring opening of epoxide. The ring opening of epoxides with *N*-protected amino acids also gave the corresponding products in high yields. Acefylline (acetyloxy theophylline) is a stimulant drug, which acts as cardiotic, diuretic, antispasmodic, and bronchodilator [7]. The application of acefylline in the present protocol was also afforded the corresponding 1,2-diol mono-esters in excellent yields.

In summary, we have developed a simple, highly efficient and mild protocol for chemoselective preparation of 1,2-diol mono-esters. In this method, reaction of structurally diverse epoxides and carboxylic acids in the presence of catalytic ammount of tetrabutylammonium silica sulfate in refluxing anhydrous MeCN affords the corresponding 1,2-diol mono-esters in good to excellent yields and in short reaction times.

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## PP 59. Cu/GRAPHENE/CLAY NANOHYBRIDE: A HIGHLY EFFICIENT HETEROGENEOUS NANO CATALYST FOR HUISGEN'S 1,3-DIPOLAR CYCLOADDITION

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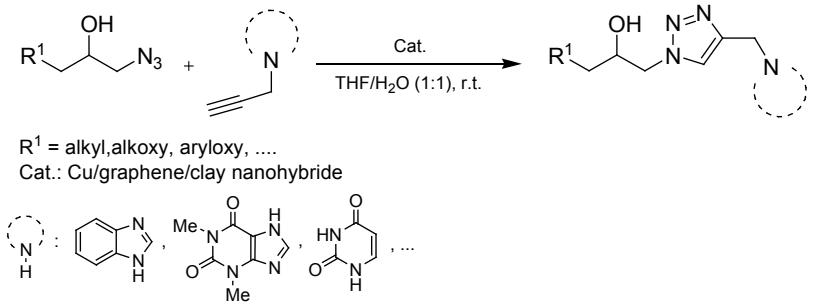
The 1*H*-1,2,3-triazoles [1] are an important class of *N*-heterocyclic compounds with a wide range of applications in organic and medicinal chemistry. Many bioactive compounds with a broad spectrum of activities such as anti-inflammatory, antiviral, anticancer, anti-allergic, anticonvulsant, antibiotic, antibacterial, and antimicrobial activity [2], contain a 1*H*-1,2,3-triazole core in their scaffolds. Additionally, they have found significant industrial applications as dyes, agrochemicals, corrosion inhibitors, photo stabilizers, and photographic materials [3].

The most common route for accessing 1,2,3-triazoles involves Huisgen 1,3-dipolar azide-alkyne cycloaddition [4]. However, the major limitations of this non-catalyzed process are the requirement of high temperature and poor regioselectivity giving a mixture of 1,4- and 1,5-disubstituted triazoles. The synthetic utility of the Huisgen 1,3-dipolar cycloaddition between azides and alkynes was significantly improved since Sharpless [5] and Meldal [6] have found that CuI salts dramatically accelerate the reaction. The Cu(I)-catalyzed Huisgen cycloaddition, has enabled the practical and efficient preparation of 1,4-disubstituted 1*H*-1,2,3-triazoles, with favorable selectivity. Active copper (I) as the catalytic species can be *in situ* prepared by reduction of copper(II) salts, copper(II)/copper(0) comproportionation or oxidation of copper(0). The catalysts might be copper(0) nanosize clusters, or appropriate copper(I) salts with triphenylphosphine, iminopyridine, or mono- or polydentate *N*-ligands. To improve reusability and recovery, copper species have been immobilized onto various supports such as activated carbon, amine-functionalized polymers, zeolites, aluminium oxyhydroxide nanofiber, Wyoming montmorillonite, alumina, silica-supported *N*-heterocyclic carbenes, amine-functionalized silica, and melamine-formaldehyde resin [7]. However, the immobilized catalysts on solid supports frequently suffer from leakage of catalysts, high reaction temperatures, low activity, and requiring additives. In this context, we now

report the application of Cu/graphene/clay nanohybride as a novel and efficient heterogeneous catalyst for synthesis of some novel carboacyclic nucleosides having 1*H*-1,2,3-triazole cores via 1,3-dipolar cycloaddition of β-azido alcohols and alkynes at room temperature (Scheme 1).




**Scheme 1.** Synthesis of 1,4-disubstituted 1,2,3-triazoles using Cu/graphene/clay nanohybride

To obtain the optimized reaction condition, we selected the cycloaddition of *N*-propargyl uracil and 2-azidocyclohexanolas in the presence of Cu/graphene/clay nanohybride as a model reaction to afford the corresponding 1,2,3-triazole derivative. Firstly, we carried out the model reaction in $H_2O$ at different temperatures. The best result was obtained when the cycloaddition reaction was conducted at 100 °C for 1 h. Then, the influence of various 1:1 (v/v) organic solvents/$H_2O$ was examined in the presence of Cu/graphene/clay nanohybride at room temperature. Among the examined solvents, a solution of THF/$H_2O$ (1:1, v/v) afforded the best result. The obtained optimized condition was extended to the reaction of diverse structures of β-azido alcohols with terminal alkynes. The β-azido alcohols used in this research were synthesized via regioselective ring opening reaction of corresponded epoxide via azide while terminal alkynes were attained by means of $SN_2$-type reaction of propargyl halide and corresponded nucleophiles. The *N*-heterocycle residues were chosen to enhance the potential biological activities, i.e., benzimidazole, theophylline, phthalimide, uracil, azauracil, and thymine were used since these *N*-heterocycles are readily interacts with biomolecules [2]. The representative structures of synthesized 1,4-disubstituted 1,2,3-triazoles are shown in Figure 1. As shown in Figure 1, the reaction was achieved regioselectively

using Cu/graphene/clay nanohybride and the 1,4-disubstituted 1,2,3-triazoles were obtained exclusively in good to excellent yields.

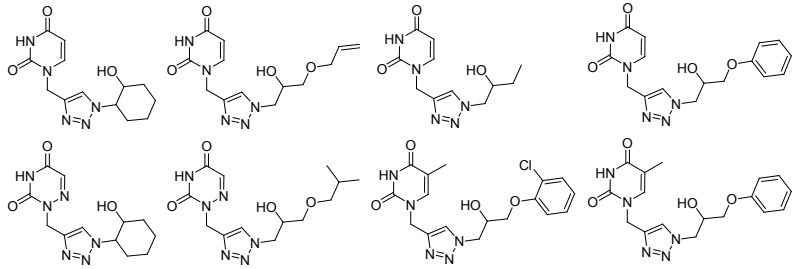


**Figure 1.** Representative structures of synthesized 1,4-disubstituted 1,2,3-triazoles

In summary, we have described a highly efficient and facile protocol for the 1,3-dipolar cycloaddition of different functionalized β-azido alcohols and alkynes in the presence of Cu/graphene/clay nanohybride. Using the present synthetic methodology, structurally diverse 1,4-disubstituted 1,2,3-triazole derivatives were regioselectively obtained in good to excellent yields. Cu/graphene/clay nanohybride demonstrates to be highly efficient, stable and low cost catalyst that can be easily prepared and reused for many times without remarkable decreases in catalytic reactivity.

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## PP 60. SIMPLE AND RAPID SYNTHESIS OF 1-ARYL-4-ACETYL-5-METHYL-1,2,3-TRIAZOLES FROM ARYLAMINES USING CROSS-LINKED POLY (4-VINYLPYRIDINE) SUPPORTED AZIDE ION

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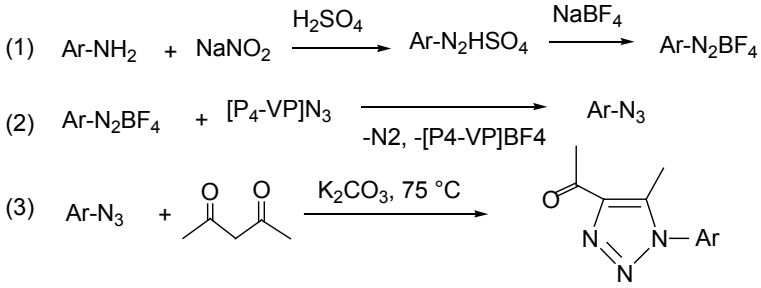
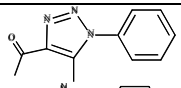
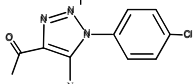
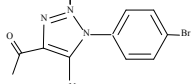
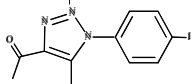
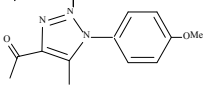
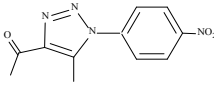
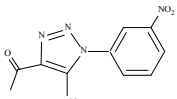
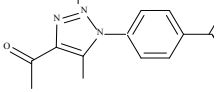
1,2,3-Triazole heterocycles derivatives have received much attention due to their wide coverage of biological properties [1]. Cross-linked poly (N-methyl-4-vinylpyridinium) azide ion was prepared according to our previously reported procedure [2].In continuation of our studies on development of application of polymeric reagents and catalysts in organic transformations [2-5] herein, we wish to report an improved, a less hazardous and practical synthesis of a regioisomers of trisubstituted-1,2,3-triazoles by using cross-linked poly (4-vinylpyridine) supported azide ion, $[P_4\text{-VP}]N_3$. For this purpose, diazonium salts of various aromatic amines were prepared. In the first step, diazotization of aromatic amines was performed by using sodium nitrite and concentrated sulfuric acid. In the second step, the obtained arenediazonium hydrogen sulfates were stabilized by using $NaBF_4$. Then the stable arenediazonium tetrafluoroborates were converted to aryl azides in the presence of $[P_4\text{-VP}]N_3$. Finally, the obtained aryl azides were condensed with acetyl acetone in the presence of $K_2CO_3$ and the corresponding 1-aryl-4-acetyl-5-methyl-1,2,3-triazoles products were obtained in good to high yields (Scheme 1).

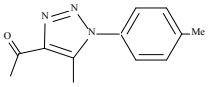
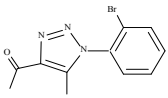



**Scheme 1.** Synthesis of 1-aryl-4-acetyl-5-methyl-1,2,3-triazoles

In order to increase the yield of triazole compounds optimization of the reaction conditions was accomplished. 4-Nitrophenyl diazonium tetrafluoroborate was chosen as a model substrate and was treated with different molar ratio of Ar-$N_2BF_4$/[$P_4$-VP]$N_3$/acetyl acetone in different solvents and at different temperature and we observed that, the 1/2.5/1 molar ratio in ethanol at 75 °C were the best conditions in order to achieve the highest yield of the product. We then applied these conditions for synthesis of different 1-aryl-4-acetyl-5-methyl-1,2,3-triazoles and the results are summarized in Table 2.

**Table 2:** Synthesis of 1-aryl-4-acetyl-5-methyl-1,2,3-triazoles by using [$P_4$-VP]$N_3$/Ar$N_2BF_4$/ acetyl acetone, in the presence of $K_2CO_3$ in ethanol at 75 °C

| # | Amine | Product | Time (min) | Yield (%) [a] | mp (°C) |
|---|---|---|---|---|---|
| 1 | $PhNH_2$ |  | 40 | 82 | 100-101 |
| 2 | 4-$ClC_6H_4NH_2$ |  | 30 | 84 | 112-114 |
| 3 | 4-$BrC_6H_4NH_2$ |  | 30 | 88 | 112-114 |
| 4 | 4-$IC_6H_4NH_2$ |  | 35 | 83 | 141-143 |
| 5 | 4-$MeOC_6H_4NH_2$ |  | 45 | 80 | 119-121 |
| 6 | 4-$O_2NC_6H_4NH_2$ |  | 20 | 90 | 145-146 |
| 7 | 3-$O_2NC_6H_4NH_2$ |  | 25 | 89 | 114-116 |
| 8 | 4-$MeCOC_6H_4NH_2$ |  | 20 | 92 | 122-124 |

| | | | | | |
|---|---|---|---|---|---|
| 9 | 4-$MeC_6H_4NH_2$ |  | 40 | 86 | 110-111 |
| 10 | 2-$BrC_6H_4NH_2$ |  | 35 | 83 | 114-115 |

[a] Isolated yield

In conclusion, this research demonstrates the synthesis of a regioisomer of trisubstituted-1,2,3-triazoles from various aniline derivatives using a polymer-supported azide ion. The advantages of this method over the conventional classical method for the synthesis of trisubstituted-1,2,3-triazoles [58] are; mild reaction conditions, safe handling, and mildness of the polymeric azide ion reagent, higher isolated yield, shorter reaction time, and very simple workup.

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## PP 61. N-LACTOSYLATION OF AMINO BENZOIC ACIDS

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O-, m-, and p-amino benzoic acids carry out important physiological functions. Derivatives of amino benzoic acids which, after penetration into the action area, purposefully decompose with liberation of an active ingredient are successfully applied. [1]. Such derivatives of amino benzoic acids frequently cause specific physiological effects which considerably differ from the physiological effects of initial amino benzoic acids [2], and for this reason, researchers carry out intensive investigations with the purpose of revealing such derivatives. One of the ways of synthesis of such derivatives is N-glycosylation of amino benzoic acids.

One of the prospective ways of preparation of N-glycosides of amino benzoic acids is direct interaction of aldoses and amino benzoic acids. This way of synthesis is intensively investigated, and so has not developed into a preparative method [3]. The basic barrier in the process of this synthesis is the accompanying melanoidin reaction, as a result of which N-glycosides, formed by N-glycosylation of amino benzoic acids, are transformed into a mix of melanoidine products. In this work we investigated the reaction of N-lactosylation of amino benzoic acids.

The reaction between o-, m-, p-amino benzoic acids and D-lactose was carried out in 96% ethanol medium, under the reflux, in the presence of small quantities of water and catalyst (glacial acetic acid). The synthesized N-lactosides were purified by means of recrystallization (ethanol, diethyl ether), and their purity was checked by the method of TLC and paper chromatography. The identification of synthesized N-lactosides was carried out by a method of elementary analysis, by infrared spectra (UR-20, in KBr), $^{13}C$-nuclear magnetic resonance spectra (Bruker NM-250 MGH, standard $(CD_3)_2SO$), and melting points. The results are shown in Table 1.

The data of Table 1 show that from m- and n-isomers of amino benzoic acid the corresponding N-lactosides are formed; however, despite the change of the key parameters of reaction, we did not manage to obtain the desirable N-lactoside from o-amino benzoic acid. It is known that the process of N-glycosylation is significantly influenced is rendered by the basic nature of the

reacting amine, and those factors which define the stability of sugar conformation; the more is basicity of the amine, the more actively it participates in the reaction of N-glycosylation, however subsequent transformations of the formed N-glycosides also proceed actively (Amadori rearrangement, Maillard reaction, deamination-decarboxylation, etc [4]).

**Table 1.** Formation of N-lactosides by reaction of D-lactose with o-, m-, p-amino benzoic acids

| No. | N-Lactosyl amine | Yield, (%) | M. P., °C |
|---|---|---|---|
| I | N-o-Carboxyphenyl-D-lactosyl amine | 0 | — |
| II | N-m-Carboxyphenyl-β-D-lactosyl amine | 30.0 | 138-140 |
| III | N-p-Carboxyphenyl-β-D-lactosyl amine | 50.0 | 105-106 |

By interaction of lactose with p-amino benzoic acid, the carboxylic group - because of its negative inductive and negative mesomeric effects - reduces the density of electron cloud of the nitrogen atom, by reducing its basic nature. In this case, the N-lactoside of p-amino benzoic acid, because of its high stability, is formed with higher yield than the N-lactoside of m-amino benzoic acid. At reaction of the o-amino benzoic acid with D-lactose it is not possible to isolate the desirable product – appropriate lactoside; it is possible to assume that because of spatial effects, reaction between them does not occur. The most specific reaction typical of all oligosaccharides is their hydrolysis with cleavage of glycoside bonds and formation of monosaccharides. The infra-red and $^{13}C$ PMR spectra of synthesized N-lactosides (II, III) show that in these compounds, the $1\rightarrow4$ β-glycoside bond is preserved between A and B carbohydrate rings.

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## PP 62. NOVEL 1,5-DIPHENYL-6-SUBSTITUTED PYRAZOLO [3,4-d] PYRIMIDIN-4-ONES INDUCED APOPTOSIS IN COLON CANCER RKO CELLS VIA TARGETING MITOCHONDRIAL PATHWAY

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Programmed cell death (PCD), or apoptosis, is a physiological process that leads to cellular self-destruction and plays essential roles in maintenance of homeostasis. Apoptosis occurs via one of two main signalling pathways: the extrinsic and intrinsic pathways. The intrinsic pathway is largely centered around and/or regulated by the mitochondria [1–3]. The most widely studied form of intrinsic apoptosis is initiated by the stress-mediated release of cytochrome c from the mitochondria that results in the formation of the apoptosome. The apoptosome then activates initiator caspase, typically caspase 9, which leads to the activation of the executioner caspase 3 and apoptosis can be executed through protease activity targeting substrate proteins [4]. Over the past two decades, considerable attention has been devoted to pyrazolo[3,4-d]pyrimidin-4-one as a prime target for the synthesis of antitumor agents. In this context, several 1-aryl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-ones were reported to possess anti- proliferative activity against human colon tumor cancer cell line HCT116 and other cell lines [5-8]. Encouraged by the above findings, it was attempted to synthesize a new set of pyrazolo[3,4-d]pyrimidin-4-ones comprising to be evaluated for their possible antitcancer activity. In addition to evaluation of anticancer activity of the synthesized compounds, the effect of the most active compound on cell cycle, apoptosis and expression of proteins related to intrinsic cell cycle pathway was also determined.

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## PP 63. SYNTHESIS OF SOME NEW AMIDE-LINKED BIPYRAZOLES AND THEIR EVALUATION AS ANTIINFLAMMATORY, ANALGESIC AND ANTIMICROBIAL AGENTS

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Pyrazoles represent a key structural motif in heterocyclic chemistry and occupy a significant position in medicinal chemistry because of their capability to exhibit a wide range of bioactivities. They were found to exhibit anti-inflammatory [1-3], analgesic activity [4] in addition to cox2 inhibitiory activity [5, 6]. Among the highly marketed COX-2 inhibitors that comprise the pyrazole nucleus, celecoxib was proved to be a potent and GI safe anti-inflammatory and analgesic agent [7]. Moreover, diverse chemotherapeutic activities have been ascribed to pyrazoles such as antiviral [8], antitumor [9,10], antitubercular [11] and antimicrobial against a wide range of bacterial strains including methicillin resistant staphylococcus aureus [12-14]. Moreover, extensive studies have been devoted to N-aryl pyrazole derivatives as dual anti-inflammatory and antimicrobial agents [15-17]. In view of the above-mentioned facts, we report herein the synthesis, anti-inflammatory, analgesic and antimicrobial evaluation of some new amide linked bipyrazoles. The designed compounds comprise the N-phenylpyrazole scaffold linked either to polysubstituted pyrazoles or to antipyrine moiety through different amide linkages. Some of the synthesized compounds showed promising activities.

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## PP 64. NEW DERIVATIVES OF INDOCYANINE DYES AND USING THEREOF AS FLUORESCENT LABELS

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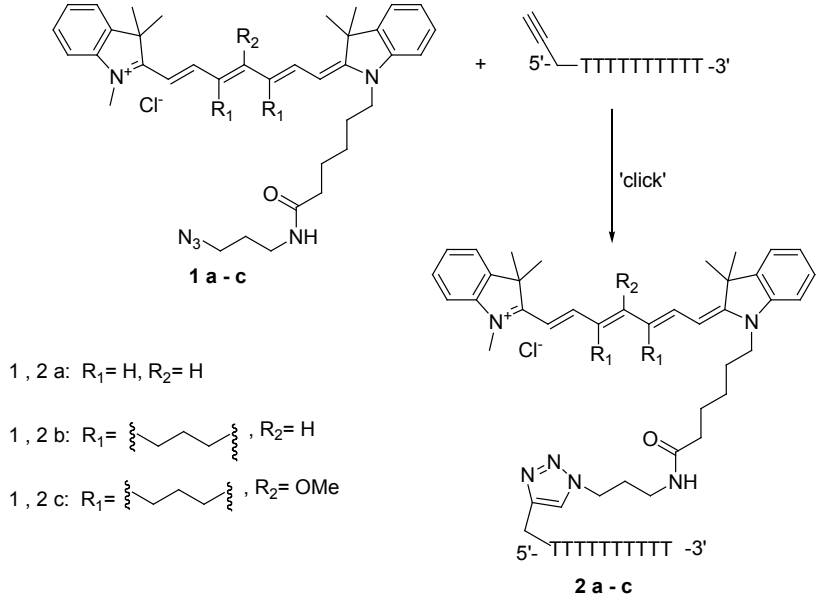
Polymethine cyanine dyes are widely used as fluorescent tags in genetic analysis, DNA sequencing, in vivo imaging, and proteomics. The advantages of polymethine dyes in bioanalytical methods include their strong spectral properties in the longer wavelength region (700-900 nm) with minimal background from biomolecules [1].

However, poor chemical stability of those dyes restrains their use as fluorescent markers in site-specific biolabeling strategies, especially those requiring additional purification steps by RP-HPLC.



To overcome this limitation, numerous studies have been performed, to reveal that incorporating a rigid cycloalkyl ring into the polymethine chain increases stability of the resulting analogues [2] and improves the quantum yields of their conjugates with DNA.
In the present paper, we report the synthesis of three heptamethine azide derivatives 1a-c with flexible (1a) and rigid cyclohexenyl fragment (1b and 1c). These three dyes were used for [3+2]-cycloaddition to the synthetic alkyne-modified oligonucleotide 5'-(Alkyne)-TTTTTTTTTT-3'. The resulting DNA conjugates 2a-c were purified with RP HPLC and their spectral properties were studied.

Absorption and emission maxima of conjugates 2a-c depend on the dye structure and correlate with the strength of electron donor groups of the substituents. The basic conjugate 2a has abs/em maxima 750/777 nm. Rigid cyclohexenyl fragment in 2b shifts maxima to 756/780 nm, and additional MeO-group in 2c results in 763/784 nm. The influence of the rigid cyclohexenyl fragment in 2b,c on the spectral properties was also studied. Quantum yield of conjugates 2b,c is about 20% higher compared with basic conjugate 2a.

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## PP 65. SYNTHESES OF FUSED FURANONE CONTAINING SYSTEMS VIA ENAMINES OF γ-LACTONE AND INVESTIGATION OF BIOLOGICAL ACTIVITY

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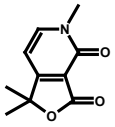
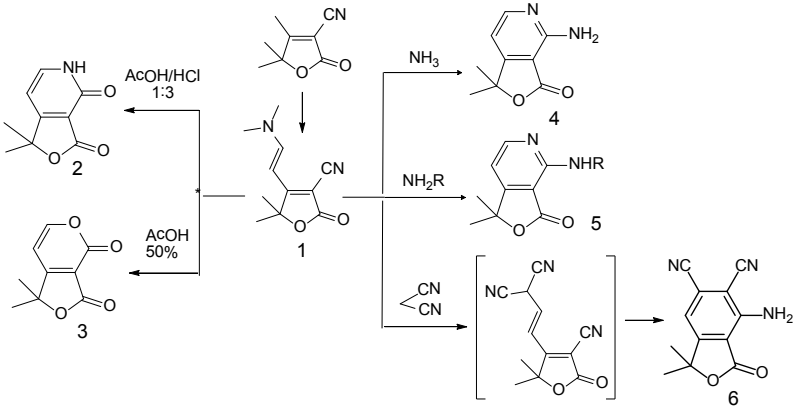
In recent years fused dihydrofuropyridines and their derivatives have attracted much interest because of their useful biological and pharmacological properties such as antibacterial, anticancer and spasmolytic activeties. Furthermore, fused dihydrofuropyridines and dihydrofuropyrimidines are also a structural unit of a series of natural products, i.e. alkaloid cerpegin [1]:



As a continuation of our previous investigations in this field [2], we report a facile synthesis of new functionalized fused dihydrofuranones.




Common initial 4-((β-dimethyl)amino)vinyl-2-oxo-2,5-dihydrofuran-3-carbonitrile derivative **1** was obtained by interaction of 4-methyl-2-oxo-2,5-dihydrofuran-3-carbonitrile with dimethylformamide dimethylacetal in

boiling xylene with 95% yield. Within 3h condensation occurs at the expense of the methyl group in C-4 with formation of the corresponding derivative **1.** Depending on conditions of cyclization various condensed compounds could be obtained. Cyclization in acetic ambiance led to compounds **2, 3.**

Cyclization of compound **1** in an AcOH/HCl (3:1) mixture under the conditions of reflux for 4 h. led to high yield of nor-cerpegin **2**.

While the cyclocondensation occurs in a 50% AcOH a new derivative - furo[3,4-c]pyran-3,4-dione **3**, oxygen-containing analog of cerpegin, was obtained.

Various amino derivatives of furanone containing fused systems were obtained as well.

The non-substituted aminofuropyridine **4** was obtained from the initial β-dimethylaminovinyl compound **1** by cyclocondensation with 20% ammonia.

For the syntheses of 4-substituted aminofuropyridines **5** the condensation of **1** with primary amines in ethanol solution has been used. It should be noted, that similar compounds previously were obtained in two steps: by condensations of primary amines with 4-chloro derivatives.

During these investigations a new rearrangement in the reaction with malononitrile has been observed. Possible mechanism for the synthesis of 4-amino-1,1-dimethyl-3-oxo-1,3-dihydroisobenzofuran-5,6-dicarbonitrile **6** has been proposed.

A set of new derivatives of cerpegin was assayed for inhibition of CT-L, T-L and PA proteolytic activities of 20S constitutive proteasome and 20S immunoproteasome. It has been shown, that compound **5** with a benzylamino group at C4 and dimethylated at C1 of the furopyridine ring was the most efficient PA site-specific inhibitor of the c20S (ICcPA 50 of 600 nM) without noticeable inhibition of the i20S PA site (iPA) [2].

Thus, in this investigations we show the possibility to obtain a range of fused condensed systems: furo[3,4-c]pyridine-3,4-dione, furo[3,4-c]pyran-3,4-dione, 4-aminofuro[3,4-c]pyridine-3-one, 4-amino-3-oxo-1,3-dihydro-isobenzofuran-5,6-dicarbonitrile from the common β-dimethylaminovinyl derivative **1.**

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# AUTHORS INDEX

## F



## G



## H



## I



## J



## K

## L



## M



## N



## O



## P

## Y



## Z

# INDEX

# ⏩ NOTEBOOK

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