EAMHC-2014 | TBILISI, GEORGIA 20-24 SEPTEMBER, 2014

AGRICULTURAL UNIVERSITY OF GEORGIA
ASSOCIATION OF PROFESSIONAL CHEMISTS OF GEORGIA

2014 Tbilisi 8th EAMHC

PROGRAM
ABSTRACT BOOK
NOTEBOOK

8-th EURASIAN MEETING ON HETEROCYCLIC CHEMISTRY

TBILISI, GEORGIA
20-24 SEPTEMBER, 2014

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AGRICULTURAL UNIVERSITY OF GEORGIA

ASSOCIATION OF PROFESSIONAL CHEMISTS OF GEORGIA

8-th EURASIAN MEETING ON HETEROCYCLIC CHEMISTRY

(EAMHC-2014)

September 20-24, 2014
Tbilisi, Georgia

Wellcome!

Dear Colleagues,

The Organizing Committee cordially invites you to the 8-th Eurasian Meeting on Heterocyclic Chemistry (EAMHC-2014) which is organized by the Agricultural University of Georgia and Association of Professional Chemists of Georgia.

The conference series “Eurasian Meeting on Heterocyclic Chemistry” is a scientific event that has been established in Russia since 2000 attracting attendees from both industry and academia from Europe and Asia.

The 8-th Eurasian Meeting on Heterocyclic Chemistry will continue the same tradition of the prior EAMHCs, offering a scientific program dealing with the latest developments in new methods in heterocyclic chemistry, biologically active heterocycles (both pharmaceuticals and agrochemicals) heterocyclic natural products and analogues, and heterocycles in synthesis presented by leading international experts. The meeting will create an environment for in-depth, informed discussions highlighting the importance of heterocyclic chemistry in the industry and academia. There is also wide space for oral and poster contributions to allow established colleagues as well as young researchers to discuss their latest results and achievements. Besides the scientific aspects of the program, you will have a chance to appreciate the scenes of Georgia and visit historic regions of our country.

It is an honor and challenge for us to organize EAMHC-2014 for the first time in Georgia, and we will work hard to ensure a rewarding event, both scientifically and socially.

Organizing committee

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Conference Scheduler

SESSIONS OF THE CONFERENCE

20 September 2014

15.00-18.00	Registration
18.00 -18.30	Opening Ceremony
18.30-20.00	Welcome Party
20.00 -	Transfer to Hotel

21 September 2014

Session 1

Chairmen: Prof. Spinelli, Prof. Attanasi

09.15-09.30	**Address of Organizing committee**
09.30-10.10 **PLENARY LECTURE**	**Enaminones in the synthesis of heterocyclic systems. [2+2] Cycloadditions, ring expansion reactions and other transformations** Branko Stanovnik *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia*
10.10-10.35 **INVITED LECTURE**	**Design, synthesis and pharmacological properties of new thiazole and thiadiazole derivatives** Athina Geronikaki *Aristotle University, Greece*
10.35-11.00 **INVITED LECTURE**	**Design, Synthesis, And Pharmacological Properties Of New Cb2 Cannabinoid Receptor Ligands** Pier Giovanni Baraldi *University of Ferrara, Italy*
11.15-11.30	**Development of a Safe Cyano(nitro)methylation Agent and Its Application to the Synthesis of Heterocycles** Haruyasu Asahara *School of Environmental Science and Engineering , Kochi University of Technology, Japan*

11.30-11.50 **COFFEE BREAK**

Session 2
Chairmen: Prof. El-Kashef, Prof. Katsarava

11.50-12.05 **Synthesis of polyhydroxylated quinolizidine and indolizidine scaffold from sugar-derived lactams via one-pot reduction/Mannich/Michael sequence**
Bartlomiej Furman
Institute of Organic Chemistry, Polish Academy of Sciences, Poland

12.05-12.20 **Synthesis of Novel Thienopyrazole derivatives**
Adel Mohamed Kamal El-Dean
Assiut University, Egypt

12.20-12.35 **Transformations of 3-substituted 2-oxo -2H-1-beznopyranes via enolate derivatives**
Nevena Petkova
University of Sofia St. Kliment Ohridski, Bulgaria

12.35-12.50 **Multicomponent Sequential Synthesis of Heterocyclic[3.3.3]Propellanes**
Abdolali Alizadeh
Department of Chemistry, Tarbiat Modares Univer, Tarbiat Modares University, Iran

12.50-13.50 **LUNCH**

Session 3
Chairmen Prof. Geronikaki, Prof. Yus

13.50-14.30 **PLENARY LECTURE** **Novel Rearrangements in Targeted Synthesis of Natural Compound Analogs**
Victor G. Kartsev
VP, CSO&CEO InterBioScreen, Russia

14.30-14.55 **INVITED LECTURE** **Cultivating over thirty years the passion to build heterocycles from 1,2-diaza-1,3-dienes**
Orazio Antonio Attanasi

Department of Biomolecular Sciences, Section of Organic Chemistry and Organic Natural Compounds, University of Urbino "Carlo Bo", Italy

14.55-15.20 **INVITED LECTURE** **Aliphatic Nitrocompounds as Strategic Sources of Heterocycles**
Roberto Ballini
School of Science and Technology of the University of Camerino, Italy

15.20-15.35 **Structure-activity relationship in the oxygen-containing heterocycles**
Nana Kavtaradze
Tbilisi State Medical University, Institute of Pharmacochemistry, Georgia

15.35-15.50 **Synthesis of new mercaptopyrimidines and thienopyrimidines**
Abdel-Raheem A. Saddik
Chemistry Department, Faculty of Science, Assiut Univrsity, Egypt

15.50-16.10 **COFFEE BREAK**

Session 4
Chairman: Prof. Yavari

16.10-16.35 **INVITED LECTURE** **Heterocyclic compounds in the design of biodegradable polymers**
Ramaz Katsarava
Agricultural University of Georgia, Georgia

16.35-17.00 **INVITED LECTURE** **Synthetic Strategies for New Pyrazoles of Potential Biological Activities**
Hussein El-Kashef
Department of Chemistry, Faculty of Science, Assiut University, Egypt

17.30-20.00 Visit to museum

22 September, 2014

Session 5
Chairman: Prof. Stanovnik , Prof. Botta

9.30-10.10 **PLENARY LECTURE**	**[1,4]Thiazino[3,4-c][1,2,4]oxadiazol-3-ones: an examination of their reactivity and of their biological profile** Domenico Spinelli *Department of Chemistry 'G. Ciamician', Alma Mater Studiorum-Università degli Studi di Bologna, Bologna, Italy*
10.10-10.35 **INVITED LECTURE**	**Discovering new applications of chiral N-sulfinyl imines in heterocyclic chemistry** Migel Yus *Spain*
10.35-11.00 **INVITED LECTURE**	**Recent Advances in Appel Salt Chemistry** Panayiotis A. Koutentis *Department of Chemistry, University of Cyprus, Cyprus*
11.00-11.15	**An entry to carbapenem antibiotics scaffold via asymmetric reaction** Marek Chmielewski *Institute of Organic Chemistry, Polish Academy of Sciences, Poland*
11.15-11.30	**COFFEE BREAK**

Session 6
Chairmen: Prof. Ballini, Prof. Najera

11.30-11.45 **INVITED LECTURE**	**A new general 3CR leading to 1,4,5-trisubstituted-1,2,3-triazoless** Wim Dehaen *Molecular Design and Synthesis, Department of Chemistry, Belgium*
11.45-12.00	**Coumarins derivatives - synthesis and applications** Rostica Nikolova *University of Sofia St. Kliment Ohridski, Bulgaria*

12.00-12.25 **Synthetic Inversigations in the field of Non-symmetrical Bi-indoles and Tri-indoles**
Ioseb Chikvaidze
Javakhishvili Tbilisi State University, Georgia

12.25-12.40 **A new rearrangement during the preparation of condensed furo[2,3-b]pyridines**
Anush A. Hovakimyan
Institute of Fine Organic Chemistry, NAS RA, Armenia

12.40-13.40 **LUNCH**

Session 7
Chairmen: Prof. Dehaen, Prof. Cirrincione

13.50-14.30 **PLENARY LECTURE** **Progress towards the Development of Ligands for Separating Actinides from Lanthanides**
Laurence Harwood
University of Reading, UK

14.30-14.55 **INVITED LECTURE** **Benzopyran building blocks: herald of hope for multitarget drug discovery**
Fernanda Borges
CIQUP/Department of Chemistry and Biochemistry, Faculty of Sciences of Porto, Porto, Portugal

14.55-15.20 **INVITED LECTURE** **Tetrapyrrolic macrocycles: Synthetic features and potential applications**
Joze. Cavaleiro
Aveiro University, Portugal

15.20-15.35 **Nucleophilic Transformations Of Five-Membered 2,3-Dioxo Heterocycles By Action Heterocyclic Enamines**
Valeriya V. Konovalova
Institute of Technical Chemistry, Ural Branch of Russian Academy of Sciences, Russia

15.35-15.50 **COFFEE BREAK**

Session 8
Chairaman: Prof. Kartsev, Prof. Abu-Orabi

15.50-16.15 **INVITED LECTURE**
Marine alkaloid nortopsentin analogues inhibitors of cyclin-dependent kinase 1 (CDK1)
Girolamo Cirrincione
Medicinal Chemistry Division, Società Chimica Italiana, Italy

16.15.-16.40 **INVITED LECTURE**
Three different approaches to target the T315I mutation: ATP-competitive, ATP-non-competitive and 14-3-3
Maurizio Botta
Chemistry and Pharmacy of University of Siena, Italy

16.40-16.55 **Cholinesterase Inhibition of Selected 4-Methylcoumarins in Comparison to their Antioxidant Activity**
Sanja Ćavar Zeljković
Centre of Region Haná for Biotechnological and Agr, Palacky University Olomouc, Czech Republic

16.55-17.15 **Brønsted acidic hydrogensulfate ionic liquid immobilized SBA-15 as a green, metal-free and recyclable catalyst for tetrahydrochromenes and hexahydroquinoline carboxylates scaffolds**
Sadegh Rostamnia
Department of Chemistry, University of Maragheh, Iran

17.15-17.30 **Density Functional Theory (DFT), Structural Properties, Natural Band Orbital and Energy Studies of Heterocyclic Compound**
Shahriar Ghammamy
Department of Chemistry, Faculty of Science, Imam Khomeini International University, Qazvin, Iran

17.30-20.00 **City tour**

23 SEPTEMBER, 2014

Session 9
Chairmen: Prof. Cavaleiro, Assoc.Prof. Koutentis

9.30-9.55 **INVITED LECTURE**
Reactivity of alpha-halogen substituted pyridinium ylides
Eugene Babaev
Moscow State University, Russia

9.55-10.20 **INVITED LECTURE**
Nef-Isocyanide Adducts as key Intermediates for Synthesis of Heterocyclic Compounds
Issa Yavari
University of Tarbiate Modares, Iran

10.20-10.40 **INVITED LECTURE**
Effective Conversion of Carbohydrate Molecules to Nitrogen-containing Heterocyclic Derivatives
Jim-Min Fang
National Taiwan University, National Taiwan University, Taiwan

10.40-10.55
Synthesis Of Nitropyridines By Three Component Ring Transformation Of Dinitropyridone
Le Thi Song
School of Environmental Science and Engineering , Kochi University of Technology, Japan

10.55-11.10
One-Pot Synthesis And Antioxidant Activity Of Novel Polyhydoxylated 3-Arylcoumarins
Milen G. Bogdanov
Faculty of Chemistry and Pharmacy, University of S, University , Bulgaria

11.10-11.25
Encapsulation Of Anti-Arrhythmic Heterocyclic Compounds Into Nanoliposomes For Oral Delivery

Lia Tsiklauri
TSMU Iovel Kutateladze Institute of Pharmacochemis, TSMU, Georgia

11.25-11.40 **COFFEE BREAK**

Session 10
Chairmen: Prof. Babaev, Prof. Harwood

11.40-11.55 **Synthesis And Reactions Of Some Novel Selenolopy-razole Compounds**
Yasser A. El-Ossaily
Chemistry Department- Faculty of Science, Assiut University- Egypt

11.55-12.10 **Recent Developments Of The Chemistry Of 1,2,4-Benzotriazinyl Radicals**
Georgia A. Zissimou,
Department of Chemistry, University of Cyprus

12.10-12.25 **Designing of Ugi/post-transformation reactions for the synthesis of functionalized heterocyclic compounds**
Saeed Balalaie
K. N. Toosi University of Technology, Iran

12.25-12.40 **N-Arylation of Protected Azamacrocycles**
Mate Erdelyi
Department of Chemistry and Molecular Biology, University of Gothenburg, Sweden

12.40-12.55 **Benzimidazoles: synthesis, biological activity and perspectives of their application**
Tinatin Bukia
Iv. Javakhishvili Tbilisi State University, Georgia

12.55-13.55 **LUNCH**

Session 11
Chairmen: Prof. Borges, Prof. Fang

13.55-14.20 **INVITED LECTURE**
Synthesis And Study Of Some Triazolo Isoxazole Heterocyclic Compounds
Sultan Abu-Orabi,
Secretary General of Arab Union of Chemists and President of Jordanian Chemical Society, Jordania

14.20-14.45 **INVITED LECTURE**
Multicomponent 1,3-Dipolar Cycloadditions of Stabilized Azomethine Ylides
Carmen Najera
Department of Organic Chemistry, Universidad de Alicante, Spain

14.45-15.00
A Convenient Synthesis, Reactions and Anti-microbial activity of Some Novel selenolo[2,3-c]pyrazole Compounds
Remon M. Zaki,
Chemistry Department- Faculty of Science, Assiut University- Egypt

15.00-15.15
New Route for Synthesis of Cyclic Ketene Dithioacetals
Azizollah Habibi
Kharazmi University, Tarbiat Modaes University, Kharazmi, Iran

15.15-15.30
Thioureas as Versatile Precursors for Synthesis of Important Heterocyclics: Benzothiazolyl Substituted Iminothiazolidinones and Benzamido-oxothiazolidines
Hummera Rafique
University of Gujrat, Pakistan

15.30-15.45
Porphyrazine-Derived Pd Catalysts: Biphasic Suzuki Reactions Where The Catalyst Can Be Tracked
D. Bradley G. Williams
Research Centre for synthesis and Catalysis, University of Johannesburg, South Africa

15.45-16.15 **COFFEE BREAK**

16.15-17.15	**Poster presentations**
17.15-18.30	**Closing Ceremony**
18.30-19.00	Free time
19.00-19.20	Transfer to Restaurant
19.20-22.00	Banquet
22.00-22.20	Transfer to hotel

24 SEPTEMBER, 2014

9.00-20.00	**Ecxursion**

Plenary Lectures

PL 1. ENAMINONESIN THE SYNTHESIS OF HETEROCYCLIC SYSTEMS. [2+2] CYCLOADDITIONS, RING EXPANSION REACTIONS AND OTHER TRANSFORMATIONS

B. Stanovnik
Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia
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Enaminones and related compounds turned out to be extremely versatile reagents in the synthesis of many heterocyclic systems [1], including many nitrogen containing natural products and their analogues [2].

Recently, we reported regio specific microwave-assisted [2+2], [4+2] cycloadditions and Michael additions of substituted 2-amino-3-(dimethylamino)propenoates and other enaminones, derived mostly from methyl ketones, with electron poor acetylenes, such as acetylenecarboxylates, and azodicarboxylates, which gave highly functionalized 1-amino-4-(dimethylamino)buta-1,3-dienes as intermediates for the preparation of polysubstituted pyrroles, azapentalenes, triazafulvalenes, 2-heteroarylpyridines and their *N*-oxides, 1-aryl (orheteroaryl)imidazol-2-ones and other heterocyclic systems [3].

[2+2]Cycloadditions of substituted acetyleneiminium salts to enaminones, ring-expansion reactions, rearrangements of heterocyclic systems and other transformations will be presented [4].

Refernces

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[2] Wagger, J.; Grošelj, U.; Svete, J.; Stanovnik, B. Synlett2010, 1197 and references cited therein.
[3] (a) Uršič, U.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, B.Tetrahedron Lett., 2008, 49, 3775;
(b) Uršič, U.; Svete, J.; Stanovnik, B. Tetrahedron,2008, 64, 9937;
(c) Uršič, U.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, B. Helv. Chim. Acta,2009, 92, 481;
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(e) Bezenšek, J.; Koleša, T.; Grošelj, U.; Wagger, J.; Stare, K.; Meden, A.; Svete, J.; Stanovnik, B. Tetrahedron Lett 2010,51, 3392;
(f)Bezenšek, J.; Koleša, T.; Dobravc, T.; Grošelj, U.; Meden, A.; Stare, K.; Svete, J.; Stanovnik, B. Curr. Org. Chem.2011,15, 2530;

(g)Bezenšek, J.; Grošelj, U.; Stare, K.; Svete, J.; Stanovnik, B. Tetrahedron2012, 68, 516;
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i) Salomone, A.; Perna, F. M; Sassone F. C.; Falcicchio, A.; Bezenšek, J.; Svete, J.; Stanovnik, B.; Florio, S.; Capriati, V. J. Org. Synth.. 2013, 78, 11059;

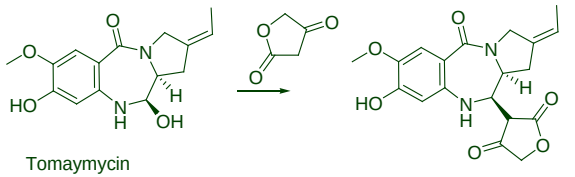
[4] a) Bezenšek, J.; Prek, B.; Grošelj, U.; Golobič, A.; Stare, K.; Svete, J.; Kantlehner, W.; Maas, G.; Stanovnik, B. Z. Naturforsch. 2014, 69b, 554;
b) Prek, B.; Bezenšek, J.; Kasunič, M.;Grošelj, U.; Svete, J.; Stanovnik, B. Tetrahedron2014, 70, 2359;
c) Bezenšek, J.; Grošelj, U.;Stare, K.; Svete, J.; Stanovnik, B. ARKIVOC2014 (ii), 294;
d) Prek, B.; Grošelj, Kasunič, M.; Zupančič, S.; Svete, J.; Stanovnik, B. Aust. J. Chem.2014, in print.

PL 2. NOVEL REACTIONS AND REARRANGEMENTS IN TARGETED SYNTHESIS OF NATURAL COMPOUND ANALOGS

V. Kartsev
InterBioScreen, Moscow, Russia
screen@ibscreen.chg.ru

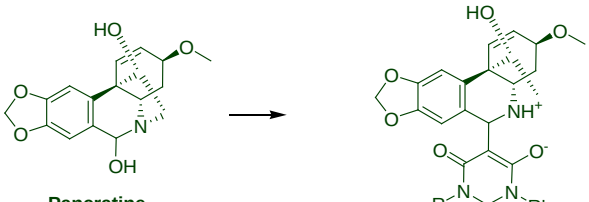
Several types of chemical reactions have been applied for modification of alkaloids in the frame of InterBioScreen' Project "Modification of Natural Products in Drug Discovery". Below are some examples of these transformations: Mannich reactions (A), Addition reactions (B), Cyclocondensation reactions (C),T-Reactions (D) and New Hemiaminal rearrangements (E) etc.

A



Tomaymycin
from *Streptomyces achromogenes*

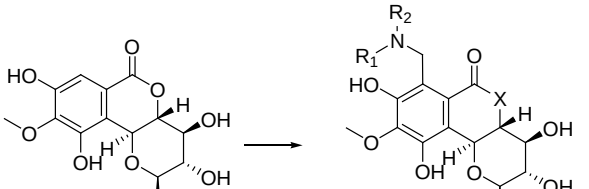
A



Pancratine
from Haemanthus spp.

R,R': Me, Ph

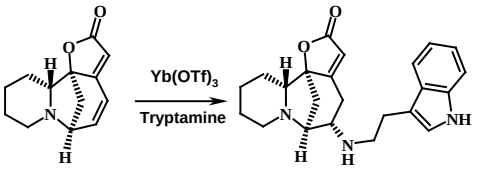
A



Bergenin

X=O, N

B



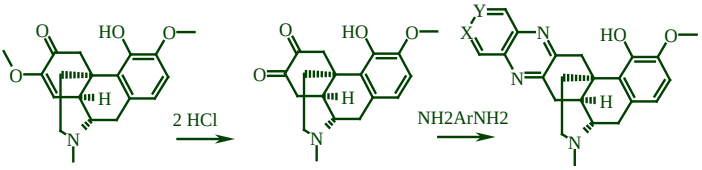
Securinine

from *Securinega spp*.

epi-Margaritarine

potent GABA blocker

C

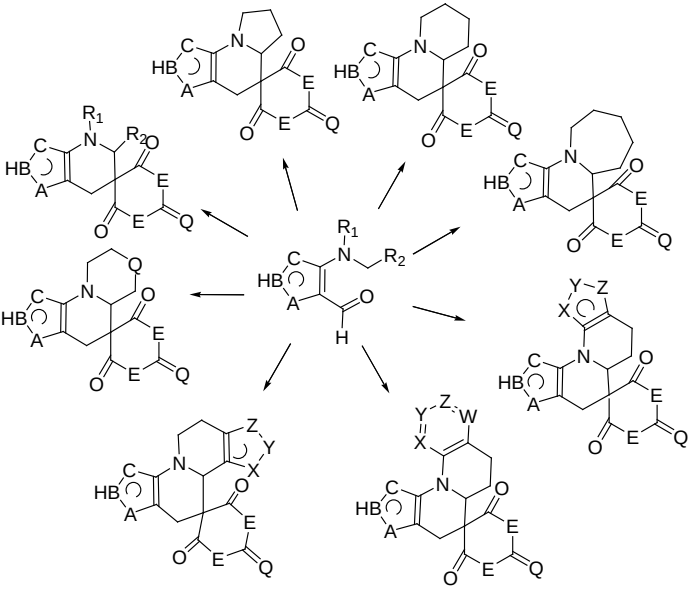


Sinomenine

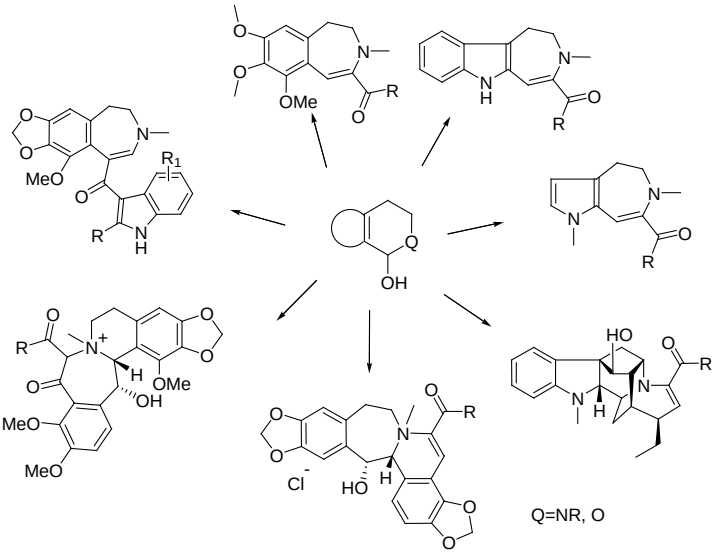
from *Sinomenium acutum*

Potent antineoplastics

D



E



Refernces

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[6] Krasnov K.A, Kartsev V.G., Khrustalev V.N., Heterocycles 2007, Vol.71, №1, 2007, p.13-18.
[7] K.Krasnov, V.Kartsev, Heterocycles, vol.71, No.1, 2007, p.19-25.

PL 3. [1,4]THIAZINO[3,4-*C*][1,2,4]OXADIAZOL-3-ONES: AN EXAMINATION OF THEIR REACTIVITY AND OF THEIR BIOLOGICAL PROFILE

A. Bottoni[a], M. Calvaresi,[a] B. Cosimelli,[b] A. Mazzanti[c], D. Spinelli[a]

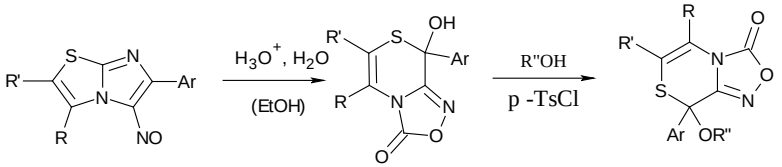
[a] Department of Chemistry 'G. Ciamician', Alma Mater Studiorum-Università degli Studi di Bologna, Italy

[b] Department of Pharmacy, University of Naples 'Federico II', Italy

[c] Department of Industrial Chemistry 'T. Montanari', Alma Mater Studiorum-Università degli Studi di Bologna, Italy

domenico.spinelli@unibo.it

5-Nitroso-6-arylimidazo[2,1-*b*][1,3]-thiazoles (**1**) react with hydrochloric acid giving the 8-aryl-8-hydroxy-8*H*-[1,2,4]oxadiazolo[3,4-*c*][1.4]thiazin-3-ones (**2**), whose structures were determined by means of different spectrometric techniques (infrared, NMR, and mass) and confirmed by X-ray crystallography [1a,b]. Compounds **2** have been obtained with yields ranging from low (12%) to good (70%) as a function of the substituents on the aryl group or bound to the thiazole ring [1c].



1 **2** **3**

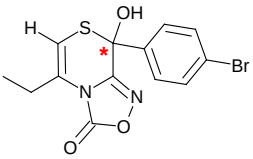
Scheme 1

8-Aryl-8-hydroxy-8*H*-[1,2,4]oxadiazolo[3,4-*c*][1.4]thiazin-3-ones are hemithioacetals and contain a chiral 'unstable' center at C-8. Of course the relevant acetals (**3**) include a stable chiral center [2a-d].

Both hemithioacetals **2** and acetals **3** show very interesting biological features: as pointed out by some of us they are interesting hits thanks to their L-type Calcium Channel (LTCC) (*2a-d*) and MDR activities.(*3a,b*) Because of this reason we have synthesized a lot of compounds **2** and **3** and we have

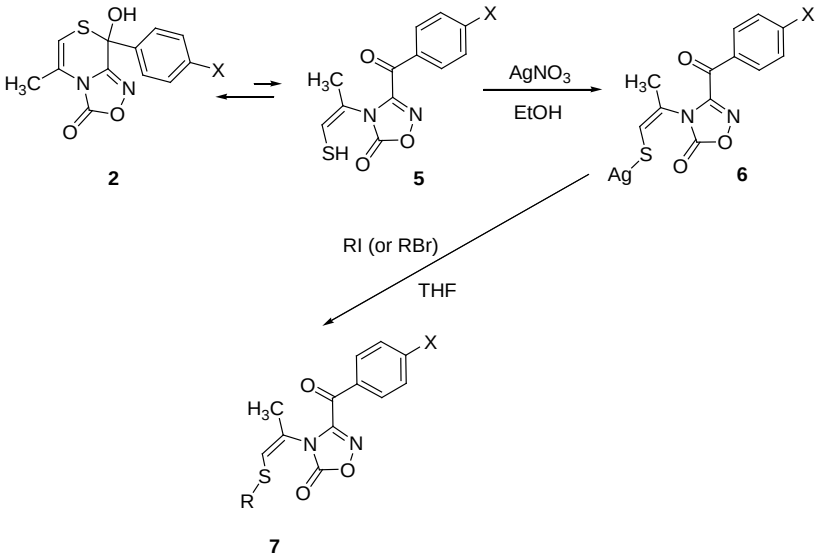
obtained very promising results also with the help of *in-silico* predictions [2c,d; 3b].

In solid state hemithioacetals **2** exist as stable bicyclic compounds,(*1b*) in contrast in toluene at high temperature (383 K, following the process by ^{1}H-NMR) we have observed that 5-ethyl-8-hydroxy-8(4-bromophenyl)-8*H*-[1,2,4]oxadiazolo[3,4-*c*][1.4]thiazin-3-one (**4**) leads to a *R*/*S* equilibrium at the C-8 chiral center.



4

The occurrence of this kind of equilibrium (open-chain/thiazine) has been also demonstrated chemically by freezing the open-chain structure [4].



Scheme 2

We have obtained interesting information on the hemithioacetal ring-opening process from a DFT computational analysis of the corresponding potential energy surface. We have estabilished that the cyclic structure is much more stable than the open one ($\Delta G°$>7 kcal mol^{-1}). Also, we have identified a reaction path characterized by an energy barrier of about 18 kcal mol^{-1} [5] which is consistent with the value determined by ^{1}H-NMR experiments (about 20 kcal mol^{-1}) [6].

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PL 4. PROGRESS TOWARDS THE DEVELOPMENT OF LIGANDS FOR SEPARATING ACTINIDES FROM LANTHANIDES

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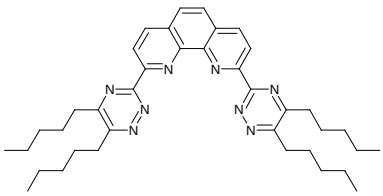
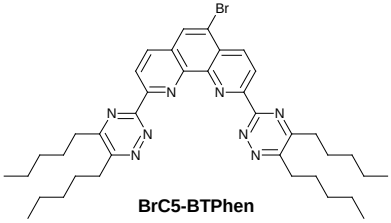
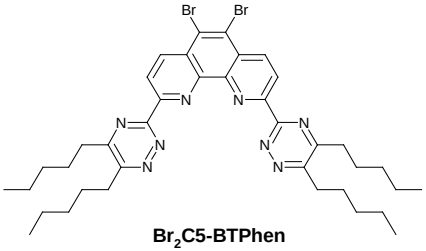
Separation of the minor actinides from lanthanides and other fission products is a key step in the partitioning and transmutation scenario for reprocessing of used nuclear fuel, and has been achieved using nitrogen-bearing ligands; for instance the bis-triazinyl-phenanthroline (BTPhen) ligands [1]. In recent developments modulation of electronic effects by substituting at the 5 and 5,6-position of BTPhen ligands has enabled these ligands to be fine-tuned in order to enhance the selectivity of Am(III) from Eu(III) [2].



C5-BTPhen



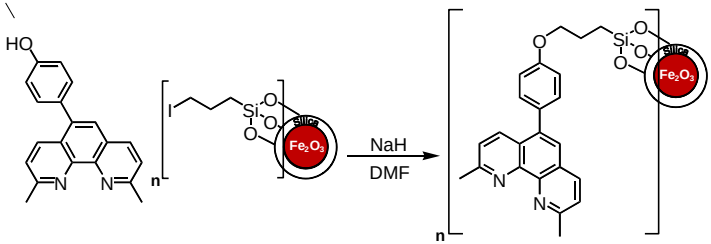
BrC5-BTPhen



Br_2C5-BTPhen

Magnetic iron oxide (Fe_2O_3) nanoparticles (MNPs) have attracted much interest over recent years because of their large surface area and magnetic properties, meaning they can be extracted from solution by the Iron oxide MNPs can be modified with a surface coating of silica or zirconia in order to

reduce aggregation and provide a means of attachment of additional functionality. The particle surface can thus be modified with ligands that have affinity for metal ions (Scheme). The present work combines the stability of SiO_2 coated MNPs and the complexing power of neocuproine in order to study the capabilities of such materials for the effective removal of metal ions from aqueous solutions at different pH.



Scheme: Immobilisation of neocuproine on MNPs

The maximum removal efficiency for Cu(II) from a 12.5 ppm aqueous solution was 99% at pH 2. Extraction was complete within 5 min and about 12 mg of the neocuproine-functionalized MNPs were able to alter the concentration of Cu(II) in 10 mL of solution from 12.33 ppm to 0.13 ppm. Our work is also focused on attaching BTPhen ligands to MNPs and their applications in nuclear waste treatment by investigating their ability to extract Am(III) and Eu(III) from 4M HNO_3; in which medium the MNPs were stable [3-4].

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Invited Lectures

IL 1. DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW THIAZOLE/THIADIAZOLE DERIVATIVES

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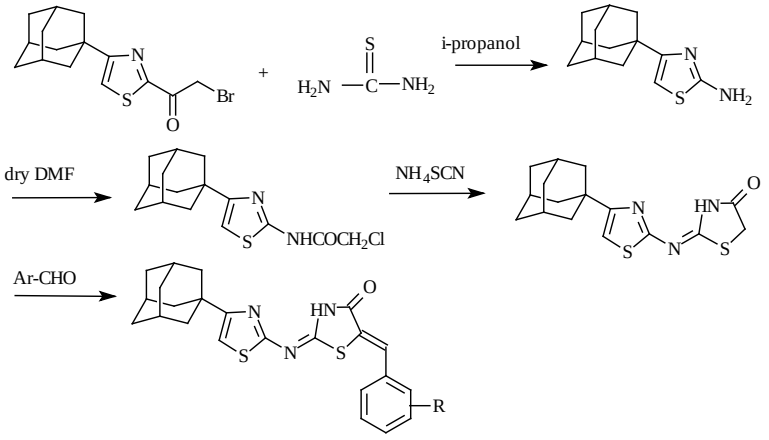
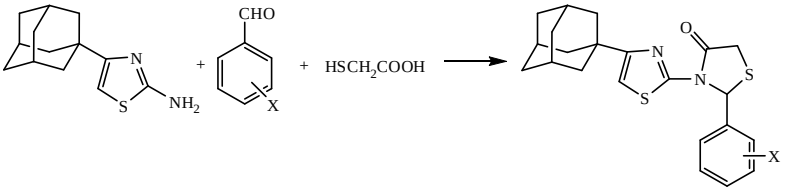
Despite the success to date in development of antimicrobial agents, the inexorable, ongoing emergence of resistance worldwide continues to spur the search for novel compounds to replace or supplement conventional antibiotics and antifungals. Taking into account the interesting antimicrobial and chemical properties of thiazole, thiadiazole as well as adamantane derivatives, herein is presented the synthesis and evaluation of antimicrobial activity of twenty compounds presented in Schemes 1 and 2.



Scheme 1.



Scheme 2.

The antimicrobial assay was carried out by microdilution method. For the evaluation of the antifungal activity of the compounds, the following fungi were used: *A. ochraceus,*, *A. fumigatus*, *A. niger*, *A. versicolor*, *A. flavus, P. funiculosum*, *P. ochrochloron*, *T. viride, C. albicans* and *F. Sporotrichoides* while for the antibacterial tests were used Gram-negative bacteria *E. coli*, *P. aeruginosa*, *S. typhimurium*, *En. faecalis* and Gram-positive bacteria *L. monocytogenes*, *B. cereus*, *M. flavus*, *En. cloacae* and *S. aureus*. As reference drugs were used a) ketoconazole, bifonazole and b) ampicillin, streptomycin for the antifungal and antibacterial assays respectively.

The tested compounds exhibited outstanding antimicrobial activity, being in most of the cases more potent than reference drugs.

The synthesized compounds having thiazolidine-4-one moiety have been docked at the active side of the *Staphylococcus aureus* Mur B active site (PDB: 1HSK). The most active compound in the series was found to have hydrogen bond contact with the backbone nitrogen of GLY249. The thiazolidine-4-one is mainly responsible for the activity of the molecule as it is a potential surrogate of the di-phosphate moiety present in UDP-N-acetylenolpyruvylglucosamine. [1]

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IL 2. DESIGN, SYNTHESIS, AND PHARMACOLOGICAL PROPERTIES OF NEW CB_2 CANNABINOID RECEPTOR LIGANDS

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Interest in the potential medicinal use of cannabinoids grew recently with the discovery of 2 cannabinoid receptors, CB_1 and CB_2. The CB_1 receptor is abundantly expressed in the central nervous system (CNS) and is responsible for the psychotropic side effects. The CB_2 receptor is mainly found in cells of the immune system, though it may be upregulated in the CNS under pathological conditions. The main signal transduction pathway triggered is through G_i proteins, resulting in an inhibition of adenylate cylase activity and a decrease in cyclic AMP levels. Recent developments indicate that CB_2 receptor ligands have the potential to become therapeutically important. To explore this potential, it is necessary to develop compounds with high affinity for the CB_2 receptor.

Within a research program to identify novel CB_2 agonists, our group designed a hybrid chemical structure that incorporated the structural features of known cannabinoid ligands. The new series of oxazinoquinolone derivatives exhibiting high affinity and selectivity for the CB_2 receptor (hCB$_2$ K_i = 8.12 nM, hCB$_1$ K_i > 10000, selectivity index (SI) > 1231) [1]. The potency of the new oxazinoquinoline-6-carboxamides was measured in functional assays, revealing that the novel series behaved as CB_2 receptor full agonists. The effect of a novel CB_2 agonist (MT178) was evaluated in different animal models of pain [2].

In this context, very recently, we have also reported the medicinal chemistry of a series of heteroaryl-4-oxopyridine/7-oxo-pyrimidine derivative which displayed high affinity at the CB_2 receptor (hCB_2 K_i=11.4 nM, hCB_1 K_i = 4568, SI=401) [3]. In this study, additional CB_2 ligands were synthesized by replacing the pyrazolo ring with different heterocycles that were found to be potent CB_2 receptor ligands. Moreover, it was shown that the functionality

of these ligands is controlled by the nature of the heteroaryl function condensed with the pyridine ring. In 3,5-cyclic adenosine monophosphate (cAMP) assays, they showed a dose-dependent effect in the modulation of forskolin-induced cAMP production, revealing different behaviors as full agonists, partial agonists and inverse agonists.

Finally, we synthesized the structural isomers of our previously reported pyrazolo[3,4-*b*]pyridines that allowed us to conduct a pharmacophore exploration and optimization effort around the heteroaryl central scaffold. The newly synthesized 7-oxo-pyrazolo[1,5-*a*]pyrimidine-6-carboxamides were tested in competition binding assays toward both rat CB_1 and CB_2 receptors expressed in native tissues (rat brain or spleen) and human CB_1 and CB_2 receptors expressed in CHO cells. Affinity data (K_i, nM) were used to calculate the selectivity of newly synthesized compounds for the CB_2 receptors. All of the new compounds showed high affinity and selectivity for the CB_2 receptor in the nanomolar range. In 3,5-cyclic adenosine monophosphate (cAMP) assays, the novel series shows stimulatory effects on forskolin-induced cAMP production acting as inverse agonists [4].

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IL 3. CULTIVATING OVER THIRTY YEARS THE PASSION TO BUILD HETEROCYCLES FROM 1,2-DIAZA-1,3-DIENES: THE FORCE OF IMAGINATION

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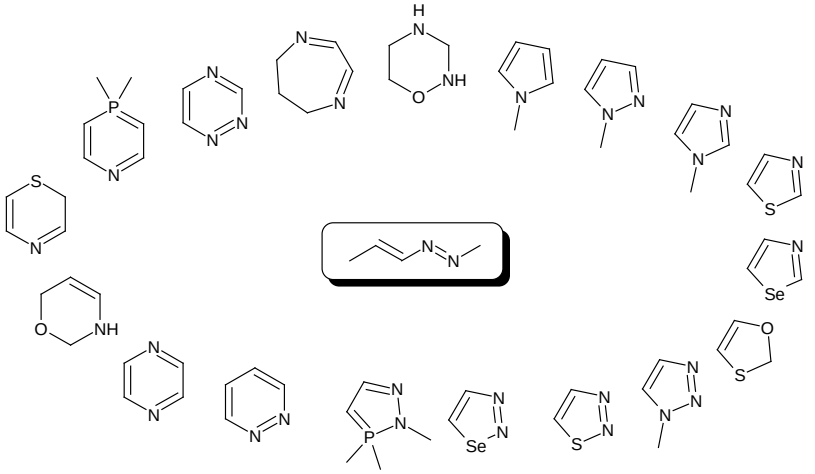
Pyrroles, pyrrolines, pyrazoles, pyrazolines, imidazoles, imidazolines, imidazolidindiones (hydantoins), 2-thioxoimidazolinones (2-thiohydantoins), thiazoles, thiazolines, thiazolidines, 2-iminothiazolidinones, selenazoles, selenazolines, 1,3-oxathioles, 1,2,3-triazoles, 1,2,3-thiadiazoles, 1,2,3-selenodiazoles, 1,2,3-diazaphospholes, pyridazines, dihydropyridazines, tetrahydropyridazines, pyrazines, dihydropyrazines, tetrahydropyrazines, piperazines, 1,3-oxazines, 1,4-thiazines, dihydro-1,4-thiazines, tetrahydro-1,4-thiazines, dihydro-1-aza-4-phosphinine, 1,2,4-triazines, tetrahydro-1, 2,4-triazines, 1,2,4-oxadiazines, tetrahydro-1,4-diazepinones, 1,4-benzodiazepines and mixed heterocyclic systems have been obtained from 1,2-diaza-1,3-dienes [1-14].



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IL 4. ALIPHATIC NITRO COMPOUNDS AS STRATEGIC SOURCES OF HETEROCYCLES

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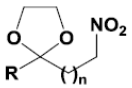
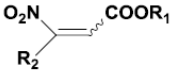
Aliphatic nitro compounds, nitroalkanes and nitroalkenes, are a class of compounds prone to give the easy formation of C,C bond by reaction with electrophiles or nucleophiles, respectively [1,2]. Moreover, the final adducts still retains the nitro group moiety and, due to the great chemical versatility of this functionality, they can be converted into a plethora of other molecules [3,4].

In the last decade there has been an explosion of synthetic procedures for the synthesis of heterocycles starting from aliphatic nitro compounds [5,6] and in this context I wish to present some results obtained (mainly in our laboratory) from protected nitro ketones **1** and β- nitroacrylates **2**.



1



2

Procedures and results will be presented.

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IL 5. HETEROCYCLIC COMPOUNDS IN THE DESIGN OF BIODEGRADABLE POLYMERS

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Synthetic biodegradable polymers (**BP**s) are of special interest because of technological challenge, commercial potential and environmental friendliness. These polymers take center stage in a great variety of research efforts. Materials that can decompose and disappear from the body are desirable for a variety of biomedical applications. BPs have become increasingly important for the development of surgical and pharmaceutical devices like wound closure devices, vascular grafts, nerve guidance tubes, absorbable bone plates, orthopedic pins and screws, body-wall/hernia repair, sustainned/controlled drug delivery systems, to name a few. **BP**s have a high potential for practical applications in agriculture and food industry as well. An important limitations in the use of **BP**s is the possible toxicity of the degradation products. Therefore, the research is focused on **PB**s entirely composed of nontoxic building blocks such as hydroxy acids and amino acids. Heterocyclic compounds made of these building blocks play an important role in the synthesis of **BP**s *via* either (i) ring-opening polymerization (**ROP**) or (ii) step-growth polymerization (**SGP**).

BP via ROP. Various heterocyclic compound are used for synthesizing BPs *via* **ROP**. Dilactones like glycolide and lactides are successfully used for the synthesis of biodegradable polyesters including functional polyesters like poly-α-malic acid; p-dioxanone is used for the synthesis of biodegradable poly(ether ester). β-Lactones are used for the synthesis of poly-β-hydroxyalkanoates and poly(β-malic acid). Caprolactone is used for obtaining elastomeric polyesters. Copolymerization of lactones with lactams leads to biodegradable poly(ester amide)s having random structure. Alternating poly(ester amide)s - AB-type polydepsipeptides, including functional polydepsipeptides, are obtained by ring-opening polymerization of dioxomorpholines and substituted dioxomorpholines.

BP via SGP. Various bis-lactones and cyclic-bis-carbonates are used as

starting bifun-ctional monomers for synthesizing either polyesters or polyamides *via* the interaction with fatty diols or diamines, accordingly. More active monomers are bis-azlactones obtained by cyclization of N,N'-diacyl-bis-α-amino acids. **SGP** of bis-azlactones with fatty diols leads to poly(ester amide)s, with diamines or bis-trimethylsilylated diamines – to polyamides, with di-p-toluenesulfonic acid salts of bis(α-amino acid)-α,ω-alkylene diesters – to poly(ester amide)s containing dipeptide fragments in the polymeric backbones.

IL 6. SYNTHETIC STRATEGIES FOR NEW PYRAZOLES OF POTENTIAL BIOLOGICAL ACTIVITIES

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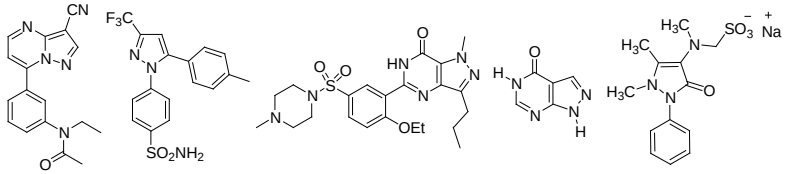
Pyrazole and its derivatives play an important role in medicinal and pesticide chemistry. They possess a wide range of bioactivities such as antimicrobial, anticancer, anti-inflammatory, antidepressant, anticonvulsant, antiparasitic, antipyretic, antiallergic, antihypertensive, antiviral activities [1-12] and as adenosine receptor antagonists [13].

Zaleplon [14], celebrex [15], sildenafil [16], allopurinol [17] and dipyrone [18] are some examples of pyrazole-based drugs which exist already in the market.



Zaleplon ***Celebrex*** ***Sildenafil*** ***Allopurinol*** ***Dipyrone***

Many synthetic procedures exist for the synthesis of substituted pyrazoles. However, the development of simple, facile and efficient methodologies to get pyrazole derivatives and biologically active heterocycles containing the pyrazole moiety is always desired.

Several new pyrazole derivatives and pyrazole-containing heterocyclic systems have been synthesized using 1,3-disustituted-1*H*-pyrazol-5(4*H*)-one, or pyrazoleaminonitrile and pyrazoleaminoester derivatives as starting materials. Different synthetic strategies leading to different new pyrazole-based heterocyclic systems will be presented and discussed. The biological activities of some of the compounds prepared will be highlighted.

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IL 7. DISCOVERING NEW APPLICATIONS OF CHIRAL *N*-SULFINYL IMINES IN HETEROCYCLIC CHEMISTRY

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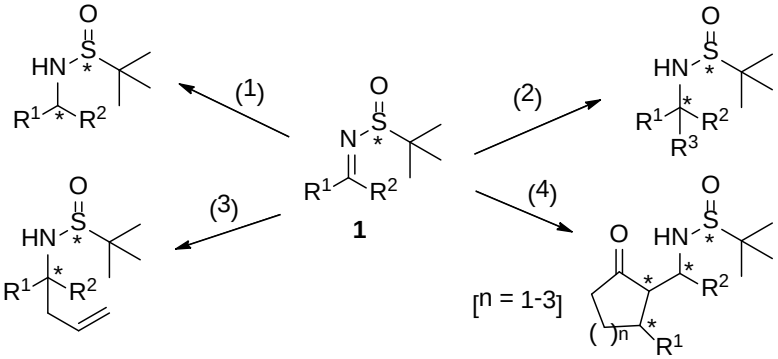
Chiral *N*-sulfinyl imines, especially the corresponding *N*-*tert*-butyl substituted derivatives **1** [1] are interesting starting materials in asymmetric synthesis because (a) they are easily accessible in both enantiomerically pure form, (b) the sulfinyl group activates the imine moiety towards nucleophilic substitution so, in the reaction with different nucleophiles an asymmetric induction takes place giving an diastereoenriched product, which can be easily separated into the corresponding pure diastereomers, and (c) the deprotection of the amino group, after the addition of the nucleophile can be easily achieved by simple treatment with hydrochloric acid. In this presentation, the reactivity and synthetic applications of these materials in the (1) ruthenium-catalyzed hydrogen transfer [2], (2) addition of alkyl zincates [3], (3) indium-promoted allylation [4], and (4) multicomponent reactions involving cycloalkenones and dialkyl-zinc reagents [5] (Scheme 1). Especial attention is paid to the synthetic applications of the mentioned processes, mainly for the preparation of natural or unnatural alkaloids and aminoacids.



Scheme 1.

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IL 8. RECENT ADVANCES IN APPEL SALT CHEMISTRY

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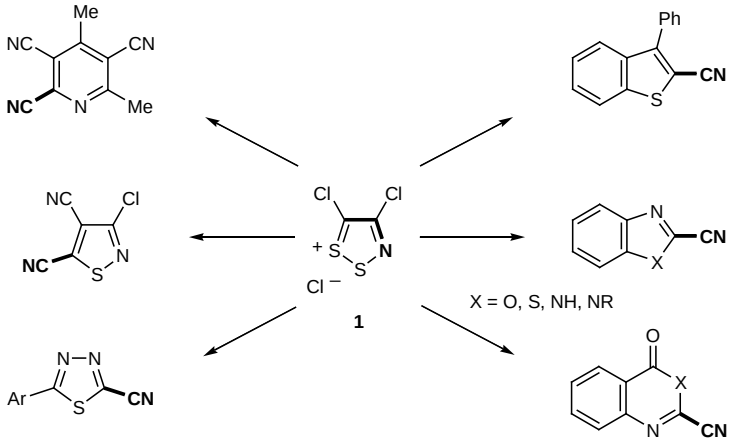
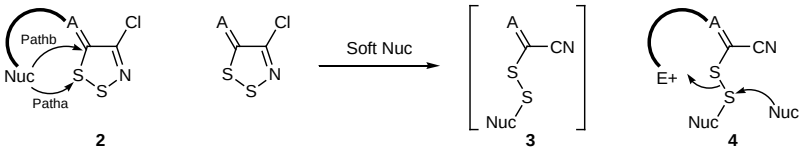
The preparation of 4,5-dichloro-1,2,3-dithiazolium chloride **1** in 1980 by Rolf Appel [1] was followed by a rapid development of synthetic methods which utilised dithiazolium **1** for the synthesis of various heterocyclic systems. [2] The salt **1** effectively provides an umpolung source of **C-CN** (shown below in BOLD).



The majority of these ring transformations involve the initial preparation of a neutral dithiazole **2** which supports a nucleophilic side chain or substituent capable of attacking the electrophilic dithiazole at either S-1 (Path a) or at C-5 (Path b) with subsequent ring opening. Dithiazoles **2**, however, can also be ring opened with the use of soft nucleophiles to afford the disulfide intermediate **3**. This disulfide can be a source of both electrophilic and nucleophilic sulfur.



Various dithiazole-ylidenes have been prepared with these mechanistic possibilities in mind to broaden the capability of dithiazolium **1** as a useful synthetic tool. Emphasis will be made on the generation of disulfides such as **4** endowed with electrophilic traps for nucleophilic sulfur.

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IL 9. A THREE-COMPONENT REACTION FOR THE REGIOSELECTIVE SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES

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Heterocycles containing 1,2,3-triazole rings belong to a class of well studied molecules due to their diverse applications such as in pharmaceuticals, agrochemicals, material chemistry etc. Copper-catalyzed azide-alkyne cyclo-addition reaction (CuAAC) has proven very valuable for the regioselective synthesis of 1,2,3-triazoles [1]. However, the toxicity of the heavy metals in living cells made this strategy not ideal for some biological applications. Several alternative methods were developed, but the major drawbacks are the formation of other regioisomers and the difficulty in making the starting materials. Therefore, the design and discovery of a new metal-free triazole synthesis is of great current interest.

In this work, we developed new organocatalytic three-component reaction of very wide scope for the regioselective synthesis of highly functionalized 1,2,3-triazoles from readily available building blocks such as nitroalkanes, aldehydes and azides [2]. The details of the reaction will be communicated at the conference. The mechanism involves the Knoevenagel reaction and the 1,3-dipolar cycloaddition of nitroalkene to azide as intermediate steps. Intramolecular variants lead to fused 1,2,3-triazole derivatives.

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IL 10. BENZOPYRAN BUILDING BLOCKS: HERALD OF HOPE FOR MULTI-TARGET DRUG DISCOVERY

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Over the past two decades, one of the key goals of rational drug design has been the discovery of selective ligands for specific binding sites on individual molecular targets. Thus, in the target-based approach the ligand's potency and selectivity for the desired target is increased and in turn, there should be a corresponding decrease in undesirable side effects that may arise from binding to secondary targets.

For some time, drug discovery players have been questioning the success of this reductionist philosophy to ameliorate disease states with multifactorial and polygenic nature. The multi-target approach, where a single chemical entity may be able to modulate simultaneously multiple targets, seems to be of particular interest in areas that involve multiple pathogenic factors, like neurodegenerative diseases, cancer and infectious diseases. In this context, the development of neuroprotective and/or disease-modifying multi-target agents can be a significant promise for the long-term central nervous system (CNS) disorders, such as Alzheimer's disease (AD) or Parkinson's disease (PD). Certainly this is a daunting challenge but given the current unmet medical needs, and the advantages if successful, such a venture is worthwhile.

The lecture will be focused on our recent studies based on benzopyran scaffold-based compounds towards discovery of multi-target agents [1,2].

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IL 11. REGULAR AND *N*-CONFUSED PORPHYRINS: SYNTHESIS, REACTIVITY AND POTENTIAL APPLICATIONS

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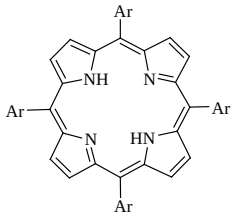
Natural porphyrins play vital functions in Nature (*e.g*. respiration, photosynthesis and drug detoxification). In recent decades potential applications became known for such type of heterocycles, which can be obtained by using simple synthetic methodologies. Quite remarkable are those applications in cancer treatment (photodynamic therapy-PDT) and in the photoinactivation of microorganisms, mainly those which are multidrug-resistant (PDI) [1,2].

Structural features in a porphyrin derivative might contribute to significant biological action of the molecule. The derivatization of the macrocycle leading to new tetrapyrrolic species conjugated with other biologically active molecules is not only a synthetic target but also a good approach to look for new potential drugs.

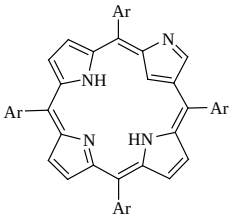
We have been performing chemical studies on the synthesis and reactivity of porphyrins and related compounds, keeping in mind such structural aspects [3].

We have been considering the use of regular tetrapyrrolics like *meso*-tetraarylporphyrins (**I**), and related compounds (**II**), the *N*-confused porphyrins. Although the structural difference between the two macrocycles is not big, the physical and chemical features have significant differences. For the synthetic studies leading to the already mentioned conjugates, certain triazole and quinolone derivatives have been chosen.

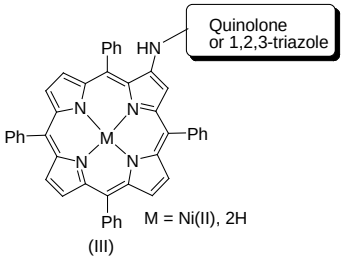
Meso-tetraaryl regular and *N*-confused porphyrins have been synthesized as well as amino- and vinyl-[1,2,3]-triazoles and bromo-quinolones. The conjugate formation has been studied by using several methodologies like the Buchwald-Hartwig and Heck reaction conditions. Conjugates like (**III**) and (**IV**) have been synthesized; the results obtained will be shown in this lecture.



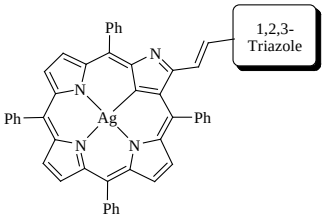
(I)



(II)



(III)



(IV)

Acknowledgements. Thanks are due to "Fundação para a Ciência e a Tecnologia" (FCT, Portugal), European Union, QREN, FEDER and COMPETE for funding the QOPNA research unit (PEst-C/QUI/UI0062/2013) and for the award to Ana Gomes of Post-Doctoral grant (SFRH/BPD/79521/2011); thanks are also due to the National NMR Network and to the FCT-CAPES (Brazil) collaborative program. Thanks are also due to students involved in the work, mainly Dr. Ana T.P.C. Gomes.

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IL 12. MARINE ALKALOID NORTOPSENTIN ANALOGUES INHIBITORS OF CYCLIN-DEPENDENT KINASE

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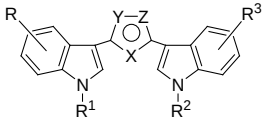
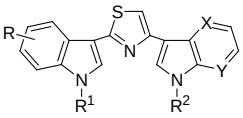
Marine indole alkaloids have emerged as an important structural class because of their great variety of biological activities including antimicrobial, antiviral and antitumor properties [1]. In particular, nortopsentins A-C, having a characteristic 2,4-bis(3'-indolyl)imidazole skeleton, have been considered important lead compounds for the discovery of new biologically active derivatives [2]. Due to the remarkable biological activities shown, several analogues of nortopsentins, in which the imidazole ring has been replaced by other five membered heteroclycles such as thiophene **1**, pyrazole **2**, isoxazole **3**, furan **4**, pyrrole **5**, and thiazole **6** have been synthesized. All these series of compounds showed antiproliferative activity against a wide range of human tumor cell lines with GI_{50} values from micromolar to submicromolar concentrations [3-5].



1-6



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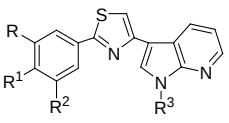


9

Nortopsentin X=N; Y=CH; Z=NH;
1: X=S; Y=Z=CH; **2**: X=CH; Y=N; Z=NH;
3 X=CH; Y=N; Z=O; **4**: X=O; Y=Z=CH;
5: X=NH; Y= Z=CH; **6**: X=N; Y=S; Z=CH

7: X=N; Y=CH;
8: X=CH; Y=NH

More recently it was thought to verify whether the aza-substitution of indole moiety could have improved the antiproliferative activity. Thus, 3-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl)-1H-4-azaindole derivatives 7, in which the 4-azaindole ring substituted one indole system and the thiazole moiety replaced the imidazole nucleus of nortopsentin were synthesized and tested against a panel of cell lines with different histologic origin, including breast cancer, androgen-independent prostate cancer, pancreatic carcinoma and peritoneal mesothelioma. Some compounds consistently reduced the growth of all experimental with IC_{50} values ranging from 2.20 to 19.36 μM,

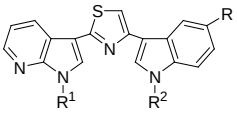
and were also able to inhibit cyclin-dependent kinase 1 (CDK1) activity with IC50<1 μM. Moreover, the most active compound, which induced the greatest in vitro inhibition of CDK1 (IC50=0.66 μM), also reduced the cyclin B1-associated CDK1 kinase activity in a peritoneal mesothelioma cell line and increased by 4-fold and 3-fold caspase-9 and caspase-3 respectively.[6]

Contemporaneously, 3-[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl)-1*H*-7-azaindole of type **8**, in which the spacer is constituted by the thiazole ring and one of the indole units is replaced by a 7-azaindole moiety were synthesized. All compounds of this series were selected by the NCI for evaluation against the full panel of human cancer cell lines and several compounds showed GI_{50} values from micromolar to sub-micromolar range. The biological activity was also investigated in STO and MesoII cells, derived from human Diffuse Malignant Peritoneal Mesothelioma (DMPM). The most active compounds, that act as cyclin-dependent kinase 1 inhibitors, consistently reduced DMPM cell proliferation and induced a caspase-dependent apoptotic response, with a concomitant reduction of the expression of the active Thr34-phosphorylated form of the anti-apoptotic protein survivin. Moreover, the combined treatment of DMPM cells with the most active derivative and paclitaxel produced a synergistic cytotoxic effect, which was parallel by an enhanced apoptotic response. In the mouse model, i.p. administration of active derivatives was effective, resulting in a significant tumor volume inhibition of DMPM xenografts (range, 58-75%) at well-tolerated doses, and two complete responses were observed in each treatment group [7]. Due to these interesting biological properties this seres of compounds was patented [8].

Also, 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles **9** were synthesized and tested against a panel of about 60 tumor cell lines and were particularly active showing antitumor activity in a wide range of tumor cell lines from micromolar to nanomolar concentration. Two of them exhibited a high affinity for CDK1, with IC_{50} values of 0.41 and 0.85 μM [9].

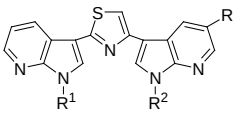
Lately, three further series of nortopsentin analogues were synthesized. In particular, in the series **10** the azaindole and the indole moieties have been switched; in the series **11** the central heterocycle is bounded to two 7-azaindole portions and in the series **12** the aza-substitution was moved from

position 7 to position 6. The antiproliferative tests of these series are in progress.



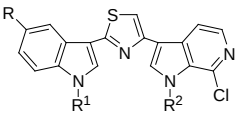
10

R= H, F
R^1= H, Me
R^2= H, Me, C_6H_4-Me



11

R= H, F, Br
R_1= H, Me
R_2= H, Me



12

R= H, F, Br, OMe
R_1= H, Me, Boc
R_2= H, Me

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IL 13. THREE DIFFERENT APPROACHES TO TARGET THE T315I MUTATION: ATP-COMPETITIVE, ATP-NON-COMPETITIVE AND 14-3-3 INHIBITORS

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A serious problem in the treatment of Chronic Myeloid Leukemia (CML) is represented by the development of resistance to Imatinib (IM, Gleevec®), which is currently used in frontline therapy. The insurgence of drug-resistance, especially in the advanced phases of the disease, can be caused by both Bcr-Abl-dependent mechanisms (e.g. mutation in the kinase domain of the enzyme, Bcr-Abl gene amplification) and Bcr-Abl-independent mechanisms (e.g. Src family kinase activation). As a consequence, there is a growing interest in developing novel TK inhibitors able to target IM-resistant forms of CML, especially the T315I mutant. The application of molecular modeling and combinatorial techniques led our Research Group to the identification of three different families of compounds active on three different targets: 1) The ATP binding site of the Bcr-Abl T315I mutant [1]; 2) the myristate binding pocket of Bcr-Abl [2] and 3) the 14-3-3s protein [3[]. While coumpounds active on the first two targets represent valuable inhibitor of IM-resistant Bcr-Abl dependent forms of leukemia, 14-3-3s inhibitors could allow to overcome Bcr-Abl dependent and Bcr-Abl-independent form of resistance targeting an alternative pathway involved in the regulation of the causative events of CML.

The successful application of these three approaches for the inhibition of the T315I Bcr-Abl mutant will be discussed.

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IL 14. REACTIVITY OF ALPHA-HALOGEN SUBSTITUTED PYRIDINIUM YLIDES

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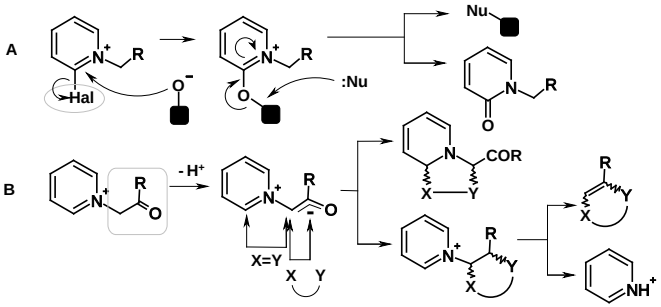
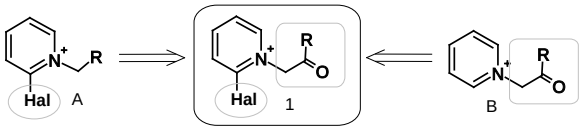
N-Alkylpyridinium salts have found applications as reagents in the organic synthesis of other classes of substances. The most striking examples are 2-halopyridinium salts (**A**), known as Mukayama reagents, and *N*-phenacylpyridinium Kröhnke salts (**B**, R = Ar), readily forming ylides (traditionally called phenacylides) with bases:

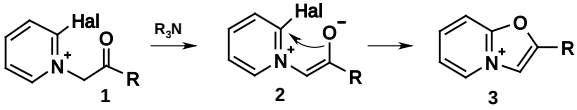


Mukayama salts **A** have a unique ability to undergo stepwise transformations into N-alkylpyridones by “withdrawing” the oxide ion from many oxygen-containing nucleophiles and donating their electrophilicity to the remaining species. The use of Kröhnke salts **B** in the synthesis was dictated by other properties of pyridinium salts, namely, the ability of their phenacylides to undergo 1.3-dipolar cycloaddition and the ability of the charged ring to initially involve the methyleneketone unit in various (cyclo)condensations.

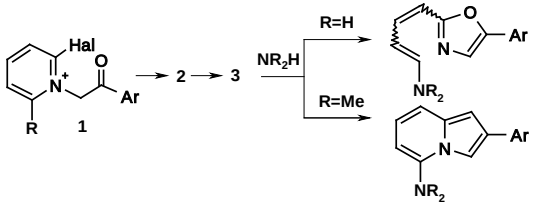
The present talk deals with the chemistry of salts 1, whose structure contains both strong functionalities: the α-halogen of Mukayama salts and the keto-methylene unit of Kröhnke salts.



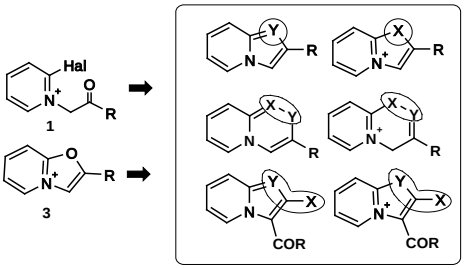
In contrast to the transformations of Mukayama and Kröhnke salts, the reactions of salts 1 have never led to the elimination of the pyridine (or pyridone) residue. Instead, another distinction of salts 1 (and their ylides 2) was found, namely, their close relationship with oxazolopyridinium salts 3. The first type of relationship can be called genetic; the salts 1 could be converted into 3 by reactions with bases via the formation of betaine-ylides 2:



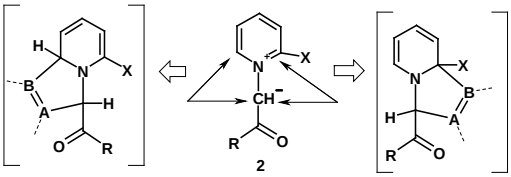
In some cases, the analogy was so complete that attempts to synthesize salts 1 gave only the corresponding oxazolium salts 3.



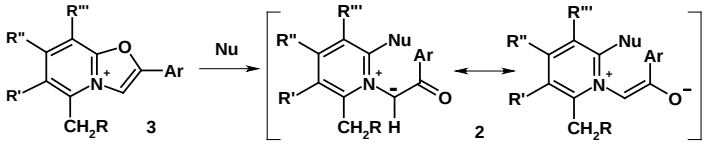
The second type of relationship is that in many reactions, monocycles 1 and bicycles 3 form exactly the same products without being converted into one another; i.e., they behave as synthetic equivalents. This relationship is due to the similarity of the mechanisms of the first stage of these reactions:



The third type of relationship between salts 1 and 3 was found recently. Pyridinium ylides 2 formed from 1 can undergo 1,3-dipolar cycloadditions; the chemistry of these compounds changes due to the presence of α-halogen (or another X leaving group) in phenacylides 2.



The ability of pyridinium "ylidogens" 1 to undergo cycloaddition would seemingly differentiate them from electrophilic bicycles 3. We proved, however, that 1 and 3 are also related in this respect because the oxazolium ring is opened in several cations 3, also generating ylides 2 and the products of their transformations.



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IL 15. NEF-ISOCYANIDE ADDUCTS AS KEY INTERMEDIATES FOR SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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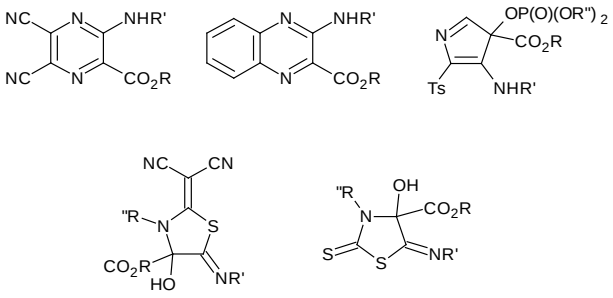
The unique properties of the isocyano group, which may function as both an electrophile and a nucleophile, have made these compounds useful reagents in organic synthesis [1]. Apart from their role in classical multicomponent reactions, the most important applications of isocyanides are in the synthesis of various heterocycles [2]. A number of isocyanide reactions have seen their potential largely unexplored. For example, the Nef reaction, which involves the α-addition of acyl chlorides to isocyanides forming imidoyl chlorides [3-5].

One of the main problems of the Nef isocyanide reaction is the selectivity of the nucleophilic attack on the Nef adducts: either the imidoyl or the carbonyl function which may lead to isocyanide elimination. We anticipated that the use of an α-carboalkoxy substituent would make the ketone more electrophilic and would probably lower the potential for elimination of isocyanide leading to acylation derivatives. This modification was found to be successful. Thus, intramolecular trapping of Nef adducts with various nucleophiles, led to the preparation of dihydro-1*H*-pyrroles, phosphorylated 3*H*-pyrroles, thioxothiazolidines, and iminothiazolidines. Various features of these reactions will be presented and discussed.



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IL 16. EFFECTIVE CONVERSION OF CARBOHYDRATE MOLECULES TO NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVES FOR SENSITIVE DETECTION AND BIOLOGICAL APPLICATIONS

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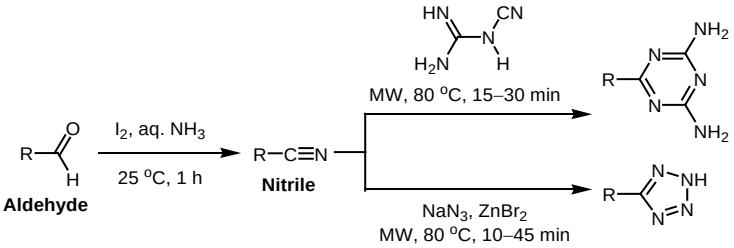
In 2001, we reported a practical method for direct transformation of aromatic, heterocyclic, aliphatic, conjugated, and polyhydroxy aldehydes to the corresponding nitriles in high yields (83–97%) by stirring with iodine, as the oxidant, in ammonia water at room temperature for a short period (<2 h) [1]. Such reaction is easily monitored by discharge of the yellowish brown color of iodine. Utilization of ammonia water, instead of ammonia gas saturated methanol, without external base (e.g. MeONa) rendersvery simpleoperation to avoid side reactions. The oxidative condensation reactions are further promoted by using a focused microwave reactor, and the intermediate nitrile products, without isolation, are heated with dicyandiamide and sodium azide to afford high yields of the corresponding [2+3] cycloaddition products of 2,6-diamino-triazines and tetrazoles in one-pot operation (Scheme 1) [2].

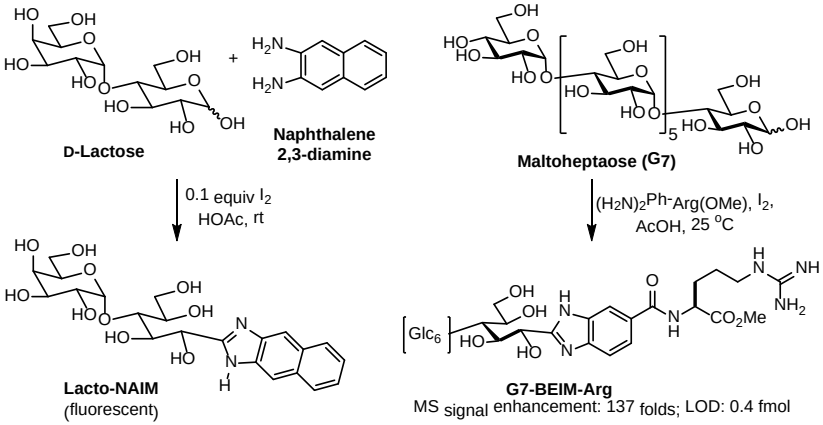


Scheme 1. *Direct conversion of aldehydes to nitriles in ammonia water, and the microwave-assisted one-pot tandem reactions to triazines and tetrazoles*

In another aspect, the reactions of aldoses, which often exist in the forms of hemiacetals, with iodine in ammonia water at roomtemperature produce the corresponding saccharide amides in high yields [3]. The saccharide amides are presumably derived from the lactone intermediates by in situ

ammonolysis. This reaction protocol is also successfully applied to ligation of carbohydrate molecules, without prior protection or modification, with a variety of primary amines including bifunctional amines and peptides [4]. We further explored an iodine-promoted decarboxylativeamidation of α-keto acids in mild reaction conditions [4]. This novel conjugation method by amide bond formation can be utilized for preparation of neoglycoproteins such as that derived from bacterial lipopolysaccharides.

Using iodine as an oxidant in acetic acid solution, a series of mono-, di- and trialdoses, including those containing carboxyl and acetamido groups, undergo an oxidative condensation reaction with o-phenylenediamine or 2,3-naphthalenediamine at room temperature to give the aldo-benzimidazole (BEIM) and aldo-naphthimidazole (NAIM) products in high yields [5].



Scheme 2. *Facilitated HPLC, CE and MS analyses of carbohydrate molecules via the benzimidazole and naphthimidazole derivatives*

The BEIM and NAIM products are isolated simply by trituration of the crude reaction mixture with ethyl acetate. No racemization of saccharides or cleavage of the glycoside bonds occurs under such mild reaction conditions.The fluorescent NAIM derivatives facilitate HPLC analysis ofthe composition of

saccharides.Due to the hydrophobic nature of the NAIM moiety, the glycol-NAIM compounds also show enhanced responses in capillary electrophoresis [6] and MALDI-TOF MS spectrometric analysis [7–9]. Ultrasensitive MS analysis of oligosaccharides is realized with the arginine-linkedBEIM derivatives [9].

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IL 17. MULTICOMPONENT 1,3-DIPOLAR CYCLOADDITIONS OF STABLILIZED AZOMETHINE YLIDES

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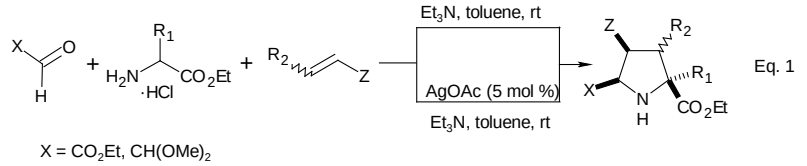
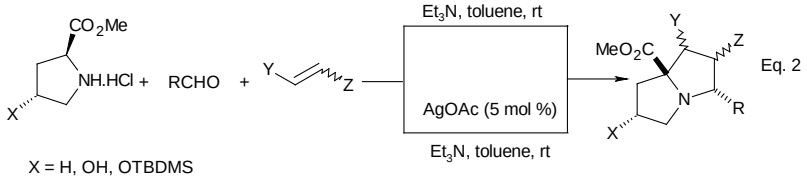
Multicomponent reactions, and particularly cycloadditions, have very interesting perspectives and applications because do not waste atoms during their whole processes [1]. 1,3-Dipolar cycloadditions (1,3-DC) involving metallo-azomethine ylides and electrophilic alkenes are good examples for this type of transformation but are not so frequently described [2]. In this lecture, the thermal and silver mediated multicomponent 1,3-DC between α-amino esters, dipolarophiles and functionalized aldehydes such as ethyl glyoxylate [3] and 2,2-dimethoxyacetaldehyde will be considered. In addition, the multicomponent 1,3-dipolar cycloaddition between proline esters, aldehydes and dipolarophiles to afford highly substituted pyrrolizidines will be also described [4].





Ethyl glyoxylate and 2,2-dimethoxyacetaldehyde reacted with ethyl α-amino esters hydrochlorides at rt in the presence of Et_3N (1.1.eq) thermally or in the presence of AgOAc (5 mol%) at rt with dipolarophiles affording *endo*-prolines with high 4,5-*endo*-2,5-*cis*-diastereoselection (Eq. 1). On the other

hand, the multicomponent reaction of proline-derived methyl esters hydrochlorides with aldehydes and dipolarophiles occurred just adding stoichiometric amounts of triethylamine at rt in the absence or in the presence of catalytic amounts of AgOAc. The corresponding highly substituted pyrolizidines are obtained in all cases with 2,5-*trans*-relative configuration between two electron-withdrawing groups and major *endo*-selectivity, 2,4-*cis*-relative configuration (Eq. 2). The use of (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride allowed the synthesis of enantiomerically enriched pyrrolizidines [5].

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[5] This work has been supported by the Spanish Ministerio de Ciencia e Innovación (MICINN) (Consolider INGENIO 2010 CSD2007-00006, CTQ2010-20387), FEDER, Generalitat Valenciana (PROMETEO/2009/039), and by the University of Alicante.

Oral Presentations

OP 1. DEVELOPMENT OF A SAFE CYANO(NITRO)METHYLATION AGENT AND ITS APPLICATION TO THE SYNTHESIS OF HETEROCYCLES

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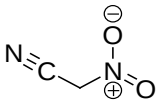
Nitroacetonitrile (NAN), a methylene connected with a nitro and a cyano functionalities, is used as a cyano(nitro)methylation agent, which serves as a building block for the synthesis of versatile polyfunctionalized compounds (Figure 1). Indeed, several reactions of the NAN have been reported, such as Knoevenagel condensation with a ketone/aldehyde, addition reactions to polar multiple bonds, and Michael addition [1]. In spite of the great potential of the NAN, it has not been widely used in organic syntheses because preparative methods for NAN suffer from somewhat troublesome manipulations, poor yield and low stability of the NAN. Even more problematically, Thomas recently alerted on the explosive property of the NAN [2]. In this context, the development of an alternative cyano(nitro)methylation agent with safety is required even now.



Nitroacetonitrile (NAN)

On the other hand, we have reported that the pyridinium salt of nitroisoxazolone 1 undergoes the ring opening reaction quantitatively under mild conditions upon treatment with pyrrolidine (2A) to give dianionic cyano-aci-nitroacetate 3, which possesses three different functional groups on the same carbon (Scheme 1) [3]. Since the dianion 3 is regarded as the masked framework of the NAN, the above - mentioned features enabled to use as the easily treatable synthetic equivalent of the anionic NAN accompanied by decarboxylation. Indeed, the dianion 3 reacts with ketones and aldehydes to afford polyfunctionalized nitriles, such as glutaronitriles, α-nitro-α,β-unsaturated nitliles and α-nitro-δ-keto nitrile.

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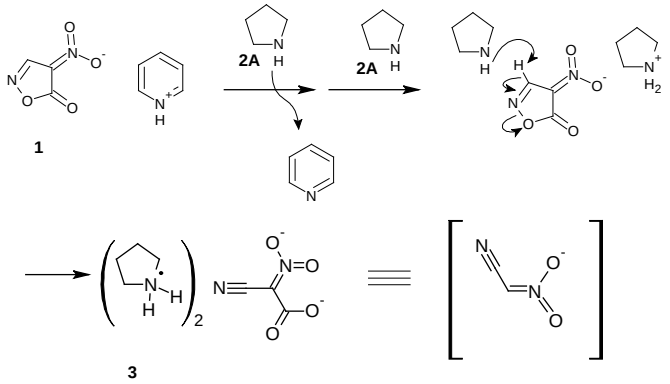
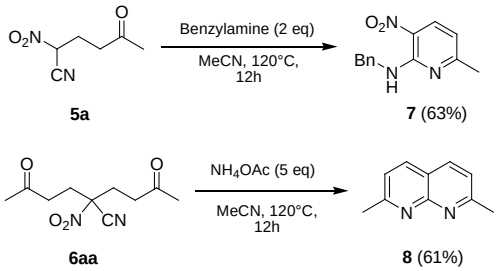


Scheme 1. *Generation of Cyano-aci-nitrocetate 3 derived from nitroisooxazolone 1*

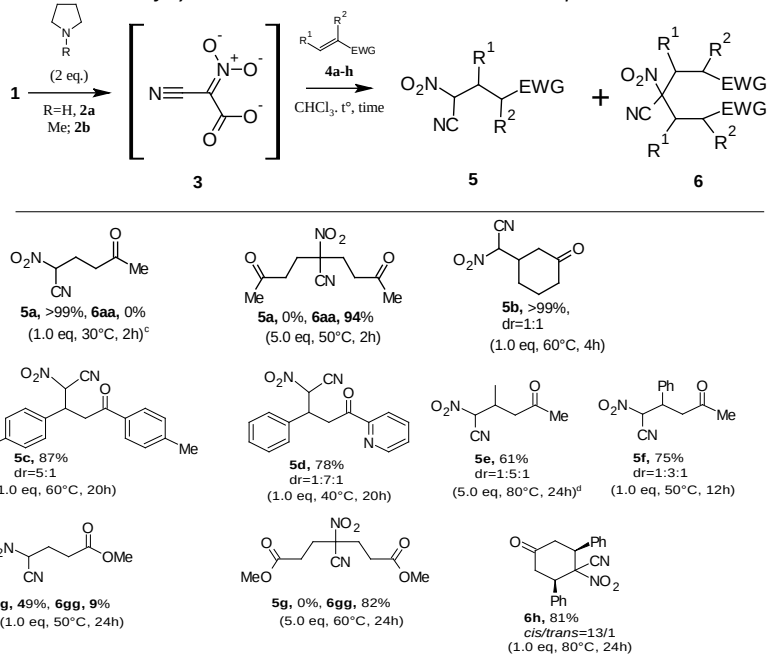
In this work, we demonstrate cyano-*aci*-nitroacetate **3** can be regarded as a practically usable and safe cyano(nitro)methylation agent, which react with Michael acceptors **4** to afford both single/double adducts **5** and **6** (Table 1).

The prepared single adducts **5** served as substrates of pseudo-intramolecular process to afford vicinally functionalized pyridines **7**. In addition, double adducts **6** were also converted to naphthyridines **8** by intramolecular double condensation upon treatment with ammonium acetate (Scheme 2).



Scheme 2. *Applications of Michael addition products, the construction of heterocylces*

Table 1. *Reaction of cyano-aci-nitroacetate 3 to Michael acceptors 4a-h*[a,b]



a Unless otherwise noted; 2b was used as a base; b In the parentheses, amount of Michael acceptors, reaction temperature and reaction time are shown; c 2a was used as a base; d Ethanol was used as a solvent

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OP 2. SUGAR-DERIVED CYCLIC IMINES: ONE-POT SYNTHESIS AND DIRECT FUNCTIONALIZATION

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Efficiency is the central goal in organic synthesis [1]. Towards this goal, the development of one-pot and economy reactions constitute two valuable approaches. In this context, we have recently reported the stereoselective one-pot method for the transformation of easily available sugar lactams into the corresponding imines, iminosugars [2], bicyclic dihydropyrans and some other related compounds by Schwartz's reagent reduction followed by alkylation with various nucleophilic reagent. The most important advantages as well as limitations of the methodology developed by us will be presented during the lecture.

Acknowledgments. 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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OP 3. SYNTHESIS OF NOVEL THIENOPYRAZOLE DERIVATIVES

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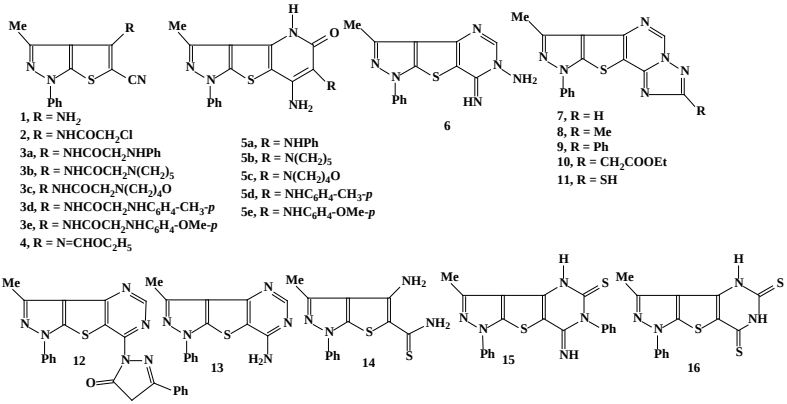
4-Amino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile (**1**), was synthesized and used as precursor intermediate for synthesis many fused heterocyclic compounds. It was reacted with chloroacetyl chloride in dioxane to afford 4-chloroacetylamino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile (**2**). The latter compound underwent nucleophilic substitution reaction with aromatic, aliphatic and cyclic amines in ethanol to give compounds **3a-e**. when the previous reaction was carried under neat condition and in the presence of excess amine compound (**5a-e**) were produced. Also compound **1** was reacted with triethyl orthoformate to afford 4-ethoxymethyleneamino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile (**4**). Compound **4** was reacted with hydrazine hydrate to produce 3-amino-4-Imino-4,6-dihydro-8-methyl-6-phenyl-pyrazolo[3,4-b] thieno [5, 4-d]pyrimidin (**6**).



1-phenyl-3-methyl-8-substituted-1,6-dihydro-pyrazolo[3',4':2,3]thieno[4,5-e][1,2,4]-triazolo[1,5-d]pyrimidine (**7-11**) were synthesized from the reaction of compound **6** with triethyl orthoformate, acetic anhydride, benzaldehyde, diethyl malonate and carbon disulfide respectively. When compound **6** allowed to react with benzoyl acetate affording 8-methyl-6(H)-

6-phenyl-4-(5-oxo-3-phenyl-pyrazolin-1-yl)pyrazolo[3,4-b]thieno[5,4-d]pyrimidin (**1**2).

In other hand, compound **1** was reacted with formamide, propane diamine in the presence of carbon disulfide, phenyl isothiocyanate and carbon disulfide to give compounds (**13-16**) respectively.

OP 4. TRANSFORMATIONS OF 3-SUBSTITUTED 2-OXO-2H-1-BENZOPYRANES VIA ENOLATE DERIVATIVES

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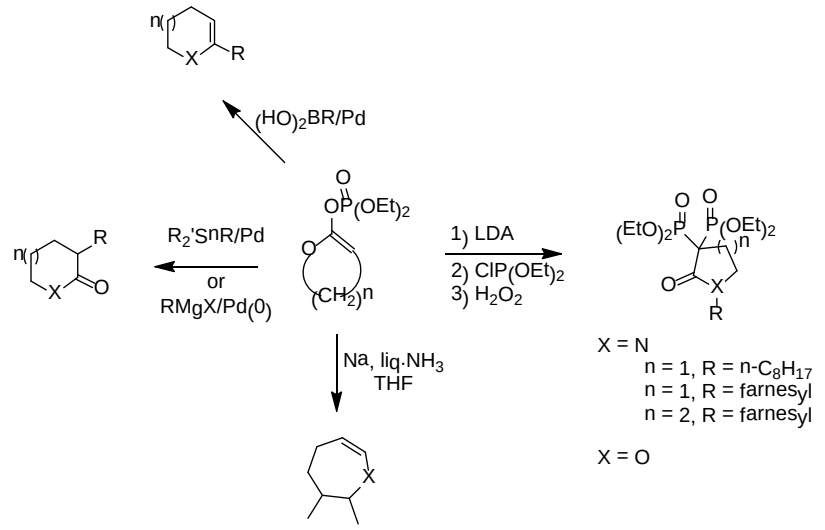
Enolates are common and useful intermediates as well as substrates in a variety of synthetic strategies. The potential of enol phosphates to sustain different transformation makes them desired building blocks for construction of complex phosphonates and diverse analogues of natural products [1]. It is known that enol phosphates have higher stability and reaction yield over triflate counterparts on the other hand phosphates can be prepared in mild reaction conditions.

Phosphorus activated enol derivatives can take place in different transformations some of them are metal-catalysed cross-coupling reactions, intramolecular olefin metathesis, alkylations, 1,3-rearrangements and reductions.



Our previous studies have presented [2] a tandem reaction on acylation of coumarin derived enols as a method for incorporation of subsequent functional groups to chromane systems. Enolate structure presumes formation of C- or O-acylated products; however, under our optimized reaction conditions we could isolate only C-acylated products. Computational studies on the regioselectivity of the reaction as well as the presence of Lewis acids have brought additional evidences for the observed reaction pathway [3,4]. In contrary, acylation reaction with diethyl phosphorochloridate took place with formation of O-phosphorylated product as a main compound. Here, we report the synthesis of P-trapped enols of 3-substitutes coumarins under Michael and Arbuzov reaction conditions, moreover under phase-transfer conditions. Furthermore, enol phosphates were involved in subsequent reactions of phosphorylation or transformations on the base of nucleophilic substitution.

Current study shows and confirms the ability of lactone derived enol phosphates to be used as starting material as well as reagents for further phosphorylation during the reaction procedures. Our preliminary results present methodology for synthesis of compounds with complex structures and interesting behaviour. Structure elucidation of the compounds was mainly done by two-dimensional NMR spectra.

Acknowledgments. This work was supported by the Project “Beyond Everest” FP7-REGPOT-2011-1 “Development of the research potential of the Faculty of Chemistry, Sofia University, in the area of advanced functional materials for successful participation in world-class research at EU level”

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OP 5. MULTICOMPONENT, ONE-POT AND SEQUENTIAL SYNTHESIS OF HETEROCYCLIC[3.3.3]PROPELLANES

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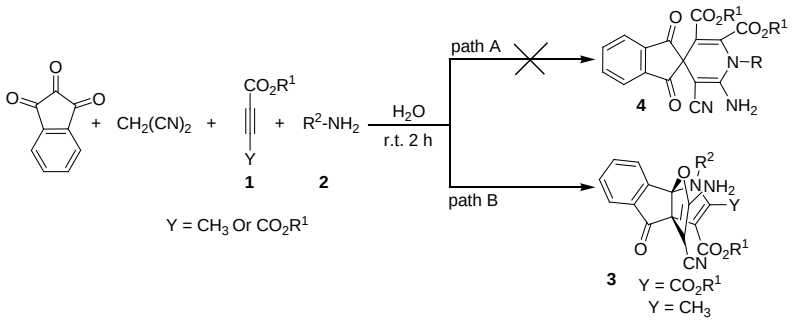
The propellane skeletons occupy a privileged place in synthetic organic chemistry owing to their presence in various biologically active and natural products [1]. Heterocyclic propellanes like Acutumine exhibit fundamental biological properties, including selective T-cell cytotoxicity [2] and antiamnesic activity [3]. Indeed, in the literature, the most reported processes for the preparation of propellanes usually involve a Diels-Alder reaction [1,4]. Other methods include: photochemical addition [5], palladium [6] or manganese catalysis [7], rearrangement of spiroketones [8], and nucleophilic substitutions of 1,1,2,2-tetrasubstituted alkenes [9].

However, regardless of the many efforts dedicated in this field only limited approaches to propellanes are known according to multicomponent reaction methodologies.

Inspired by these results and with given our interest and experience in the area of one-pot-multicomponent reactions, we became attracted how Knoevenagel adduct generated in situ from ninhydrin and malononitrile could be trapped by enamine to give a heterocycle product. For this purpose we investigated the reaction of ninhydrin, malononitrile, dialkyl acetylenedicarboxylate **1** and primary amine **2** in water at room temperature. Quite surprisingly, instead of the anticipated spiropyridine product **4** (Scheme 1), we observed an unexpected process leading to heterocyclic propellane **3** in excellent yields.



The structures all of the products were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra and unambiguously confirmed by X-ray crystal structure analysis.

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OP 6. STRUCTURE-ACTIVITY RELATIONSHIPS IN SOME OXYGEN-CONTAINING HETEROCYCLES

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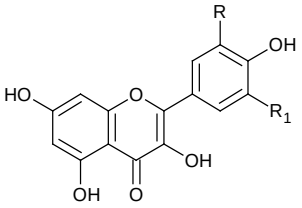
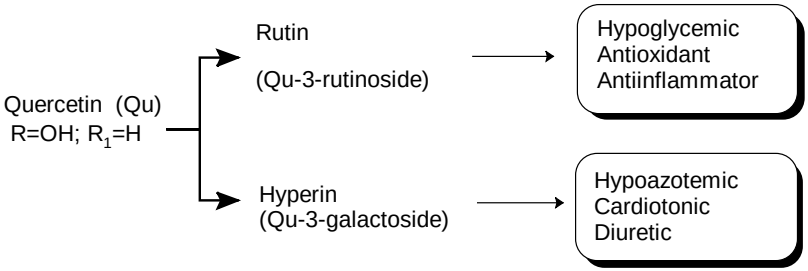
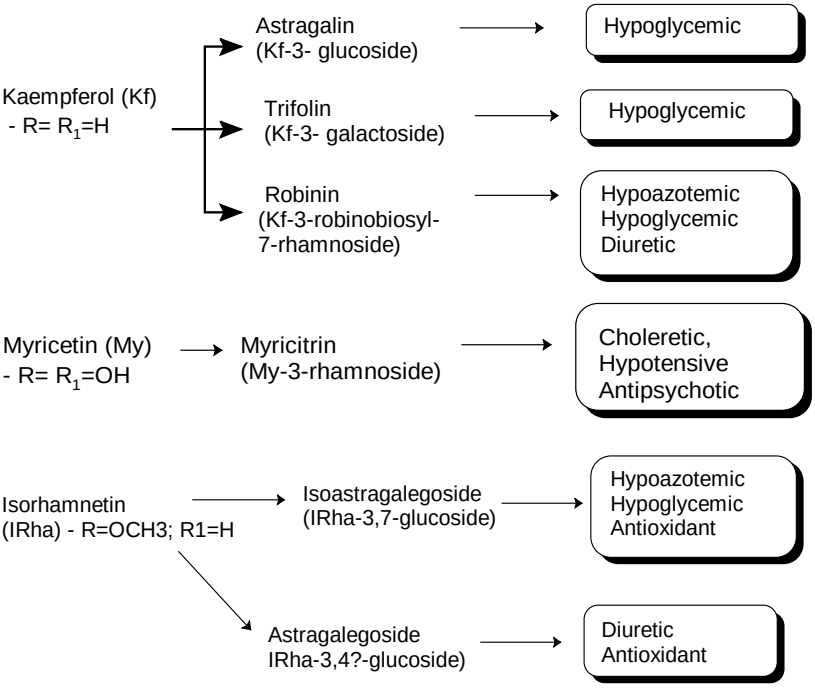
Drug development based on the investigation of chemical composition, biological and pharmacological activity of the compounds of vegetable origin remains a challenge for phytochemists. Oxygen-containing heterocycles that are claimed to have a wide range of therapeutic action occupy a special place among physiologically active substances. Determination of structure-activity relationships of some representatives of these compounds holds particular place.

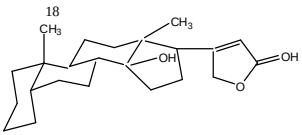
In the Laboratory of Phenolic Compounds of the Institute of Pharmaco-chemistry several heterocyclic compounds with various activities depending on the structure (I-III) have been isolated and identified from different plants of the Georgian flora [1-3].



I

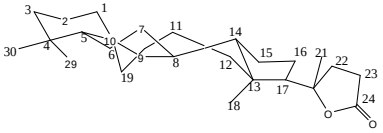






II

Cardiotonic with cumulation



III

Cardiotonic without cumulation

The data confirm the relationship between pharmacological activity and the degree of hydroxylation, nature of carbohydrate moiety and its localization in the molecule of flavonoid. It is likelihood that cumulative properties of cardenolides depend on their conformations.

Plants containing these compounds can be considered as potential raw material for the creation of new drugs.

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OP 7. SYNTHESIS OF NEW MERCAPTOPYRIMIDINES AND THIENOPYRIMIDINES

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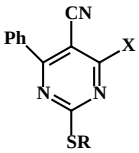
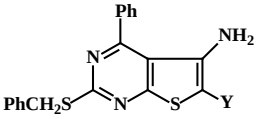
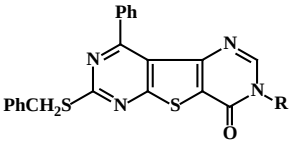
2-Alkylmercapto-4-Chloro-6-phenyl-pyrimidine-5-carbonitrile (1-3) were synthesized and converted into 2-alkylmercapto 4-mercapto -6-phenyl-pyrimidine-5-carbonitriles (4-6). Compound 6 was alylated with halogenated compounds to afford compounds 7-14. The produced compounds underwent Thorpe-Ziegler Cyclization to give thienopyrimidines 15-22. 5-Amino-2-benzylmercapto-4-phenyl-thieno[2,3-d]pyrimidine-6-carboxamide derivatives 17,20-22 underwent cyclization reaction using triethyl orthoformate to afford pyrimidothienopyrimidines 23-26.



1, R = Me, X = Cl
2, R = Et, X = Cl
3, R = CH_2Ph, X = Cl
4, R = Me, X = SH
5, R = Et, X = SH
6, R = CH_2Ph, X = SH
7, R = CH_2Ph, X = SCH_2CO_2Et
8, R = CH_2Ph, X = SC_2COCH_3
9, R = CH_2Ph, X = SCH_2CONH_2
10, R = CH_2Ph, X = SCH_2CN
11, R = CH_2Ph, X = SCH_2COPh
12, R = CH_2Ph, X = $SCH_2CONHPh$
13, R = CH_2Ph, X = $SCH_2CONHC_6H_4CH_3$-p
14, R = CH_2Ph, X = $SCH_2CONHC_6H_4OCH_3$-p



15, Y = CO_2Et
16, Y = $COCH_3$
17, Y = $CONH_2$
18, Y = CN
19, Y = COPh
20, Y = CONHPh
21, Y = $CONHC_6H_4CH_3$-p
22, Y = $CONHC_6H_4OCH_3$-p



23, R = H
24, R = Ph
25, R = $C_6H_4CH_3$-p
26, R = $C_6H_4OCH_3$-p

OP 8. AN ENTRY TO CARBAPENEM ANTIBIOTICS SCAFFOLD *VIA* ASYMMETRIC KINUGASA REACTION

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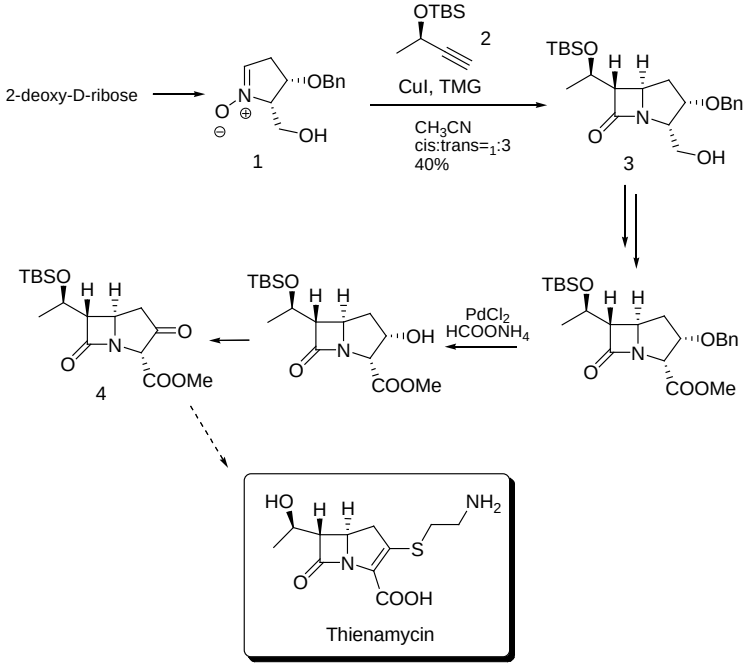
The copper(I) mediated reaction of nitrones with terminal acetylenes, which is known as Kinugasa reaction, represents an interesting method of direct formation of the β-lactam ring. We have shown that the cyclic nitrone **1**, readily available from 2-deoxy-D-ribose, is particularly attractive as a substrate in the synthesis of carbapenem antibiotics.



Reaction of nitrone **1** with acetylene **2** derived from D-lactic acid, in the presence of tetramethylguanidine, provides the adduct **3** having thienamycin

skeleton with the same configuration at three stereogenic centers (the β-lactam fragment and the side chain) as the parent antibiotic. The stereochemical pathway of the reaction depended on the hydroxymethyl group next to the double bond of the nitrone, whereas the trans configuration of hydrogen atoms of the four membered ring was induced by the base used. Subsequent standard transformations provided the ketone **4** which offers an entry to a variety of carbapenems.

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OP 9. COUMARIN DERIVATIVES – SYNTHESIS AND APPLICATIONS

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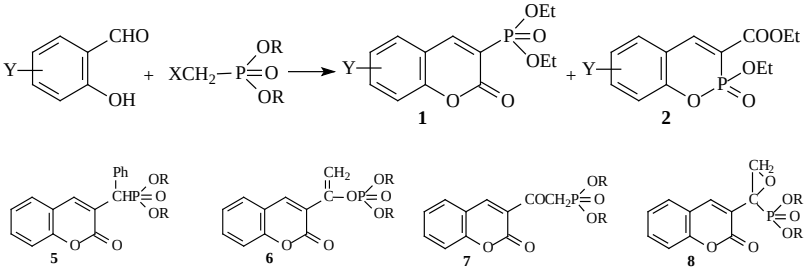
Coumarin derivatives and analogues have had multidisciplinary application in organic synthesis, agrochemistry, medicine, laser technologies, and etc. The object of our investigations is concerned on the chemical behaviors of the coumarins because they are good acceptors in reactions with nucleophillic reagents, they can be used as dienophiles in Diels–Alder reaction, 1,3-dipolar cycloaddition reactions etc. The combination of coumarin structure and phosphono moiety assumes a biological activity, which can be a result of each of both units as well as a blend of both. It is clear that coumarins can be used as ligands in complexes with variety metal ions. Another aspect about coumarins which is of great interest for us is the possible photochemical properties of these compounds.

The phosphorus-containing coumarin derivatives synthesized so far are known to exhibit various types of biological activity; they are used in the medicine, as pesticides etc.

Here we report two main routes for synthesis of phosphorous containing coumarin derivatives:

- Building the coumarin structure - Knoevenagel reaction between different salicylic aldehydes and CH-acidic phosphono containg compounds [1,2]
- Incorporating a phosphono moiety into the coumarin compound by means of Arbuzov reaction [3].



It is considered the chemical behavior of the newly synthesized compounds via different nucleophillic reagents-organometallic compounds, trialkyl phosphites [4], nitromethane [5], tandem reactions of hydration/acylation [6], hydration/ phosphorrylation etc. and the reactions of cycloaddition [7].

Pt(II) complexes of some new phosphorous containing coumarins are synthesized and spectroscopically characterized [8].

Acknowledgments. 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 and by the Project "Beyond Everest" FP7-REGPOT-2011-1 "Development of the research potential of the Faculty of Chemistry, Sofia University, in the area of advanced functional materials for successful participation in world-class research at EU level".

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OP 10. SYNTHETIC INVESTIGATIONS IN THE FIELD OF NON-SYMMETRIC BISINDOLES AND TRIINDOLES

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Among physiologically active natural substances, compounds with two or more indole rings are prevalent, because of which bi- and triindolic substances have been of major interest among researchers. First intentional research was conducted in 1887, when R. Ardehit [1] synthesized bisindole substances. E. Fischer [2] also synthesized bisindolic substances. Symmetric 5,5'-bisindoles were synthesized by H. Plieninger and by us [3-7]. Asymmetric 2,5'- and 3,5'-bisindoles are described [4,7]. Few asymmetric bisindoles are described by Japanese researchers (15 articles). Several interesting bis- and triindoles were extracted from raw materials. Several hundreds of natural alkaloids containing two or more indole rings are described. In 1987, highly active anticancerogen – antibiotic "CC-1065" was extracted, which contained three pyrroloindolic fragments.

We have derived a way of synthesis for such non-condensed systems containing two or more indole rings, where indole fragments are bonded through carbon atoms in pyrrole and benzene rings. The strategy and tactics for synthesis of these oligoindolic heterocyclic systems was selected considering the particularity of the structure of these systems, and is based on the alternating build of indole rings. General method for synthesis of bis- and triindole systems is worked out, where succession of indole rings can be selected by using latent functional groups containing intermediate and main compounds. The main method for realizing offered principles is E. Fischer indolization reaction of arylhydrazones. Initial, intermediate, and main latent functional groups were selected such as isomeric aminoacetophenones, derivatives of acetoacetic ester, also 2-etoxycarbonyl derivatives of, 5-acetylindole, 3-p-nitrophenylindole, and 5-acetyl-3-p-nitrophenylindole, and their analogues containing two indole rings. By alternating conversion acetyl- and nitro- groups of these compounds, objective isomeric triindole system is synthesized. It is displayed that based on this strategy and tactics, it is possible to obtain oligoindolic systems too.

In the report, characteristics, and some of our synthesized bi- and triindoles are discussed.

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OP 11. A NEW REARRANGEMENT DURING THE PREPARATION OF CONDENSED FURO[2,3-*B*]PYRIDINES

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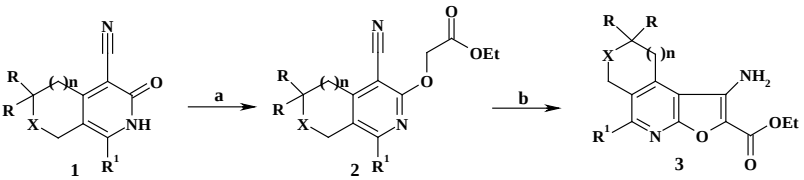
Condensed furo[2,3-*b*]pyridines are relatively unknown in nature and methods of their synthetic preparation are limited [1]. However, there is growing interest in the synthesis of these compounds due to the discovery of several biologically active derivatives [2–5].

As shown in scheme 1 cyclization of compounds **2**, obtained by the reaction of condensed 3-oxopyridines **1** with chloroacetic ester, in the presence of sodium ethoxide gave 1-amino-2-carbethoxyfuro[2,3-*b*]pyridines **3** (Scheme 1). Attempts to convert the ester group in compounds **3** to an amide group by treatment with various amines, in order to obtain convenient synthons for the preparation of new condensed furan[2,3-*b*]pyridine derivatives failed.

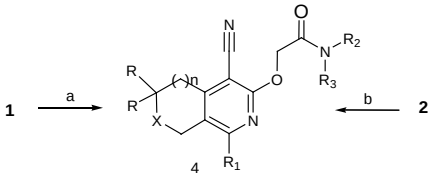


(a) $ClCH_2CO_2Et$; K_2CO_3, DMF, 75-80°C; (b) EtONa, reflux 15 min

X = CH_2, O; R = H, Me; R^1 = alkyl, aryl; n = 0, 1.

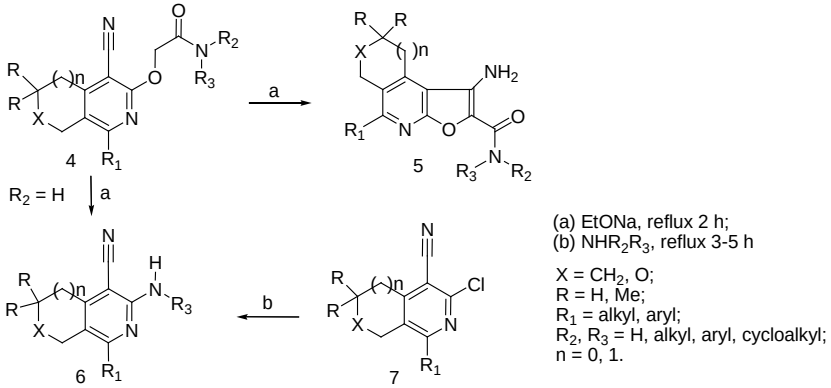
Scheme 1

Therefore, we replaced the ester group before cyclization in compounds **2** by reacting with amines. Using aromatic amines, diethylamine and ammonia it was not possible to obtain the corresponding acetamides **4**. These compounds were prepared by the direct alkylation of 3-oxoderivatives of pyridines **1** with appropriate chloroacetamides (Scheme 2).



Scheme 2.

For the synthesis of the aminoamides **5**, alkoxyacetamides **4** were treated with sodium ethoxide in ethanol. In contrast to alkoxy esters **2**, treatment of alkoxyacetamides **4** with sodium ethoxide followed a different pathway. Thus, the condenced furo[2,3-*b*]pyridines **3** were obtained only when the amine of the alkoxyacetamides **4** was substituted by an aromatic moiety, a cyclic or secondary amine. Reaction of primary amines and ammonia gave unexpected products, uncommon for this type of reaction – products of a rearrangement. The NMR ^{1}H spectra of these compounds were not in accordance with the expected compounds **4** and could be assigned to compounds with general formula **6**. The structure of these compounds was confirmed also by counter-synthesis from appropriate chloro derivatives **7** (Scheme 3).



Scheme 3

It can be argued that during the reaction of compounds **4** with sodium ethoxide the activated CH^- group attacks to the C≡N group with formation

of condenced furan derivatives **5**. At the same time, intramolecular nucleophilic substitution at position 3 of the pyridine by the nitrogen atom of amide takes place as well giving 3-aminopyridine-4-carbonitriles **6**. This process in the literature is known as the Smiles rearrangement [6].

In conclution, for the first time in the series of condensed pyridine during the cyclization of the third cycle – furan, a new realignment was discovered and investigated, which has not only theoretical but also practical importance. Despite the fact that it was not possible to synthesize some condensed furo[2,3-*b*]pyridines **5** due to this rearrangement, it gives the possibility to synthesize 3-aminopyridines **6** the synthesis of which was not successfull from the appropriate chloro derivatives **7**. This rearrangement was subsequently used as a new method for the synthesis of interesting, from the biological point of view, 3-amino derivatives of condensed pyridines **6**.

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OP 12. NUCLEOPHILIC TRANSFORMATIONS OF FIVE-MEMBERED 2,3-DIOXO HETEROCYCLES BY ACTION HETEROCYCLIC ENAMINES

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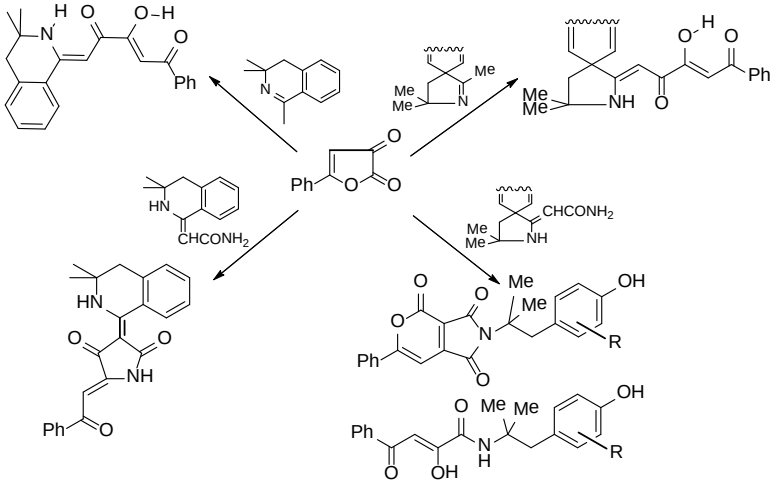
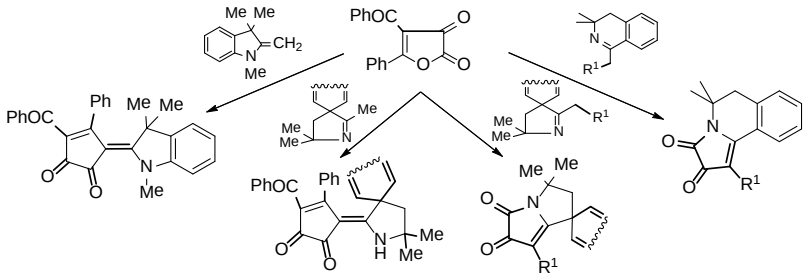
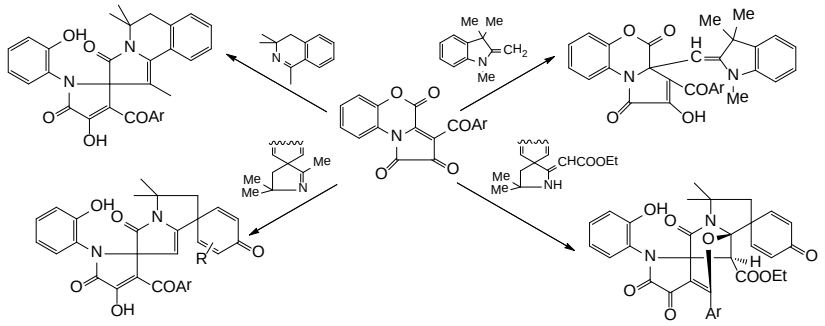
5-Arylfuran-2,3-dione interacted with heterocyclic enamines of isoquinoline or spiropyrroline classes and resulted in the formation of new heterocyclic systems [1,2] and ensemble from two polyfunctional heterocyclic systems [3]:



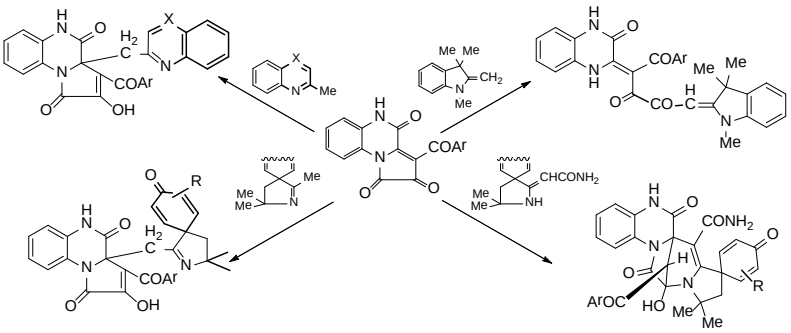
4-Benzoyl-5-phenylfuran-2,3-dione react with heterocyclic enamines to produce analogs of pyrrolizidine alkaloids, substituted pyrrolo[2,1-a]isoquinolines and ensemble from two polyfunctional systems [4]:



Nucleophilic transformations of 3-aroyl-1H-pyrrolo[2,1-c][1,4]benzoxazine-1,2,4-triones by the action of heterocyclic enamines are convenient methods for the synthesis of products of addition, spiro-bis-heterocyclic [5], bis-spiro-heterocyclic [6,7] and bridged systems [8]:



3-Aroylpyrrolo[1,2-*a*]quinoxaline-1,2,4(5*H*)-triones react with series heterocyclic enamines to produce products of addition [9,10] and bridged systems:



This work was supported by RFBR grants № 12-03-00146, 12-03-00696.

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OP 13. CHOLINESTERASE INHIBITION OF SELECTED 4-METHYLCOUMARINS IN COMPARISON TO THEIR ANTIOXIDANT ACTIVITY

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Alzheimer's disease (AD) is a deadly neurodegenerative disease with progressive character and has become a major health problem especially in industrialized countries in which the life standards are higher. This disease is also known to be associated with oxidative stress and metal accumulation in senile plaques formed in the patients [1]. Coumarins occupy an important place in the realm of natural products and synthetic organic chemistry. They have been used as anticoagulants, additives in food and cosmetics, and in the preparations of insecticides. As substitutions can occur at any of the six available sites of their basic molecular moiety, these compounds are extremely variable in structure and activity. This structural diversity leads to coumarins displaying multiple biological properties that promote human health and help reducing the risk of diseases. The medicinal properties of coumarins include inhibitions of platelet aggregation, cytochrome P450, and steroid 5α-reductase, spasmolytic, anticoagulant, antibacterial, anticancer, and anti-HIV activities [2].

Continuing our research on biological activity of 4-methylcoumarins (4-methyl-*2H*-1-benzopyran-2-ones), [3-5], this study presents evaluation acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity of series 4-methylcoumarin derivatives.

The coumarins were synthesized by the well-known Pechmann condensation in quantitative yield. The preparation of acetoxy- and benzoyloxy-derivatives of hydroxy 4-methylcoumarins is based on the methodology used by Fisher. Products were identified by determination of melting points, elemental and spectral analyses [6]. Antioxidant activity was examined using radical scavenging tests (ABTS and DPPH), reducing ability and ORAC assays [4-5]. Cholinesterase inhibitory activities were determined *in vitro* using a modified Ellman´s method [7-8].

All of tested 4-methylcoumarin derivatives showed inhibitory activity against acetylcholinesterase, 1.5 to 3-fold higher than activity against with butyryl-cholinesterase (Table 1).

Table 1. *Anticholinesterase activity of selected 4-methylcoumarins*

Entry	Compound name	AchE (IC_{50} μM)	BchE (IC_{50} μM)
1	7-hydroxy-4-methyl-2*H*-chromen-2-one	423.42 ± 11.34	171.17 ± 4.52
2	7-hydroxy-4,8-dimethyl-2*H*-chromen-2-one	346.98 ± 28.59	176.48 ± 2.34
3	7-hydroxy-4,5-dimethyl-2*H*-chromen-2-one	411.19 ± 28.59	240.40 ± 19.60
4	7,8-dihydroxy-4-methyl-2*H*-chromen-2-one	243.65 ± 6.53	77.64 ± 1.79
5	4-methyl-2-oxo-2*H*-chromen-7-yl acetate	901.44 ± 92.76	871.58 ± 40.13
6	4,8-dimethyl-2-oxo-2*H*-chromen-7-yl acetate	819.29 ± 21.61	621.49 ± 16.40
7	4,5-dimethyl-2-oxo-2*H*-chromen-7-yl acetate	1064.32 ± 55.70	926.34 ± 24.82
8	4-methyl-2-oxo-2*H*-chromene-7,8-diyl diacetate	1403.05 ± 73.43	1270.05 ± 73.98
9	4-methyl-2-oxo-2*H*-chromen-7-yl benzoate	2671.59 ± 71.57	1064.32 ± 55.70
10	4,8-dimethyl-2-oxo-2*H*-chromen-7-yl benzoate	1660.76 ± 76.46	794.89 ± 36.60
11	4,5-dimethyl-2-oxo-2*H*-chromen-7-yl benzoate	3415.35 ± 90.10	1015.71 ± 54.83
12	4-methyl-2-oxo-2*H*-chromene-7,8-diyl benzoate	3067.39 ± 82.17	2157.96 ± 150.04

In general, coumarins containing hydroxyl group showed the highest antioxidant activity in all testing methods, and coumarins containing benzoyloxy group showed the lowest antioxidant activity (Table 2), that was also the case in the testing the anticholinesterase activity. This confirms the statement that electron releasing groups enhance both antioxidant [9] and

anticholinesterase activity [10].

Table 2. Antioxidant activity of selected 4-methylcoumarins.

Entry	DPPH IC_{50} mM	ABTS IC_{50} mM	RP IC_{50} mM	$ORAC_{OH}$ mmol TE/mol	$ORAC_{OOR}$ mmol TE/mol
1	7.45 ± 0.16	0.63 ± 0.03	9.45 ± 0.17	-0.07 ± 0.02	9.16 ± 0.37
2	6.99 ± 0.15	0.54 ± 0.03	9.53 ± 0.16	45.17 ± 0.32	61.34 ± 0.91
3	7.17 ± 0.14	0.64 ± 0.02	10.10 ± 0.18	43.48 ± 0.68	58.92 ± 1.17
4	0.01 ± 0.01	0.003 ± 0.001	0.22 ± 0.03	-2.20 ± 0.09	71.15 ± 1.54
5	3.77 ± 0.11	0.26 ± 0.01	7.46 ± 0.16	7.66 ± 0.72	14.07 ± 0.41
6	63.50 ± 0.13	2.30 ± 0.09	84.30 ± 0.38	1.45 ± 0.21	12.78 ± 0.82
7	76.20 ± 0.43	3.49 ± 0.06	75.10 ± 0.19	3.79 ± 0.18	14.03 ± 0.46
8	1.14 ± 0.10	0.06 ± 0.00	2.29 ± 0.08	-0.69 ± 0.11	21.28 ± 0.25
9	32.30 ± 0.27	2.45 ± 0.06	61.10 ± 0.35	23.69 ± 0.50	47.25 ± 0.77
10	37.60 ± 0.37	2.68 ± 0.07	66.60 ± 0.43	2.28 ± 0.17	9.18 ± 0.24
11	48.50 ± 0.43	3.70 ± 0.09	48.50 ± 0.72	6.57 ± 0.32	15.94 ± 0.26
12	21.30 ± 0.43	1.74 ± 0.16	25.10 ± 0.25	44.31 ± 0.72	68.39 ± 1.02

This study indicates that 4-methylcoumarins are capable of inhibiting AchE and BchE in a similar manner as they are capable to scavenge reactive oxygen species and reduce transition metals. Thus, 4-methylcoumarins can be considered as a new class of compounds that can be potential leads in the search of new therapies for curing Alzheimer's disease, and since the inhibition of AchE and BchE is relatively low, this study have spurred the designing and synthesis of novel coumarin derivatives as potent cholinesterase inhibitors.

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OP 14. BRØNSTED ACIDIC HYDROGENSULFATE IONIC LIQUID IMMOBILIZED SBA-15 AS A GREEN, METAL-FREE AND RECYCLABLE CATALYST FOR TETRAHYDROCHROMENES AND HEXAHYDROQUINOLINE CARBOXYLATES SCAFFOLDS

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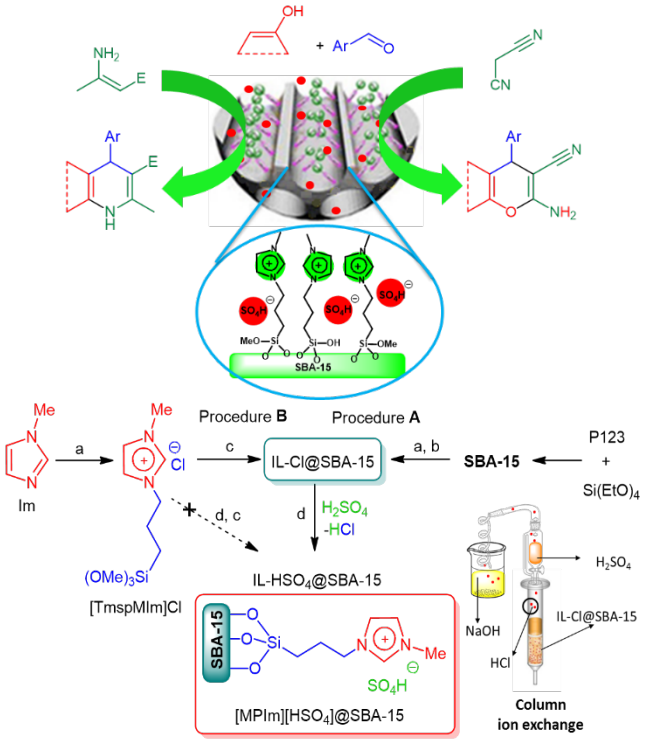
Previously, we developed synthetic methods for the synthesis of biologically interesting organic heterocyclic molecules [1]. The challenge in this field, was the development of efficient green methods. Moreover, the synthesis of these molecules has usually been carried out in hazardous polar solvents leading to complex isolation and recovery [1-3]. Recently, we synthesized a series of organic-inorganic hybrid heterogeneous catalysts, which displayed comparable activity and selectivity to those of homogenous system in a wide of water medium organic reactions [2-3]. Encouraged by these successful efforts and aiming to develop a stable and highly active solid porous H^+-catalyst in water, herein we report the synthesis of [MPIm][HSO_4]@SBA-15 catalysts. The IL@SBA-15 showed the highest catalytic reactivity and selectivity in water-medium multicomponent coupling procedure for synthesis of tetrahydrochromenes and hexahydroquinoline carboxylates as a model organic reaction (Fig. 1). As shown in Fig. 1, based on procedure **A** and **B**, in a typical procedures we achieved [MPIm][HSO4]@SBA-15. Finally, the [MPIm]Cl@SBA-15 (IL-Cl@SBA-15) solid product was characterized by FT-IR, SEM, TEM and XRD analysis.

As showed in Scheme 1, the reactions with 2 mol% of the catalyst proved optimum in terms of the yield. We used water as the solvent because it is inexpensive, non-toxic, and environmentally benign, also, the highest dispersion of IL@SBA-15 was achieved in water. With these results in hand and to demonstrate the diversity of the supported ionic liquids of halogen-free imidazolium hydrogensulfate, and to expand the scope of the process, the optimized conditions were applied to a series of substrates **1**, and **2** as shown in Scheme 1.

We next explored the scope of our method in the synthesis of polyhydroquinolines **5**, via the condensation of dimedone, an aldehyde and enaminone **4**. In fact, encouraged by this promising result, we proceeded to further study the catalytic performance of **5** in the one-pot preparation of polyhydroquinolines. Various types of aromatic aldehydes with electron-donating groups, electron-withdrawing groups and even *ortho*-substituted aldehydes were cleanly and rapidly converted to the corresponding tetrahydro-4*H*-chromenes **3** polyhydroquinolines **5** in good to excellent yields.



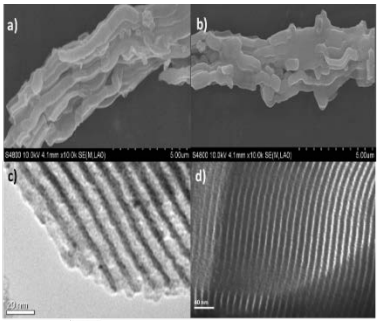
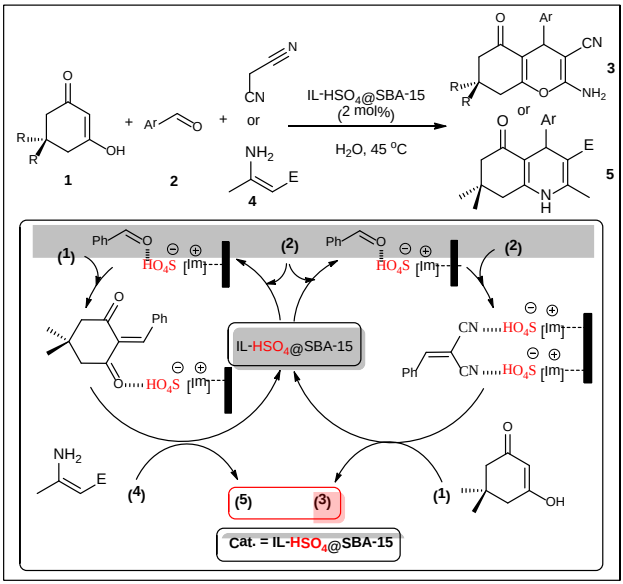


Figure 1. *Synthesis, characterization and application of the IL-HSO$_4$@SBA-15.*



Scheme 1. *The use of IL-HSO$_4$@SBA-15 for the synthesis of 3 and 5.*

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OP 15. DENSITY FUNCTIONAL THEORY (DFT), STRUCTURAL PROPERTIES, NATURAL BAND ORBITAL AND ENERGY STUDIES OF HETEROCYCLIC COMPOUND

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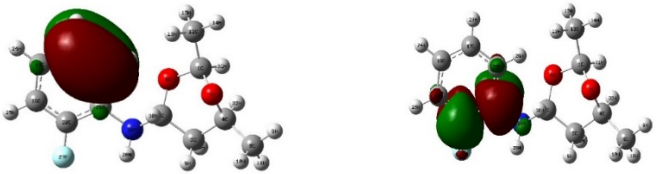
A major objective of the present course of discourses is the explanation of the reactivity of heteroaromatic compounds. Heteroaromatic compounds with 5- and 6-membered rings are best deliberated as modified benzenes. There are two quite separate ways in which benzene can be modified by the substitution of a heteroatom for one or more of the carbon atoms of the ring. The number of heteroatoms affects mainly the magnetic properties.

Dioxan is a general solvent that is often used in place of glacial acetic acid when mixtures of substances are to be counted. It is also used [1] as a stabilizer in chlorinated solvents and in many organic syntheses. There are only a very few [2–4] reports in the literature on oxidation of dioxan with other oxidants dioxan molecules, which had been used for crystallization, engaged the pocket in a similar way to that of the two leucine side chains in the N-terminal arm bound structure. Dioxan is used as a solvent in chemical synthesis, as a fluid for scintillation calculating, and as a dehydrating agent in the research of tissue sections for histology. 1,3-dioxans are cyclic acetals with a six-membered ring. The chemistry of 1,3-dioxans is closely related to the protection of functional groups, therefore , the central application of 1,3 dioxans in organic synthesis is the security of ether carbonyl compounds. Many reviews dealing with the research and hydrolysis of 1,3-dioxans or related cyclic acetals can be establish in works. [5-8] Since the first synthesis of a 1,3 dioxan for the protection of 4- and 6-hydroxy groups in pyranose carbohydrates, [9] the protection of carbonyl compounds or 1,3-diols as 1,3-dioxans has become a standard transformation in organic synthesis.

The studying of the structures and properties of the compound is interested. During this study, we report the optimized geometries, assignments and electronic structure calculations for the compound. [10]

In this paper, *N-(2-Fluorophenyl)-2,6-dimethyl-1,3-dioxan-4-amine* ($C_{12}H_{16}FNO_2$) optimized geometries and frequencies of the stationary point

and energies in the ground state using DFT (B3LYP) methods with 6-311G^{++}(d,p) basis set. The calculated HOMO and LUMO energies also confirmed that the charge transfer occurred within the molecule. Bond length and bond angles values for $C_{12}H_{16}FNO_2$ were calculated by using B3LYP/ 6-311G^{++}(d,p).



E LUMO = 0.01190 a.u ΔE = 0.25119 a.u E HOMO = -0.23929 a.u

Figure 1. *The atomic orbital compositions of the frontier molecular orbital for N-(2-Fluorophenyl)-2,6-dimethyl-1,3-dioxan-4-amine was obtained equivalent by DFT (B3LYP)/6-311G^{++}(d,p).*

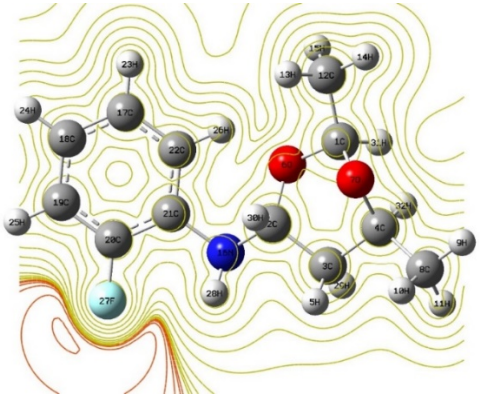


Figure 2. *Contour maps of electron density for N-(2-Fluorophenyl)-2,6-dimethyl-1,3-dioxan-4-amine in the planes of the molecules. Electron density was calculated at the DFT (B3LYP)/6-311G^{++}(d,p).*

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OP 16. SYNTHESIS OF NITROPYRIDINES BY THREE COMPONENT RING TRANSFORMATION OF DINITROPYRIDONE

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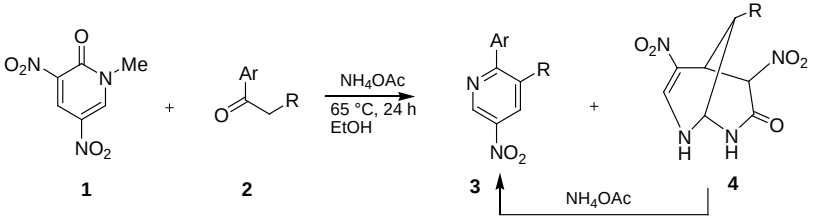
Arylated nitropyridines are widely used for synthesis of biologically active compounds such as Wnt inhibitors [1], inhibitors of stearoyl - CoA desaturase [2], beterial RAN polymerase inhibitors [3], drugs for eyes disease and Paget disease [4] and so on. In addition, the nitropyridines substituted with electron donating group exhibit push - pull property of electrons [5]. Although Suzuki reaction and Kumada - Tamao reaction are commonly used for synthesis of biaryl frameworks, it suffers from poor availability of functionalized halopyridines and coupling partners [6]. Moreover, it is difficult to prepare arylated pyridines substituted with electron - deficient group by this method. Meanwhile, ring transformation is known to be a powerful protocol for synthesis of functionalized heterocyclic compounds, which are not easily prepared by alternative methods. In this work, nitropyridines **3** were synthesized efficiently by three component ring transformation of dinitropyridone **1** with ketones **2** in the presence of ammonium acetate, in which dinitropyridone **1** serves as synthetic equivalent of unstable nitromaloaldehyde [7].



The reaction of 1 with acetonephenone 2a (Ar=Ph, R = H) was conducted at 65 °C for 24 h. In this reaction, 2,8-diazabicyclo[3.3.1]none-3-ene derivative 4 was also isolated, which is a result of insertion of ketone and a nitrogen atom between the 1- and 2-positions of dinitropyridone 1. It is noteworthy that the ratio of 3a and by - product 4a was affected by amount of ammonium acetate as shown in the table. While 2a afforded nitropyridine 3a in

19% yield together with by - product **4a** in 61% yield when using 3 equiv. of ammonium acetate, the yield of **3a** increased up to 79% and trace amount of the **4a** was obtained when 15 equiv. of ammonium acetate was used (Entries 1-4). When the reaction time was shortened, the ratio of **3a/4a** decreased, although the total yields were almost similar (Entries 4-6). These results indicate that bicyclic product **4a** is a kinetically controlled product, and is converted into a thermodynamic product, nitropyridine **3**, under heating conditions in the presence of ammonium acetate.

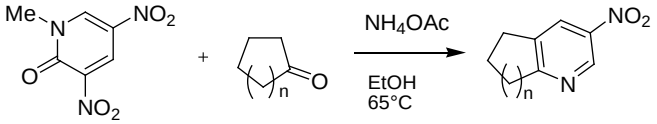
Entry	NH_4OAc	Time	Yield [%]			Ratio of
	[equiv.]	[h]	**3a**	**4a**	**3a+4a**	**3a/4a**
1	3	24	19	61	80	24/76
2	5	24	43	46	89	48/52
3	10	24	64	25	89	72/28
4	15	24	79	0	79	100/0
5	15	16	75	8	83	90/10
6	15	8	61	14	75	81/19
7[a]	5	7	92	5	97	95/5
8[a]	15	5	90	0	90	100/0

[a]: microwave heating was used

Other substituted acetophenones were then employed. The reaction of **1** with electron - rich ketones **2b** (Ar=$MeOC_6H_4$, $MeOC_6H_4$, MeC_6H_4, ClC_6H_4, R=H) using 15 equiv. of ammonium acetate, revealed high reactivity to afford the corresponding nitropyridines **3** in high yields (84−99%). The present reaction was then applied to the heterocyclic ketone **2** (Ar = pyridyl, furyl, thieyl, pyrrolyl; R=H) to afford biheteroaryl compounds **3** in good to excellent yields. It was also possible to prepare trisubstituted nitropyridines **3** (Ar=Ph, R=Me, Pr) by the reaction of **1** with propiophenone and valerophenone, respectively.

The substrate scope was then extended to a series of cyclic ketones **5** to afford cycloalka[*b*]pyridines **6** efficiently [9]. Furthermore, a double bond

can be easily introduced into the product **6** by changing the cycloalkanone into a cycloalkenone.



This method requires only simple manipulations and mild comditions during reaction and work - up. Hence, the present ring transformation provides a new methodology for the synthesis of various kinds of the nitropyridines **3**, which have either an electron - rich or an electron - poor (hetero)aryl group on demand and are not easily prepared by alternative methods.

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OP 17. ONE-POT SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NOVEL POLYHYDOXYLATED 3-ARYLCOUMARINS

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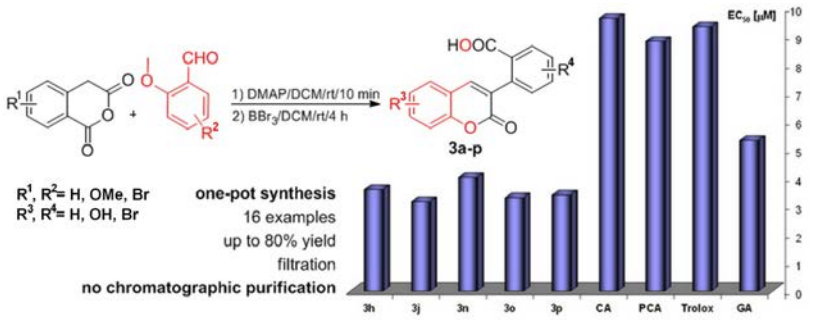
An unexpected domino rearrangement brought about the development of a novel one-pot procedure for synthesis of coumarins [1]. This protocol allowed the gram-scale synthesis of a variety of polyhydroxylated derivatives **3a-p**, from readily available starting materials at a low cost. Based on two proven intermediates, a probable mechanism consisting of five sequential steps was deduced. Compared to the common methods, used for the synthesis of coumarins, the proposed herein possesses great advantages, such as mild conditions, good yields for short reaction time, simple work-up procedure and easy isolation of the final products. The structure of the newly synthesized compounds **3a-p** was established by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS and HRMS) and their antioxidant and radical scavenging activities were evaluated *in vitro* against HO$^\bullet$, $O_2^\bullet$, 1,1-diphenyl-2-picrylhydrazyl (DPPH$^\bullet$) free radicals and Folin-Ciocalteu reagent (FCR). The results obtained showed that compounds **3h**, **3o** and **3p**, possessing two or four phenolic hydroxyl groups in their structure, exhibit higher radical scavenging activities than well-known antioxidants such as trolox, protocatechuic acid, caffeic acid and gallic acid, which in turn allows promising *in vivo* antioxidant properties of these compounds to be expected.



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OP 18. ENCAPSULATION OF ANTI-ARRHYTHMIC HETEROCYCLIC COMPOUNDS INTO NANOLIPOSOMES FOR ORAL DELIVERY

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Novel natural anti-arrhythmic component Vingerbine has been obtained at the I. Kutateladze Pharmacochemistry Institute (Tbilisi, Georgia) from the plant Vinca herbaceae Waldst et Kit distributed in Georgia [1]. The active substance represents the sum of four heterocyclic indoline alkaloids, two of which have ability to induce P-gp over expression [2]. The pharmacological studies showed that the anti-arrhythmic efficacy of Vingerbine is generated by specific activity of each compounds and therefore high intracellular accumulation of these alkaloids will results maximum therapeutic effect [3]. Lipid-based drug delivery systems are expected as promising oral carriers because of their potential to increase the solubility and improve oral bioavailability of poorly water-soluble and/or lipophilic drugs. The aim of the present study was to formulate and characterize stable, controlled release liposomal vesicles loaded with hydrophobic crude alkaloids.

Vinca alkaloids are notoriously difficult to formulate stably in liposomes [4]. Various liposomal batches were prepared using different active loading techniques. The influence of different formulation variables such as loading methodology, type of main lipid, addition of PEGylated lipid and cholesterol percentage was evaluated to achieve required entrapment efficiency, in vitro release behavior and stability. The best Vingerbine loaded liposomes were composed from native tetraether lipids extracted from archaea bacteria (TEL), dipalmitoylphosphatidyl-choline (DPPC) and dipalmitoyl phosphatidyl-ethanolamine with covalently linked poly (ethylene glycol) molecular mass 2000 (DPPE-MPEG2000) at the mole ratios: TEL: DPPC : DPPE-MPEG2000. The mean size of vesicles obtained was in range of 200 - 250 nm with narrow polydispersity index lower than 0.4; zeta potential values were around -40 mV, providing good physical stability of liposomal formulations; Atomic force microscopy (AFM) studies confirmed homogeneous distribution of particles

and spherical shape with smooth surface. The drug encapsulation efficiency was more than 65%. In vitro drug release study showed sustained drug release behaviour over a period of 48 hr at 37°C.

Conclusion: Our results demonstrate that a highly active, stable and long-circulating liposomal Vingerbine can be prepared. Liposomal delivery of antiarrhythmic heterocyclic vinca alkaloids may offer an effective new approach in the treatment of cardiac diseases.

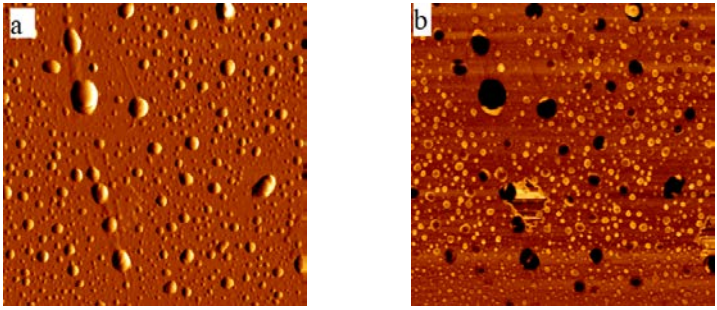

Figure. *AFM images of Vingerbine PEGylated nanoliposomal form: a - Amplitude image, b - Phase image.*

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OP 19. SYNTHESIS AND REACTIONS OF SOME NOVEL SELENOLOPYRAZOLE COMPOUNDS

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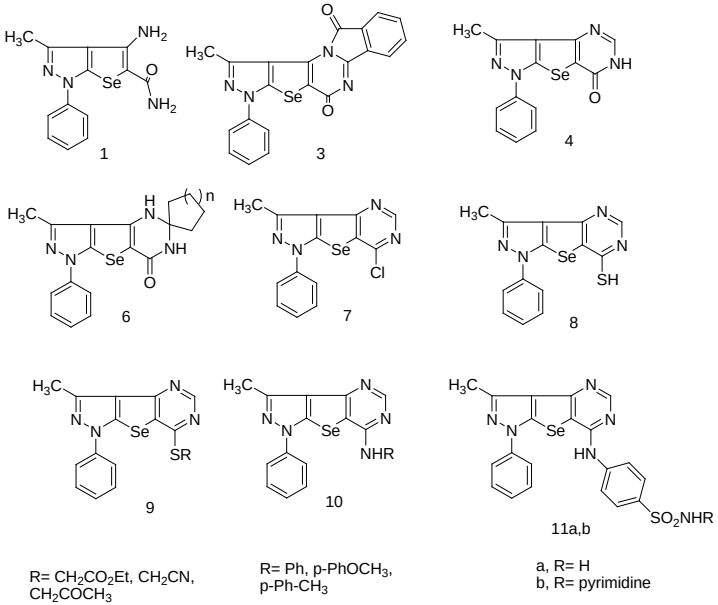
Amino selenolopyrazolecarboxamide 1 underwent various condensation reactions with phthalicanhydride, triethylorthoformate , nitrous acid and cycloalkanes to afford compounds **2-6** respectively. Chlorination and thionation of pyrimido compound 4 afforded compounds 7 and 8 respectively. Also compound 8 was prepared by heating of chloropyrimidine derivative 7 with thiourea in ethanol as a solvent. Treatment of pyrimidine thione derivative **8** with alkylhalides gave alkylthiopyrimidine derivative 9. Chloropyrimidine derivative **7** underwent various reactions with various amines, sulfanilamide and sulfadiazine to give **10** ,**11a** ,and **11b** respectively. All synthesized compounds were elucidated using ^{1}H-NMR , ^{13}C-NMR , MS , IR and elemental analysis.



OP 20. RECENT DEVELOPMENTS OF THE CHEMISTRY OF 1,2,4-BENZOTRIAZINYL RADICALS

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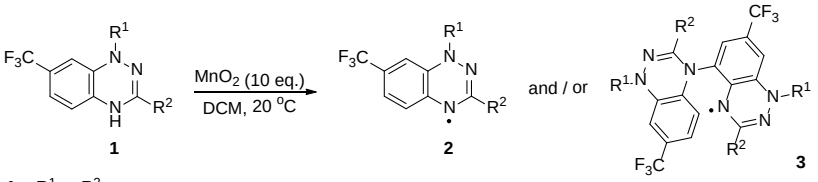
1,2,4-Benzotriazinyl radicals, commonly known as Blatter radicals, [1] have attracted much attention recently, mostly because of their air stability and their magnetic properties [2]. In order to study substituent effects on this family of radicals, we developed a general and accessible synthetic route that afforded a wide variety of these radicals [3]. During this study, we looked at the oxidation of 1,3-di(pyrid-2-yl)-7-(trifluoromethyl)-1,4-dihydro-1,2,4-benzotriazine **1a** using MnO_2 in an attempt to convert it into the radical **2a** but surprisingly X-ray crystallography revealed we had actually prepared 1,1',3,3'-tetra(pyrid-2-yl)-7,7'-bis(trifluoro-methyl)-1',4'-dihydro-1*H*-4,5'-bi-1,2,4-benzotriazinyl radical **3a**, the first example of an oxidization mediated dimerized Blatter radical.



1a: $R^1 = R^2 =$ Pyrid-1-yl
1b: $R^1 =$ Ph, $R^2 =$ Pyrid-1-yl
1c: $R^1 =$ Pyrid-1-yl, $R^2 =$ Ph

This oxidative dimerization was investigated further to understand both the scope and the reaction mechanism. A variety of oxidants and Blatter radicals have now been screened, and the dimer species characterized allowing for a comparison of their properties with their monomeric species.

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OP 21. DESIGNING OF UGI/POST-TRANSFORMATION REACTIONS FOR THE SYNTHESIS OF FUNCTIONALIZED HETEROCYCLIC COMPOUNDS

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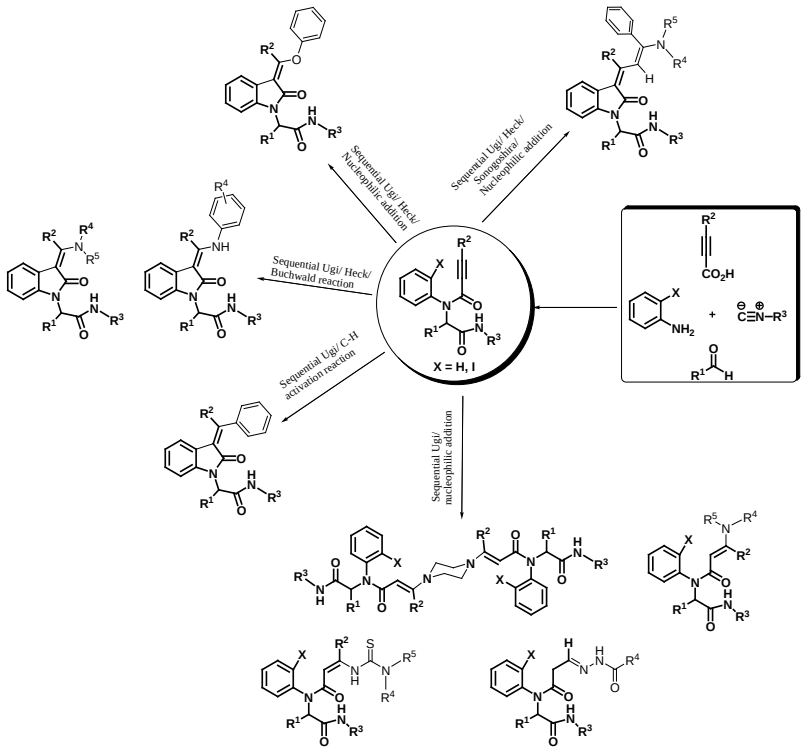
Synthesis of molecules with high diversity and complexity using readily available starting materials is an interesting approach in combinatorial chemistry and drug discovery. In this regard, combining the multicomponent reactions (MCRs) with post MCR transformation has been used as an efficient method for the synthesis of highly functionalized compounds [1]. Among these sequential reactions, Ugi-4CR/post transformation is the most powerful approach for the synthesis of polyfunctional compounds [2].

N-substituted-2-alkynamides have proved to be valuable building blocks in organic synthesis [3]. They have been involved in several types of important organic reactions including Heck-carbocyclization, and intramolecular Diels-Alder reactions [4]. *N*-Substituted 2-Alkynamides could be used as efficient starting materials for the synthesis of 3-arylidene-2-oxindoles and *α*-butyrolactam with different biological activities [5], and also for the synthesis of opthoelectronic polymers [6].

Due to importance of these compounds, some functionalized *N*-substituted-2-alkynamides were synthesized through Ugi-4CR in our research group. These functionalized *N*-substituted-2-alkynamides were synthesized through reaction ofpropiolic acids, benzaldehydes, anilines and also isocyanides. Recently, these compounds were used as suitable starting materials for further post-transformation reactions such as nucleophilic addition or cyclization reactions. Due to existence of functional group in the structure of *N*-substituted-2-alkynamides, some interested reactions which were done with compounds were categorized as follows:

a. Desinging five- and six-components reactions via carrying out the sequential Ugi/nucleophilic reaction to access functionalized enaminones, dithiocarbamates and also ethers [7].



b. Synthesis of 3-arylidene-2-oxindoles through designing of sequential one-pot six-component reaction via Ugi/Heck carbocyclization/ Sonogashira/nucleophilic addition; Ugi/C-H activation; Ugi-carbopalladative cyclizetion–Buchwald reaction sequences [8].

The results of our studies concerning the designing of novel sequential reaction, stereoselectivity, distinguished points about these reactions and the details about the mechanism of the reactions will be reported in the conference.

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OP 22. *N*-ARYLATION OF PROTECTED AZAMACROCYCLES

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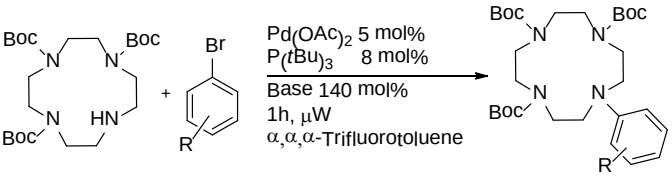
Owing to their peculiar complexation properties, azamacrocycles became a coveted compound class for a variety of uses. The past decade their applicability as scaffolds for magnetic resonance imaging (MRI) contrast agents, as tagging systems for protein labelling, and as chemical probes for selective detection of transition metals was demonstrated.

Table 1. *Buchwald-Hartwig coupling of N-tri-Boc cyclen with functionalized aryl bromides*



1 2 3

Entry	R[a]	Base[b]	Temp/^{0}C	Yield[%][c]
1	*p*-Me	A	100	85
2	*p*-OMe	A	120	83
3	*p*-NMe_2	A	120	72
4	*p*-NMe_2	B	120	75
5	*p*-SMe	A	120	82
6	*p*-COOMe	B	100	80
7	*p*-CHO	B	100	70
8	*p*-CF_3	A	80	84
9	*m*-OMe	B	100	45
10	*m*-COOMe	B	100	40
11	2-pyridyl	A	100	40
12	6-(2-methylquinolyl)	B	100	60

[a] *p* denotes relative para, whereas *m* relative meta position of bromine and the R substituent. [b] A: sodium tert-butoxide, B: sodium 2,4,6-tri-tert-butylphenoxide. [c] Isolated yield, following chromatographic purification.

Whereas procedures for efficient cross coupling of mononitrogenated macrocycles have been developed [1], efficient *N*-arylation of polynitrogenated analogues has not yet been achieved. Common features of the few available preparation methods of *N*-arylated azamacrocycles [2] are long reaction times (days), narrow scope and poor-to-moderate isolated yields.

The first rapid, microwave assisted Buchwald-Hartwig cross coupling protocol of azamacrocycles with aryl bromides will be reported [3], demonstrating its scope by efficient monofunctionalization of a range of polynitrogenated skeletons with substituted aryl bromides of varying electronic properties. The compatibility of the reaction conditions with common nitrogen protecting groups will be discussed, along with the influence of steric and electronic factors on reactivity.

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OP 23. BENZIMIDAZOLES: SYNTHESIS, BIOLOGICAL ACTIVITY AND PERSPECTIVES OF ITS USE

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Antimicrobial drugs or chemicals are the substances used to kill or slow down the growth of microorganisms. They include antibiotics, antiviral, antifungal and anti-parasitic agents.

The biological activity of the compounds depends on structure of molecule [1]. It has been shown that heterocyclic compounds are more biological active as compared to others [2]. Benzimidazole is one such compound, which attracts attention of synthetic chemists for the synthesis of antimicrobial drugs [3]. The benzimidazoles contain a phenyl ring fused with imidazole ring [4]. This compound has various applications in a number of fields. Benzimidazole contain nucleus plays an important role in various medicines. This stimulated great interest in the structural study of Benzimidazole and related compounds and much success was made in pharmaceutical industry. Some commercially used Benzimidazole based drugs are: Azomycin, Metronidazole, Benomyl, Clemizole, Enviroxime, Irtemazole, Astemizole, Omeprazole, Pentoprazole, Thiabendazole and Nocodazole [5]. It shows a wide spectrum of biological and pharmacological properties such as antifungal [6], antimicrobial [7], anthelmintic [8, 9], antiviral [10,11], topoisomerase inhibition [12] and anticancer activities [13]. Some of their derivatives are marketed as antifungal drug (Carbendazim) [14], anthelmintic drug (Mebendazole and Thiabendazole) [15], antipsychotic drug (Pimozide) [16] and antiulcer agent (Omeprazole) [17]. Anthelmintic drugs pharmacological effectiveness can be explained by influence of the carbamate group, which imparts lipophilicity, resistance to the fermentative hydrolysis to the compound and

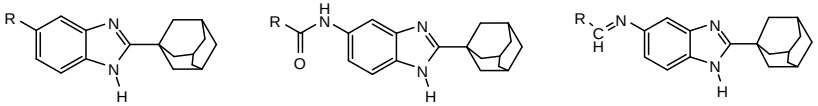
maintains its prolonged action. On the other hand, a number of compounds of this group have revealed their teratogenic, embriotoxity and other side effects [18].

It is expected that if the carbamate group (-NHCOOR) is changed by lipophilic, hydrophobic, membranotropic and immunotropic adamanatane pharmacophore will eliminate these negative effects and improve biological characteristics of the molecule. Hence the search for novel biologically active compounds through the synthesis of adamantane-containing benzimidazoles and a study of their physicochemical and biological properties is a very timely scientific task.

Thus, we may state that synthesis and analysis of new derivatives of adamantane containing benzimidazoles for creation of prophylactic and therapeutic medications that meet the modern requests is perspective and actual.

For this aim the synthesis and reactions of 5(6)-(1–adamantyl)benzimidazoles were studied and previously reported [19, 20]. The following work are connected to the syntheses and research of new 2-(1-adamantyl)benzimidazoles. For this goal of some adamantane ring containing benzimidazole derivatives (a, b, c) were synthesized by us [21–23].

a b c



The structure of the obtained compounds ware established by IR, UV, NMR and Mass-spectra date.

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OP 24. A CONVENIENT SYNTHESIS, REACTIONS AND ANTI-MICROBIAL ACTIVITY OF SOME NOVEL SELENOLO[2,3-C]PYRAZOLE COMPOUNDS

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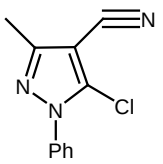
Interest in pyrazole derivatives is indicated by the great number of reports dealing with their numerous biological activities. They have been reported to possess antitumor [1–3], anti-inflammatory [4,5], and ulcerogenic [6] activities. By literature survey about selenolopyrazole we found that single paper is talking about the synthesis of the selenolopyrazole [7], which uses selenophene ring and then builds pyrazole nucleus on it. The difficulty of synthesis of likes this is to displace the chlorine with selenium at position 5 in the pyrazole nucleus. After several attempts we displaced the chlorine with selenium in the presence of sodium borohydride and using the product *in situ* without isolation to be subjected in the next reaction. In the light of the above observations, we reported novel facile synthesis method of selenolo[2,3-c]pyrazole compounds and study of their anti-bacterial and anti-fungal activities. Reaction of 5-chloro-3-methyl-1-phenylpyrazole-4-carbonitrile **3** which was prepared according to literature procedure [8] with selenium in presence of sodium borohydride and chloroacetamide afforded selanylactamide **5**, which underwent Thorpe-Ziegler cycliztion upon heating with sodium ethoxide gave the novel synthesized 4-amino-3-methyl-1-phenyl-1H-selenolo[2,3-c]pyrazole-5-carboxamide compound **(6).** The latter compound was used as a versatile precursor for synthesis of other heterocyclic rings namely: pyrimidine, imidazopyrimidine and thiadiazinopyrimidine fused to selenolo[2,3-c]pyrazole moiety. The newly synthesized compounds and their derivatives were characterized by elemental analysis and spectroscopy (IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra). Furthermore, some of these synthesized compounds were screened against various pathogenic bacterial and fungal strains. The results demonstrate that most of the synthesized compounds posses a significant antibacterial activity against gram-positive and gram-negative bacteria. In addition, most of these compounds showed a remarkable anti-fungal activity.



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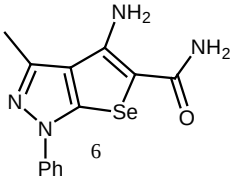

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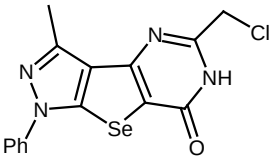

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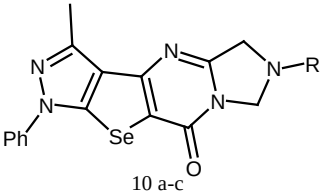
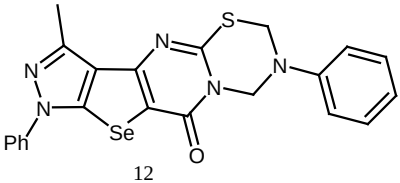


10 a-c



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OP 25. NEW ROUTE FOR SYNTHESIS OF CYCLIC KETENE DITHIOACETALS

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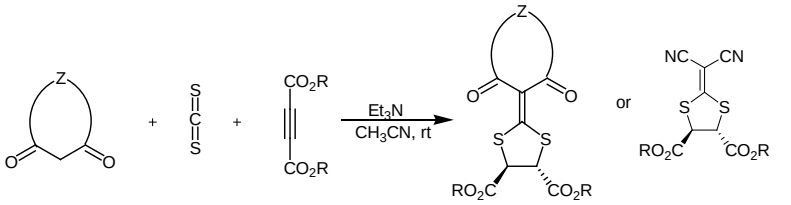
Using reactive intermediates for the synthesis of organic compounds is regarded as one of the most interesting and important strategies in organic synthesis. The chemistry of organosulfur compounds have been attracting considerably attention due to their valuable biological activities and using them as intermediates [1,2]. Ketene dithioacetals have been considered to be highly versatile starting materials for the preparation of several alicyclic, aromatic, and heterocyclic compounds, such as pyridines, pyrimidines, thiophenes, pyrazoles, etc [3]. Among ketene dithioacetals, 1,3-dithietane, 1,3-dithiolane, and 1,3-dithiane are important structure frameworks which exhibit diverse biological activities and pharmacological properties [4]. In continuation of our recent interests on the multicomponent reactions [5-7], in this study, synthesis of novel ketene dithioacetals have been presented by one-pot reaction condensation of active methylene compounds with carbon disulfide in the presence of dialkyl acetylenedicarboxylates or alkyl acetylenecarboxylate.



1 **3** **4** **5**

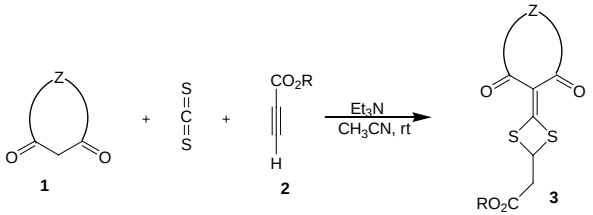
or **2 =** Malononitrile **11 Examples** (Enantiomers of trans products)

Scheme 1.

Diastereoselective condensation reaction of active methylene compounds with carbon disulfide in the presence of dialkyl acetylenedicarboxylates lead to produce a series of novel ketene dithioacetals (Scheme 1). This reaction occurred *via* a Michael addition reaction and then followed by *5-endo-trig*

intramolecular cyclization. Unambiguous evidence for the structure and stereochemistry of these products was obtainned from a single crystal X-ray analysis (one product) along with spectroscopic data of products.

The second reaction was performed through condensation reaction of active methylene compounds with carbon disulfide in the presence of alkyl acetylenecarboxylate (Scheme 2). Due to the acidity of our C-H acids, we used Et_3N as a base and allowed the reaction to take place in MeCN as a polar solvent. We proposed that this reaction proceeds *via* a regioselctive manner and provides novel relative ketene dithioacetals products in good yields. This reaction is easy, efficient and mild three-component reaction for obtaining novel 1,3-dithietane derivatives which was established for the first time. Mechanistically, double conjugate addition of geminal dithiolates to alkyl acetylenecarboxylates takes place. The structure of the all ketene dithioacetals were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra and elemental analysis.



Scheme 2.

We have successfully presented synthesis of new ketene dithioacetals which were prepared by the reaction of active methylene compounds and CS_2 in the presence of alkyl or dialkyl acetylenedicarboxylate. These reactions proceed *via* a regioselctive or diastereoselective manner and provides products in good yields.

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OP 26. THIOUREAS AS VERSATILE PRECURSORS FOR SYNTHESIS OF IMPORTANT HETEROCYCLICS: BENZOTHIAZOLYL SUBSTITUTED IMINOTHIAZOLIDINONES AND BENZAMIDO-OXOTHIAZOLIDINES

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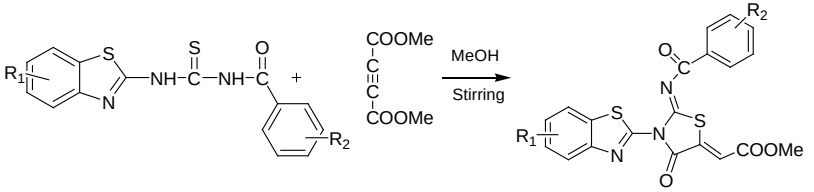
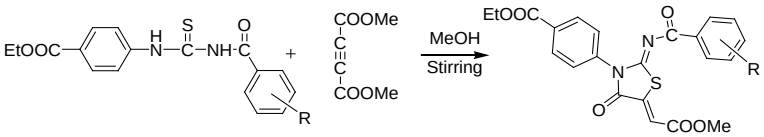
Benzothiazolyl thioureas and ester substituted thiourea precursors were synthesized by treating them with substituted aroyl isothiocyanates, generated *in situ* by reaction of potassium thiocyanate in acetone with variously substituted aroyl chlorides [1,2]. The synthesized compounds were tested *in vitro* for their antimicrobial activity against Gram negative and Gram positive bacteria and were found to exhibit moderate to potent activity as compared to the standard drugs [3].

1-[Benzo[d]thiazol-2-yl)-3-(substituted] thioureas and ethyl 4-(3-benzoyl-thiour-eido) benzoates are exceptionally versatile building blocks towards the synthesis of wide variety of heterocyclic compounds, which also possess extensive range of bioactivities. These thioureas were converted into novel five membered heterocycles with imino moiety like methyl 2-[2-benzamido-3-(2-benzothiazolyl)-4-oxothiazolidin-5-ylidene] acetates and ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates. They were prepared in good yields, by the direct cyclization of these thioureas with dimethyl but-2-ynedioate (DMAD) in methanol.



Scheme 1. *Methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene]acetate (1a-1k)*



Scheme 2. *Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl]benzoate (2a-2j)*

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OP 27. PORPHYRAZINE-DERIVED PD CATALYSTS: BIPHASIC SUZUKI REACTIONS WHERE THE CATALYST CAN BE TRACKED

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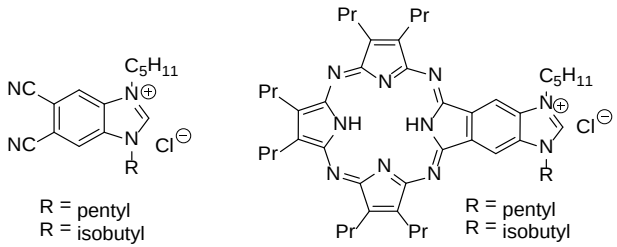
Homogeneous catalysed reactions are powerful and lend themselves to a wide array or transformations. They are particularly useful in facilitating conversions of simpler substrates into more complex products in approaches that would otherwise be quite onerous if making use of stroichiometric approaches.

Of particular note is carbon-carbon bond forming chemistry, especially that catalysed by palladium. One of the more well-known embodiments is the Suzuki reaction. Here, a boronic acid substrate and, typically, an aryl or vinyl halide (or their equivalent, e.g. an aryl triflate) reagent partner are coupled. This chemistry allows the rapid assembly of complex structures.

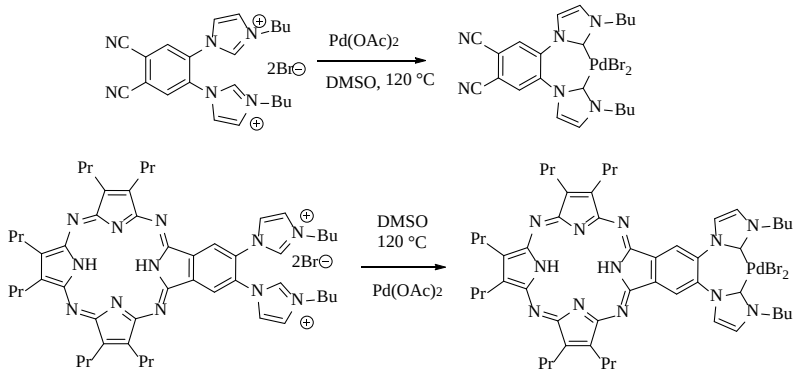
One of the major problems facing homogeneous catalysis is the recycling of the catalyst. During recycling it is important that as little of the catalyst and the ligand are lost. Several solutions based on biphasic systems have been investigated, including organic/water, organic/ionic liquid, ionic liquid/water and fluorous biphasic systems. One of the fundamental issues faced in such systems is sure knowledge of where the catalyst is.

We considered that a highly pigmented ligand might assist to solve this problem. Here, the ligand would preferably be visible at low concentrations and would thus possess a large extinction coefficient. Porphyrazines routinely display very large extinction coefficients with log ε >4. This allows them to be visualised at concentrations as low as 10^{-5}-10^{-6} M.

We therefore synthesised porphyrazines tagged with imidazolium moieties (mono-imidazolium, Scheme 1; bisimidazolium, Scheme 2). These would be converted into their Pd catalysts and would be present as their corresponding N-heterocyclic carbenes.



Scheme 1



Scheme 2

The imidazolium-functionalised porphyrazines were allowed to participate in Suzuki reactions, in both homogeneous and biphasic reactions. The biphasic reactions covered organic/water and ionic liquid/water. The outcomes were compared to those using the simpler dinitrile precursors as shown in Schemes 1 and 2. ICP-OES was employed to track the Pd while UV-Vis spectrophotometry was used to measure the ligand concentration. Recycling experiments were also pursued.

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

Poster Session

PP 1. SYNTHESIS AND APPLICATIONS OF 3-DIETHOXYPHOSPHORYLQUINOLIN-2-ONES

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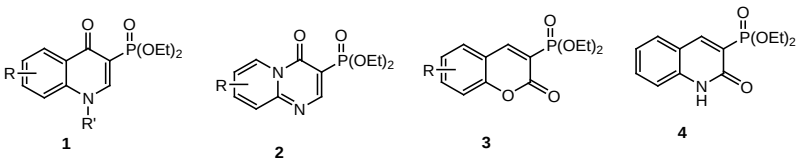
Azaheterocycles containing in their structures phopsphoryl moiety are a very important group of organic compounds. They are widely used in the medicinal and agricultural chemistry [1]. Furtheremore, they are important buliding blocks in organic syntheses, especially in the synthesis of 2-methylidene-1-oxoheterocycles [2].

As a continuation of our interest in the synthesis of phosphorylated, orto-condensed heterocycles, e.q. quinolin-4-ones **1**, pyridopyrimid-4-ones **2** or chromen-2-ones **3**, in this report we present novel and efficient synthesis of 3-diethoxyphosphorylquinolin-2-one **4**, which is useful intermediate in further transformations [3]. (Scheme 1)

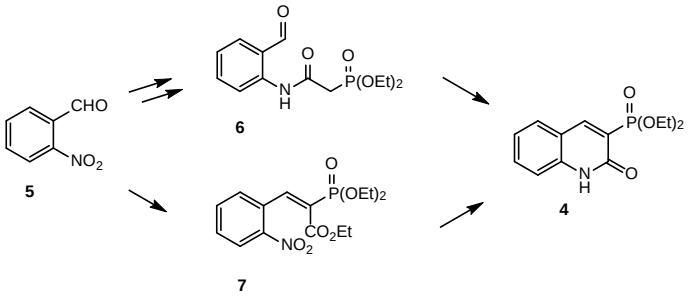


Scheme 1

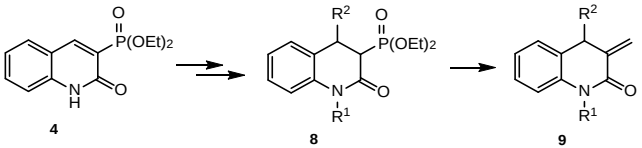
Synthesis of 3-diethoxyphosphorylquinolin-2-one **4** was accomplished starting from *o*-nitrobenzaldehyde **5**. The substrate was converted after reduction and acylation steps or Knoevenagel condensation into phosphonates **6** or **7**. The target compound was obtained by the intramolecular cyclization of phosphonates **6** or **7** in the presence of piperidine or iron respectively. (Scheme 2)

Transformation of 3-diethoxyphosphorylquinolin-2-one **4** into 1,4-disubstituted-3-diethoxyphosphorylquinolin-2-ones **8** was accomplished by N-alkylation of **4** followed by Michael addition of various Grignard reagents

to alkylated products. Finally Horner-Wadsworth-Emmons olefination of formaldehyde using 1,4-disubstituted-3-diethoxyphosphorylquinolin-2-ones **8** gave expected 2-methylidene-1-oxoheterocycles **9**. (Scheme 3)



Scheme 2



Scheme 3

This project was financed by the National Science Centre, Poland (decision No. DEC-2012/07/B/ST5/02006).

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PP 2. 1,4-ADDITION REACTIONS TO 3-SUBSTITUTED COUMARINS

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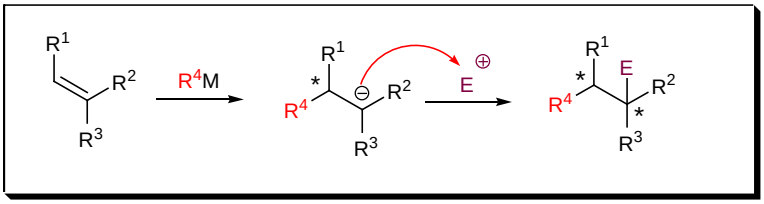
One of the most effective methods for C-C single bond formation is the 1,4-conjugated addition or also known as Michael reaction. This method is widely used in organic synthesis because of the vast variety of Michael's acceptors and organometallic compounds. By using this reaction, it is possible to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

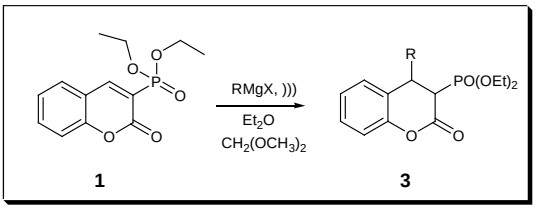


R^3 = COR, COOR, $CONR_3$, NO_2 ,$PO(OR)_2$
R^4 = alkyl, aryl, alkenyl, alkynyl

Shceme 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].

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.).



Scheme 2.

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.

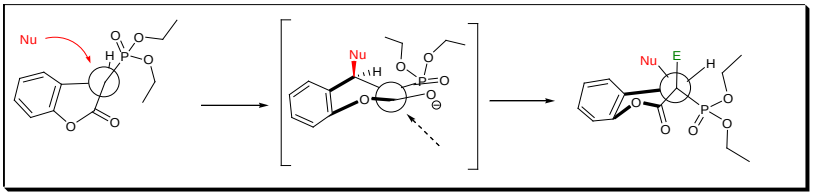


Figure 2.

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°.

Acknowledgment. This work was supported by the European Social Fund and Republic of Bulgaria, Operational Programme "Human Resources Development", 2007-2013 framework, Grant № G051PO001-3.3.06-0027 from July 2013.

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PP 3. SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW POTENT PYRAZOLO[1,5-*a*]PYRIMIDINE INHIBITORS OF CDK2 DESIGNED USING A QUANTUM MECHANICS (QM)-BASED SCORING FUNCTION

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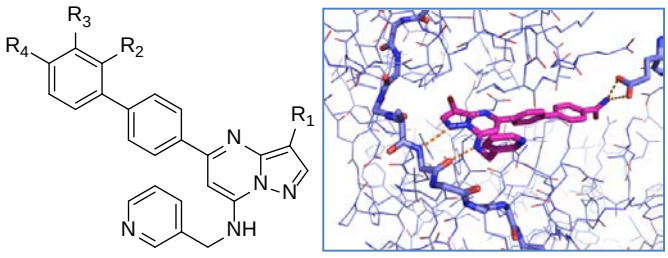
The serine/threonine kinase CDK2 (member of the cyclin-dependent kinase family) is of considerable interest as a potential drug target in oncology owing to its important role in the regulation of the mitotic progression and its association with the molecular pathology of cancer [1, 2, 3]. As a consequence, small-molecule ATP-competitive CDK inhibitors have potential therapeutic value as antitumor agents [4]. Furthermore, despite the fact that structures of many protein kinases have been characterized by X-ray crystallography, molecular modelling of new kinase inhibitors still remains a significant challenge.

Recently, we successfully applied a refined quantum mechanics (QM)-based scoring protocol to recapitulate the binding affinities of known pyrazolo[1,5-a]pyrimidine inhibitors of CDK2 kinase and their bioisosteres [5]. Utilizing the same scoring function, novel inhibitors bearing properly substituted biphenyls at the 5-position of the pyrazolo[1,5-a]pyrimidine core were modelled.



The synthesis and biological evaluation of these new CDK2 inhibitors will be discussed in order to assess the predictive power of the in silico methodology.

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PP 4. 1,2,5-CHALCOGENODIAZOLE-ANNULATED TRIPYRAZINOPORPHYRAZINES

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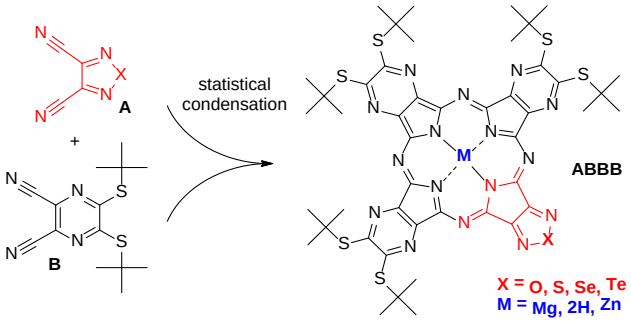
Tetrapyrazinoporphyrazines (TPyzPAs) have attracted steady attention due to their promising photophysical properties usable in photodynamic therapy. Their ability to produce singlet oxygen production and/or emit fluorescence after their excitation are important characteristics for these fields. The preferred way of relaxation is driven mostly by so called heavy atom effect which was described for the first time by McClure [1]. It was shown mostly on Pc that the presence of heavy atoms in the structure enhances the probability of compounds to undergo the intersystem crossing leading to the increase of singlet oxygen production [2].

The aim of this work was to synthesize precursors and series of low-symmetrical TPyzPAs containing chalcogenodiazole ring (oxygen, sulfur, selenium or tellurium) in their structure and to disclose their effect on TPyzPAs' photophysical properties (i.e. heavy atom effect).



Scheme 1. *Synthesis of 1,2,5-Chalcogenodiazole-annulated tripyrazinoporphyrazines*

Appropriate precursors A and B underwent statistical condensation leading to a mixture of TPyzPAs congeners from which required ABBB congener was

isolated by the mean of column chromatography. Different cyclotetramerization methods were tried and Mg^{II}, Zn^{II} complexes and metal free porphyrazines were synthesized. We will discuss stability of our compounds. Influence of the chalcogen atom on the electronic absorption and emission spectra and singlet oxygen production will be discussed too.

Acknowledgements. The Project is co-financed by the European Social Fund and the state budget of the Czech Republic. Project no. CZ.1.07/2.3.00/30.0061 and by Russian Foundation of Basic Research (Grants 13-03-00902, 13-03-90929).

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PP 5. MIXED - LIGAND RUTHENIUM COMPLEXES OF TERPYRIDINE AND 2,4 - DITHIOHYDANTOINS

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The complexation ability of a series of cycloalkane-5-spiro-2,4-dithiohydantoins with some metal ions from the first transition row has recently been studied [1,2]. General conclusions on the coordination modes of the used ligands could be drawn by employing an integrated approach of quantum-chemical and experimental spectroscopic methods [3,4]. Recent data on new Pt(II) and Ru(II) complexes of 2,4-dithiohydantoins with bulky aromatic susbstituents on the 5-th position in the hydantoin ring indicated a moderate anticancer activity against three types of human cancer cell lines. The structure description of the complexes, however, remained elusive due to expected formation of polymeric complexes through coordination of both thione groups of each ligand. Therefore, a new synthetic procedure was attempted with the use of the tridentate terpyridine ligand (terpy) to obtain mixed-ligand complexes with some 2,4-dithiohydantoins [5] that would have well-defined structure and composition by avoiding the polynuclear complex formation. The complexes with cyclohexane-5-spiro-2,4-dithiohydantoin and 9'-fuorene-5-spiro-2,4-dithiohydantoin were obtained from the $Ru(terpy)Cl_3$, which was synthesized before use. In all cases soluble, cationic complexes were obtained. The latter were isolated either through counter ion exchange or precipitation with nonpolar solvent. The products were characterized by means of vibrational (IR) and electronic (UV-Vis) spectroscopy as well as nuclear magnetic resonance (NMR) and mass-spectrometric (MS) methods. Discussions on the structure of the complexes based on the accumulated experimental data and supported by the performed quantum-chemical calculations will be presented.

Acknowledgements. Financial support from the National Science Fund of Bulgaria (Contract DFNI-B01/0014) and "BeyondEverest" project - FP7-REGPOT-2011-1 are acknowledged.

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PP 6. ADVANCES IN THE SEARCH FOR POTENT ANTIMICROBIAL 1,2-BENZOTHIAZOLE HYDRAZIDES AND THIAZOLIDINYL-1,2 CARBOXAMIDES

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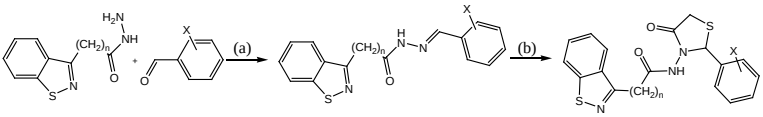
Development of new antimicrobial agents is increasingly important due to the resistance of microbes to the known antimicrobial drugs. Our design supported by our previous findings addressed the synthesis of a new class of *N*-[2-(halophenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,2-benzothiazole-3-carboxamides derived from *N*'-(halophenylmethylidene]-1,2-benzothiazole-3-carbo/acetohydrazides.



Scheme of synthesis for X= 2,6-Cl_2, 2,6-F_2, 2-Cl,6-F; n= 0, 1.
Reagents and conditions: (a) CH_3COOH, EtOH, 3h, reflux; (b) $HSCH_2COOH$, toluene, a few days or MW, reflux.

All of the compounds were screened, by means of the two-fold dilution method, for their *in vitro* antimicrobial properties against Gram positive and Gram negative bacteria and fungi. Surprisingly all the compounds selected for a preliminary evaluation resulted very potent towards all the tested microorganisms and their activity was better than that of reference drugs. The highest activity was exhibited by *N*'-[(2,6-difluorophenyl)methylidene]-1,2-benzothiazole-3-carbohydrazide that showed ten-fifty fold higher antifungal activity than bifonazole and ketoconazole. The outstanding properties of the preliminary tested compounds deserve investigation of a number of terms of the novel class synthesized in order to perform QSAR analysis and have a rational prediction of the best candidates.

PP 7. THREE-COMPONENT REACTIONS OF 5-METHYL-4-PHENYL-5,6-DIHYDRO-4*H*-PYRROLO[1,2-*a*][1,4]BENZODIAZEPINE

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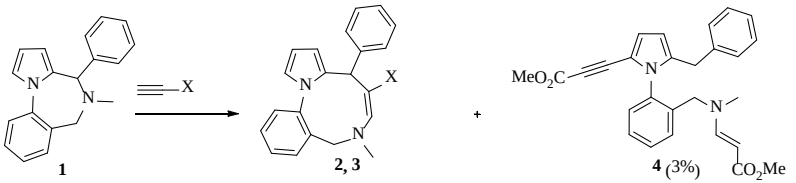
Earlier were stadied alkyne-induced transformations of 5-methyl-4-phenyl-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepine 1. In different solvents 1 produced unknown pyrrolobenzo[1,2-a][1,6]diazonines 2,3 also we isolated in a low yield pyrrole 4 [1].

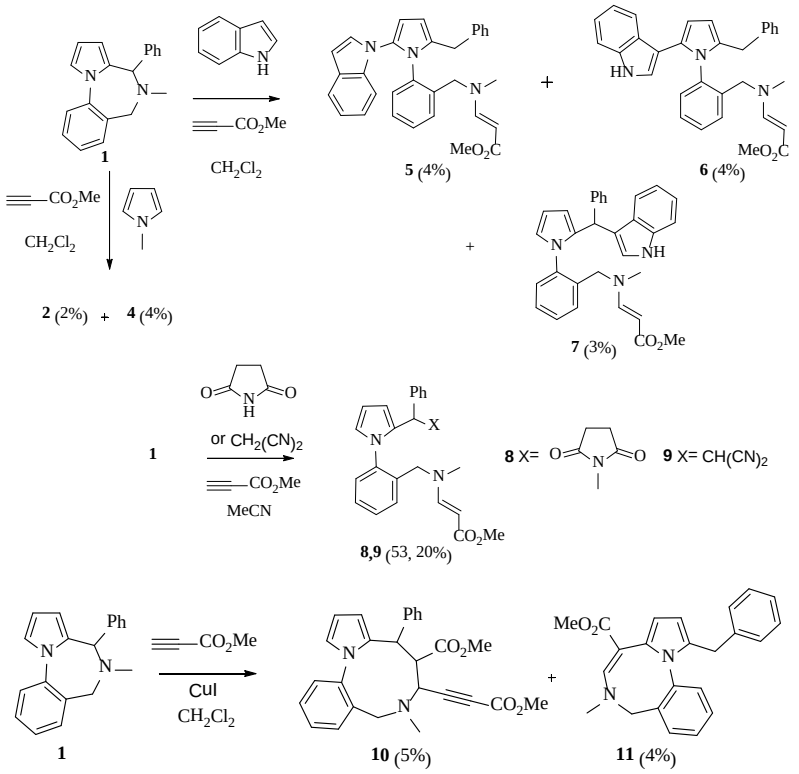


X= CO_2Me		X= COMe	
MeCN	22%	MeCN	25%
CH_2Cl_2	2%	CH_2Cl_2	54%
CF_3CH_2OH	7%	MeOH	28%

In order to optimize the synthesis of pyrrolobenzo[1,2-a][1,6]diazonines we studied three-component reaction pyrrolo[1,2-*a*][1,4]benzodiazepine **1** with methyl propiolate in the presence of indole, N-methylpyrrole, succinimide as well as CuI as possible reaction promoters.

In reactions with methyl propiolate in the presence of acids **1** formed multicomponent mixtures. From the reactions with indole we managed to isolate substituted pyrroles **5-7** and in the case of reactions with succinimide, malononitrile, N-methylpyrrole pyrroles **4,8,9**.

In the presence of CuI obtained diazonine **10** - adduct of 2 moles of methyl propiolate and pyrrolobenzodiazocine **11**.



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PP 8. DIHYDROPYRROLO[1,2-*B*]PYRAZOLES: SYNTHESIS OF NEW DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

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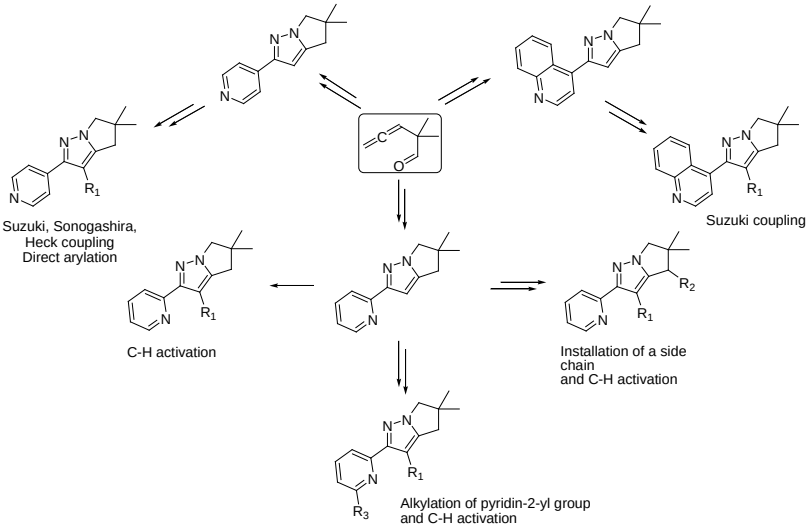
During the last two decades, compounds with dihydropyrrolo[1,2-*b*]pyrazole (DPP) core showed promising biological activity. Sawyer published series of papers dealing with this field of organic chemistry.[1-5] These DPP derivatives are inhibitors of transforming growth factor β type I of kinase receptor domain. TGF-β plays an important role in many pathological states including inflammation, fibrosis, cancer, asthma and cardiovascular diseases [6-11].



Scheme 1

In this poster, we present our recent work aimed at synthesis of some analogues of these compounds with DPP core bearing 2-pyridyl, 4-pyridyl and 4-quinolinyl moiety at position 2. Homoallenyl aldehyde, synthesized according to our improved procedure, [12] is a key intermediate for the

creation of DPP core. Various palladium catalyzed coupling reactions (Suzuki, Sonogashira, Heck, direct arylation and C-H activation) are shown in the following schemes. Conditions for substitution of position 4 were discovered and they are described in this poster as well. A series of compounds was selected for biological screening. In few cases, these tests shown a selective activity as inhibitors of ALK5 kinase and for some other derivatives lower activity in inhibition of CDK2/E was also observed. Biological testing of some recently prepared compounds is ongoing.

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PP 9. THE CONDENSATION REACTIONS OF ACETATE PREGNENOLONE WITH SOME HYDRAZINES

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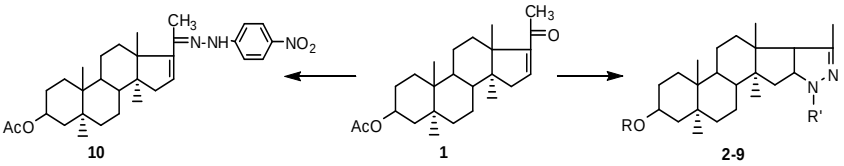
Some representatives of steroidal pyrazolines with nitrogen containing heterocycles have the properties that are not typical for natural hormones. They do not suppress immunity and simultaneously exhibit high anti-inflammatory, antimicrobial, anti-cancer activities, and decrease the level of cholesterin.

In order to receive potential biologically active new steroidal pyrazolines condensation reactions of 3β-acetoxy-5α-pregnenolone **1** with some hydrazines have been studied.

It is known, that on the first step of interaction of steroidal α-enone with hydrazines or hydrazides there were obtained intermediate hydrazones, which can be easily cyclisized to pyrazolines. Cyclization reaction is promoted by electron donating substituent at the position of amine atom of hydrazone, at the same time electron acceptor substituent prevents this process.



2, 4, 6, 8 R = Ac
3, 5, 7, 9 R = H
2, 3 R' = C_6H_5
4, 5 R' = 4-CH_3-C_6H_4
6, 7 R' = 4-Cl-C_6H_4
8, 9 R' = 4-Br-C_6H_4

By interaction of ketone **1** with phenylhydrazine, p-methyl-, p-chloro- and p-bromophenylhydrazine in ethanol were obtained intramolecular cyclocondensation products – mixture of corresponding 3β-acetoxy- and 3β-hydroxy-

5α-androstano[17,16-d]pyrazolines. These mixtures were separated with the chromatographic column in the individual compounds **2-9.**

By conducting reaction in the acetic acid the are obtained only 3β-acetoxyderivatives **2,4,6,8**. Corresponding 3β-alcohols **3,5,7,9** were received by base hydrolysis of **2,4,6,8**.

As it was expected, by interaction of acetate pregnenolone **1** with p-nitro-phenylhydrazine there was obtained hydrazone **10**, which can not be cyclisized to pyrazoline.

The structures of the all newly synthesized compounds **2-10** were established by IR-, ^{1}H and ^{13}C NMR and mass-spectral data.

PP 10. DIASTEREOSELECTIVE SYNTHESIS OF β-LACTAMS *VIA* KINUGASA REACTION WITH CHIRAL ACYCLIC NITRONES

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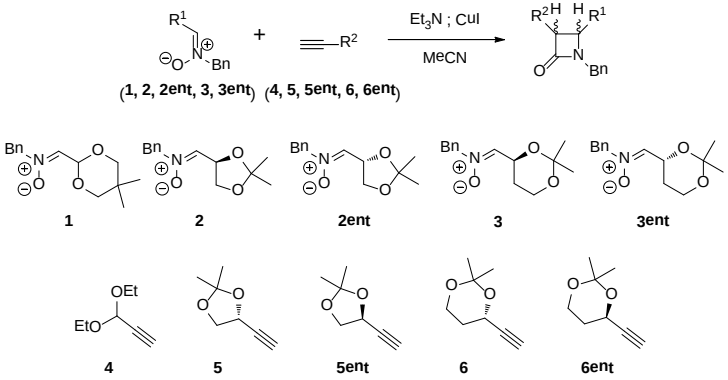
An approach to β-lactams *via* Kinugasa reaction [1] between chiral terminal copper acetylides and chiral open-chain nitrones bearing either 1,3-dioxane or 1,3-dioxolane moieties will be reported. Stereochemical preferences observed in these reactions will be discussed. The reaction provides an access 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.



Acknowledgment. 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 11. THE SYNTHESIS OF NEW ORGANIC REACTIVE BY USING 4-AMINOANTIPYRINE AND RESEARCH IT'S INTERACTION WITH SOME METAL IONS

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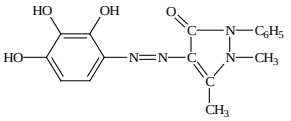
By using 4-aminoantipyrine and pyrogallol new organic reagent 1-phenyl-2,3-dimethylpyrazolon-5-azopyrogallol was synthesized. The com-position and structure of reactive has been studied by infrared and NMR spectroscopy methods. The results of the investigation confirmed that it has the following structural formula:



The dissociation constants of reactive has been determined by the method of potensiometric titration and absorption spectra has been studied in various acidic medium (pH 0-14), in a wide wavelength range. It has been determined that the reactive is a triprotic acid, dissociates partially depending on the pH of the medium and change it's colour. He was appointed to the acidity constants: pK_1=6,71±0,02, pK_2=7,85±0,04, pK_3=8,83±0,08. Depending on the acidity of the medium reactive exist in cationic - H_4R^+ (pH≤0), molecular - H_3R (pH 0-6,7) and in three anionic forms - H_2R^- (pH 6,7-7,8), HR^{2-} (pH 7,8-8,8), R^{3-} (pH≥8,8). The maximum absorptive of these forms H_4R^+, H_3R, H_2R^-, HR^{2-} and R^{3-} are respectively 383, 373, 412, 431 and 378 nm.

Reactive environment, depending on the acidity of the solution exists in two tautomeric forms - azo and quinhydrazone forms. Quinhydrazone forms dominate in acidic medium, azo form dominates in basic medium. The complex formation of reactive with some metal ions has been investigated and it has been defined that reactive form intensively colored complex compounds with Al(III), Ga(III), In(III), Fe(III) and Sc(III) ions in the acidic medium (pH 1,0-7,0).

PP 12. SYNTHESIS AND REACTIONS OF SOME NEW ISOXAZOLO [4,3-b]PYRIDINES

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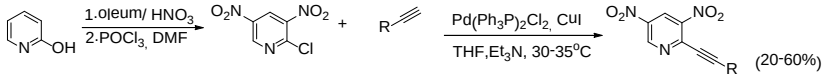
It is well-known that aromatic nitro compounds containing alkynyl substituent in the ortho position to the nitro group are suitable precursors of different heterocycles [1,2]. Currently it is one of the most interesting and developing strategy for heterocyclic ring construction. In this regard, the synthesis of new hetarylacetylenes is a problem of interest.

As a part of our research on polycyclic heterosystems we have proposed a method for the synthesis of new isoxazolo[4,3-b]pyridines from 2-chloro-3,5-dinitropyridine.

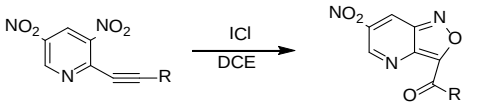
Firstly the starting compound, each bearing nitro group and alkynyl substituent in ortho position were synthesized in accordance with Sonogashira coupling between 2-chloro-3,5-dinitropyridine and terminal alkynes.



R= Ph, 4-F-C_6H_4, 4-Me-C_6H_4, c-propyl, c-pentyl, pyridyl

It should be noted that Sonogashira reactions of polynitropyridines have not been previously described.

We have shown that all prepared substrates can undergo cycloisomerization in the presence of catalytic amounts of ICl into adducts containing isoxazole ring.



R= Ph, 4-F-C_6H_4, 4-Me-C_6H_4, c-propyl, c-pentyl, pyridyl

The structure of all new isoxazoles were proved by IR-, NMR-spectroscopy and X-ray.

Thus, a method for the synthesis of new nitroisoxazolo[4,3-b]pyridines from

2-R-3,5-dinitropyridines was developed.

Acknowledgment. This work was supported by the Russian Foundation for Basic Research, Projects No. 13-03-00452, 14-03-31508 mol_a and Grant of the President of the Russian Federation for State Support to young Russian scientists, Grant MK-3599.2013.3.

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PP 13. PERHYDRO-BENZOFURANES PRECURSOR FOR THE TOTAL SYNTHESIS OF (+)-BISABOLANGELONE

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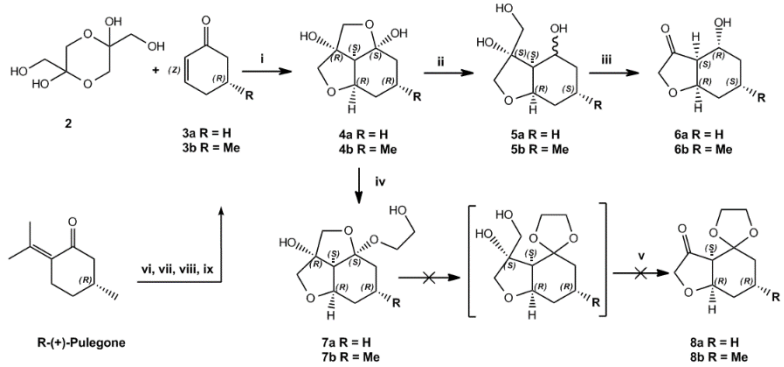
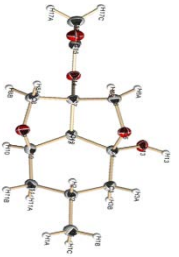
Bisabolangelone **1**, present in various Angelica species, is a potent natural substance, which displays a variety of pharmacological activities [1]. Inspired by the tricyclic hemiacetal **4a** described by Saimoto et al. [2], we considered the related analogue **4b** (scheme 1 below), as a building block to construct the target molecule **1** and establish without ambiguity the corresponding absolute configuration.



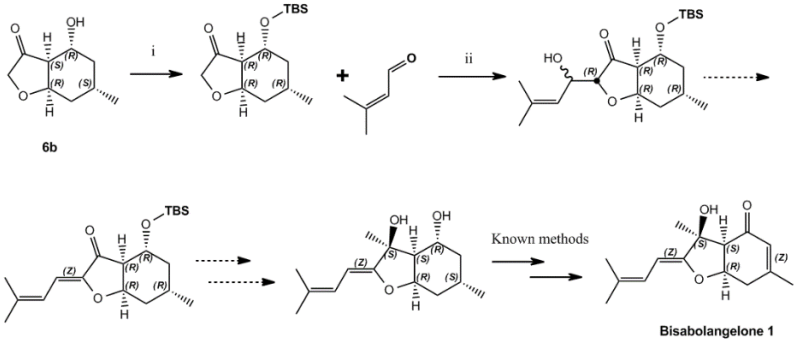
Reagents and conditions: (i) dihydroxy-acetone-dimer, 0.05 eq. NaOH, water, 0°C 20 h; (ii) 1 eq. $NaBH_4$, water 0°C, 2 h; (iii) 2 eq. $NaIO_4$, water 0-20°C, 5 h; (iv) $HOCH_2CH_2OH$, MsOH, 20°C 0.5 h; (v=iii), (vi) 2 eq. H_2O_2, 0.2 eq. LiOH, methanol/water 20°C, 20h; (vii) 1.2 eq. NaSPh, Me-THF 60°C 24 h; (viii) 1 eq. $NaBO_3$, AcOH, 20°C, 2 h; (ix) excess $CaCO_3$, tetraglyme 140°C/50 mbar (product recovered by distillation).

According to Saimoto et all [2], the base catalysed Michael addition of dihydroxy acetone dimer with (R)-5-methyl-cyclo-hexenone obtained from (R)-(+)-Pulegone, furnishes the chiral derivative **4b**, which abs. configuration has been confirmed by X-ray analysis of the corresponding acetate (figure 1 beneath). Unfortunately, intermediates **4a/b**, which can be converted to

various acetal derivatives **7,** could not be converted to the known dioxolane **8** [3]. But to our delight, intermediate **4a/b** can be readily converted *in situ* by reduction with sodium borohydride and subsequent periodate treatment to the hydroxylated cis-perhydro-benzofuranones **6** in decent yields.



The central core in place, we followed our goal to synthesis (+)-Bisabolangelone, taking advantage of the methodology already established for known dioxolane **8b** [3]. First, we introduced a TBS protecting group on the free hydroxyl in order to enable the regio-selective aldolisation with prenal at low temperature. The later succeeded according to the established conditions [3], but the dehydration with trifluoro-acetic anhydride and triethylamine failed.



Reagents and conditions: (i) 1.2 eq TBS-Cl, 1.2 eq NaBr, imidazol, THF, 25°C, 24 h; (ii) 1.2 eq. LDA, -78°C, 0.5 h, 1.2 eq prenal 0.5 h, followed by quench with acetic acid.

Despite this unexpected failure, current investigations with various dehydrating reagents will hopefully circumvent this hurdle, since once the desired enone is obtained, methylation with Grignard reagent and removal of the protecting group will provide the know [4] racemic diol **9** which can be converted to Bisabolangelone by known methods [4]. Otherwise, different approaches still using the functionalised perhydro-benzofuranone **6b** should enable the first enantio-selective synthesis of (+)-Bisabolangelone.

Acknowledgement. The authors thanks Novartis for a Master internship (P. F.); C. Guenat, R. Denay, P. Piechon for MS, NMR and X-rays investigations. My colleagues F. Gallou, M. Baenziger, M. Parmentier, Professors: D. Seebach, P. Knochel and R. Boeckman for their valuable contributions.

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PP 14. NOVEL CATALYTIC SYSTEMS CONTAINING METAL NANOOXIDES FOR ASYMMETRIC BIGINELLI REACTION

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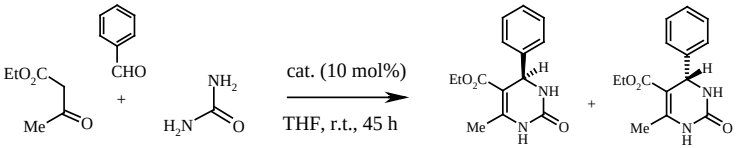
3,4-Dihydropyrimidinones (DHPMs) are well known heterocyclic units in the realm of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties. Nowadays, one of the main problems in DHPMs synthesis is to obtain them in enantiopure form. Indeed, both enantiomers of DHPMs have been found to show distinct or opposite pharmacological activities [1-3].



Previously, we showed the possibility of the stereoselective Biginelli reaction in the presence of nanosized metal oxides [4,5]. Commercially available quinine sulfate, *L*-proline and *L*-tartaric acid were used as chiral inducers, and nanosized CuO, Al_2O_3, ZnO, NiO, MgO were used as heterogeneous catalysts. Adding nanooxide to inactive chiral inducer increased the enantiomeric excess (*ee*) of the reaction product **1** from 0 to 24% in favor of (*S*)-enantiomer. The best catalytic system was L-proline together with MgO. Probably, a zwitterionic structure of *L*-proline is destroyed by sorption on nanooxide. Therefore, it becomes possible to form a chiral intermediate with ethyl acetoacetate. An additional activation of the pyrrolidine nitrogen by Brønsted acid sites of nanooxide is possible. Moreover, coordination of the reaction intermediates on the nanooxide surface active sites creates additional steric hindrances in the asymmetric reaction (Fig. 1).

4-Hydroxyproline derivative **2** was studied as a promising chiral inducer. According to the literature, in the presence of compound **2** the reaction proceeds yielding DHPM **1** of 39% *ee* [6]. Further increase of *ee* is achieved only by the addition of two or three co-catalysts (acids, amines or their salts, etc.).

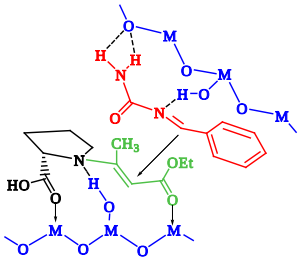
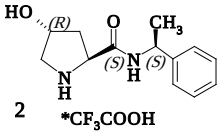


Fig. 1. *Proposed transition state in the asymmetric Biginelli condensation reaction in the presence of L-proline*

We have showed that the addition of the nanooxide increases the enantioselective effect of chiral inducer **2** in the Biginelli reaction [7]. The best results were achieved by using double nanooxides ZrO_2-SiO_2, TiO_2-SiO_2 (Table 1).

Table 1. *Results of the enantioselective synthesis of DHPM 1 (10 mol % 2, THF, 20 °C, 45 h)*



№	Nanooxide, 10 mol %	Yield, %	*Ee*, %
1	Without nanooxide	29	39*(R)*
2	[1]Al_2O_3	44	60*(R)*
3	[1]Al_2O_3 bulk	33	59*(R)*
4	[1] TiO_2	37	54*(R)*
5	[1] SiO_2	59	64*(R)*
6	[1] SiO_2 bulk	45	60*(R)*
7	[1] ZrO_2	5	0
8	[1] TiO_2-SiO_2, ω_{TiO2} = 40%	23	39*(R)*
9	[2] TiO_2-SiO_2, ω_{TiO2} = 40%	92	66*(R)*
10	[1] ZrO_2-SiO_2, ω_{ZrO2} = 50%	39	68*(R)*
11	[2] ZrO_2-SiO_2, ω_{ZrO2} = 50%	44	72*(R)*

[1] Nanooxide was added simultaneously with reagents;
[2] nanooxide was added 60 min after the reagents.

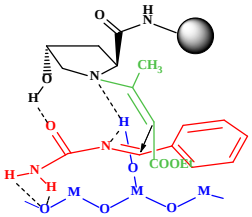


Fig. 2. *Proposed transition state in the asymmetric Biginelli condensation reaction in the presence of 4-hydroxyproline amides*

The highest *ee* was achieved when the nanooxide was added 60 min after the reagents.

Based on our results we assume that the role of nanooxide is to create additional steric hindrances in the transition state of the asymmetric Biginelli reaction (Fig. 2), as it was in the case of *L*-proline (Fig. 1). Probably, the pyrrolidine nitrogen and the imine moiety are activated by Brønsted acid sites of nanooxide.

Acknowledgment. This work was supported by the Ural Branch of the Russian Academy of Sciences (project nos. 12-P-234-2003 and 12-P-3-1030), by the Russian Foundation for Basic Research (grants 14-03-31357 mol_a, 13-03-12188-ofi_m) and by the State Program for the Support of Leading Scientific Schools (grant NSh 3656.2014.3)

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PP 15. AZIRIDINYL-SUBSTITUTED BENZO-1,4-QUINONES: PRELIMINARY INVESTIGATION ON THEIR SYNTHESIS, X-RAY STRUCTURE, REDOX ACTIVE PROPERTIES AND BIOLOGICAL ACTIVITY

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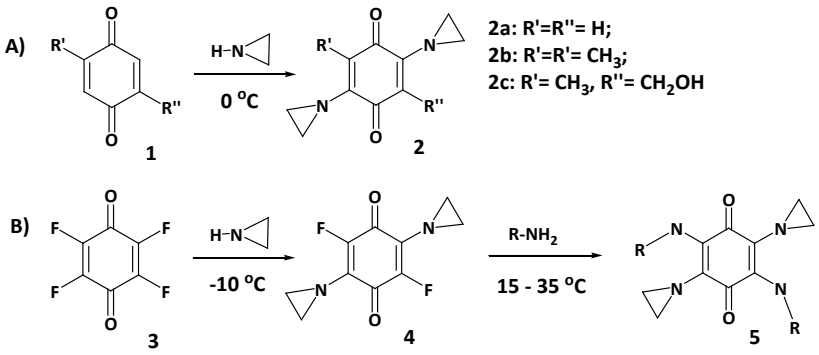
Quinones are class of compounds of natural or synthetic origin that possess a broad spectrum of biological activity: antiprotozoal, anticoccidic, antibacterial, antifungal, tuberculostatic, anti-inflammatory, etc [1].

Many of the drugs clinically approved or still in clinical trials against cancer are quinone related compounds [2]. The structural combination of benzo-1,4-quinone (BQ) and aziridine moiety yielded 2,5-bis(1-aziridinyl)-l,4-benzoquinones with remarkable antineoplastic properties but showed dose-limiting toxicity. In this work a series of new aziridinyl-substituted benzo-1,4-quinones (AzBQs) has been synthesized and and their electrochemical properties and anticancer activity were studied. The cytotoxic and/or anticancer action of AzBQs was found to stem mainly from their two-electron reduction into alkylating species thus allowing the formation of DNA and protein-alkylating products. A new derivatives of 2,5-bis(1-aziridinyl)-benzo-1,4-quinone were studied for their *in vitro* anticancer activity against human promyelocytic leukemia (HL-60) cells and obtained data were compared with cytotoxicity upon normal primary skeletal myocyte L6 cell line. We investigated application of various reaction conditions and found that use of methanol and THF as reaction media led to the improved yields in the synthesis of 3,6-bis(alkylamino)-2,5-bis(1-aziridinyl)-benzo-1,4-quinones **2** and **5** (Fig.1).

The detailed structure of the basic compound from this group, 2,5-bis(1-aziridinyl)-l,4-benzoquinone **2a**, has been studied by X-ray diffraction (Fig.2).



5a: R= CH_2CH_2OH ; 5b: R= CH_2CH_3 ; 5c: R=$CH_2CH_2CH_3$; 5d: R= $CH(CH_3)_2$; 5e: R=C_3H_5
5f: R= $CH_2CH=CH_2$; 5g: $CH_2CH_2CH_2OCH_3$;

Fig.1. *A general scheme of the synthesis of aziridinyl-substituted benzo-1,4-quinones*

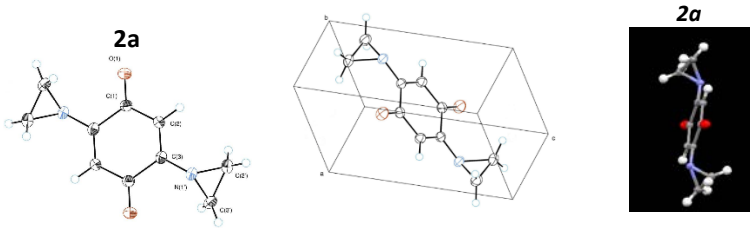


Fig.2: *Molecular structure of 2a. Thermal ellipsoids at 50% probability. (Crystals from $(CH_3)_2CO$, yellow prisms, crystal size: 0.21 x 0.16 x 0.03 mm, space system - triclinic, space group - P1). Selected bond lengths [Å]: ; C(1)-O(1) 1.227; C(1)-C(2) 1.446; C(2)-C(3) 1.348; C(3)-N(1) 1.379; N(1')-C(3') 1.473; C(3')-C(2') 1.485, selected bond angles [°]: O(1)-C(1)-C(2) 122.3; C(2)-C(3)-N(1') 124.2; C(3')-N(1')-C(2') 60.9; N(1')-C(2')-C(3') 59.7; C(1)-C(2)-C(3) 122.4. Unit cell dimensions: a [Å] 3.8859(3), b [Å] 6.8472(4), c [Å] 8.4155(8).*

2a. *Projection, showing dihedral angles*

The *in vitro* anticancer activity, expressed as CL_{50} for compounds 2 and 5 as determined against 2 different mammalian cell lines varied in the range of

2,3-25 μM. The most potent derivative was 2c from, while the best selectivity result among cytotoxicity against normal L6 line cells and human promyelocytic leukemia cells HL-60 was found for quinone 5e, which possess a hindered sterical structure, containing specific cyclopropylamine groups. No correlations were found between cytotoxic activity of compounds and their calculated lipophilicity (logP), topological polar surface area (TPSA), molecular volume (MV) and redox potential E_{pc}. The activity of aziridinyl-substituted benzo-1,4-quinones were mostly affected by the electronic effects and steric hindrance of the different substituents of quinone moiety.

Acknowledgments. The Support of the European Social Fund under the Global Grant Measure (Grant No. VP1-3.1-ŠMM-07-K-01-103) is gratefully acknowledged.

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PP 16. SOME ORGANOSILSESQUIOXANES BASED POLYMERS

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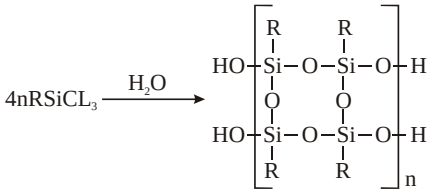
Synthesis of polyorganosilsesquioxanes was carried out in two stages. In the first stage, polycyclic prepolymers were synthesized by the hydrolysis of organotrichlorosilanes, and in the second stage, anionic polycondesantional polymerization of prepolymers was carried out.

Hydrolytic condensation of organotrichlorosilanes was carried out in different conditions: olygo-α-naphthyltetrols were obtained by alkaline hydrolysis of α- naphthyltrichlorosilanes, and oligomeric methyl- and phenylsilsesquioxanes were obtained by hydrolytic condensation of methyl- and phenyltrichlorosilanes in acetone – toluene medium at room temperature. In all cases, the reaction proceeds by the following scheme:



R=CH_3, n=4, 5, 8; R=C_6H_5, n=2, 4; R= α –$C1_0H_7$, n=2, 3.

Anionic condensational copolymerization of olygomethyl- and phenylsil sesquioxanes in the presence of various catalysts (KOH, KF, CaF_2) at the molar ratio 1:1 has been studied. In the medium of toluene at 75-85 °C in the presence of both CaF_2 and KF the reaction yields mainly the soluble polymer, while in the case of KOH a considerable amount of the unsoluble polymer is formed together with the soluble polymer. The use of KF leads to the formation of polymers of relatively high viscosity (μ 0.113-0.13), indicating that from the probed catalysts KF is the active catalyst for anionic polyendensational polymerization.

The thermooxidative stability of methyl (phenila) sesesquioxanic polymers has been investigated by means of thermogravimetric method.

The thermostability of the polymer obtained in the presence of CaF_2 is somewhat higher than of those obtained in the presence of KOH and KF.

Anionic polycondensational polymerization of olygo-α-naphthylsilsesquioxanes was carried out. Optimal conditions of the reaction holding were determined: temperature - 220-300°C, catalyst - 0,1% KOH or KF in the medium of ditolylmethane. It should be noted that the use of KF leads to the formation of only soluble polymer.

Poly-α- naphthylsilsesquioxanes are characterized by the thermooxidative stability. At 500 °C the loss of the weight is 5-8%, while at 650 °C the loss of the weight is 40%.

PP 17. SYNTHESIS OF SOME D-HOMOANDROSTANES FROM TIGOGENIN

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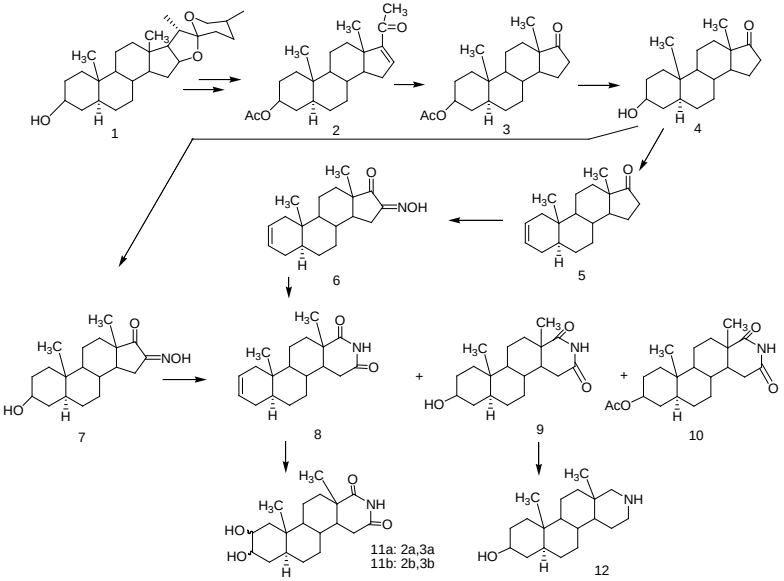
D-homoandrostanes are characterized with different biological activities including antitumor activity [1]. Recently we have synthesized some new 5α-D-homosteroids (scheme 1) based on steroidal sapogenin-tigogenin **1** (isolated from plant *Yucca gloriosa*). Synthesis of D-homoandrostene **8** was provided from ketone **4** trough the oximes **6** and **7** using Beckman rearrangement reaction. Treatment of obtained oxime **7** with H_2SO_4 gave mixture of D-homoandrostenes **8-10**.



Sharpless dihydroxilation of D-homoandrostene **8** using K_2OsO_4 and NMO according the NMR data gave 2,3-dihydroxy-D-homoandrostane **11** as a

mixture of 2α,3α- and 2β,3β isomers (75:25). Amine **12** was obtained by reduction of imide **9** with $LiAlH_4$ in THF. Synthesized compounds **11** and **12** will be proposed for antitumor activity screening.

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PP 18. A NOVEL METHOD FOR THE SYNTHESIS OF BENZIMIDAZOLE – BASED 1,4-QUINONE DERIVATIVES

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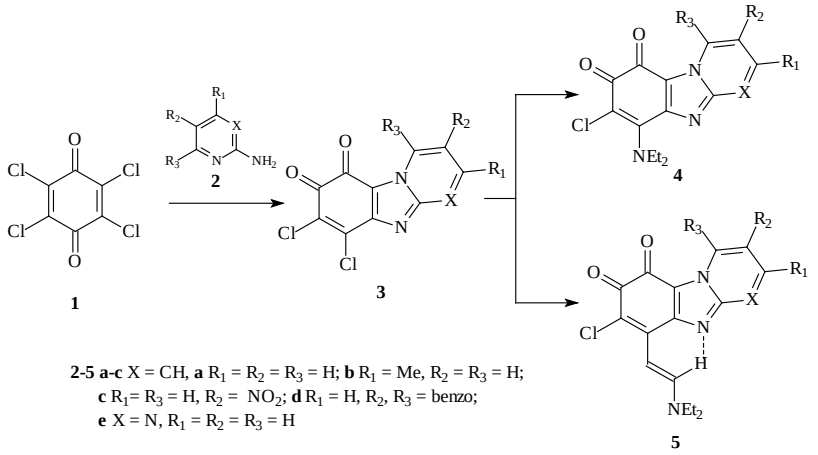
Derivatives of quinones have attracted attention due to their broad spectrum of applications in biological, pharmaceutical and material areas [1]. They are used as electron-accepting components for the production of charge-transfer complexes and radical-ion salts. We have developed a method for the synthesis of mono- and bisheteroaryl derivatives of 1,4-benzoquinones where the fragments of the heterocycle and the quinone are linked by a C–C bond [2, 3].

Our interest in quinone chemistry led us to investigate reaction between chloranil and different 2-amino(di)azines. Reaction of chloranil (**1**) with 2-amino(di)azines **2** in ethanol or 2-propanol gave single products – pyridobenzimidazole-8,9-dione derivatives **3**.

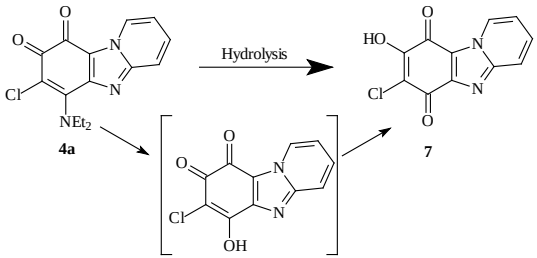


2-5 a-c X = CH, **a** $R_1 = R_2 = R_3 = H$; **b** R_1 = Me, $R_2 = R_3 = H$;
c $R_1 = R_3 = H$, $R_2 = NO_2$; **d** $R_1 = H$, R_2, R_3 = benzo;
e X = N, $R_1 = R_2 = R_3 = H$

A possible mechanism for the formation of quinones **3** involves nucleophilic attack of the ring nitrogen and chlorine atom substitution, Schiff's base formation by reaction of amino group with the quinone oxygen, and replacement of the second chlorine atom by a hydroxyl group. The final *o*-quinone structure was formed after loss of HCl [4].

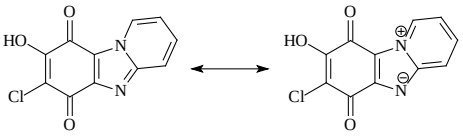
In the reaction of quinones **3** in dichloromethane with *N,N*-diethyl-*N*-vinylamine, generated *in situ* from diethylamine and acetaldehyde, a mixture of C-6 substituted products **4** and **5** was formed. Quinones **4** and **5** are deeply coloured compounds and a strong intramolecular charge transfer band was observed in their UV-Vis spectra. The hypsochromic shift in the UV-Vis spectra for aminoquinones **4** (569-573 nm in $CHCl_3$) in comparison with aminovinylquinones **5** (635-651 nm in $CHCl_3$) are due to the removal of conjugation.

Quinones **3** were converted to diethylaminoderivatives **4** by addition of diethylamine in dichloromethane. Quinone derivatives **4** contain ß-amino-vinyl ketone fragment and according to the data [5] diethylamino group can be hydrolized. The hydrolysis reaction of **4a** was carried out in ethanol in the presence of HCl or $SnCl_2$ at room temperature. The formation of compound **7** is a two-stage process: at the first stage of the hydrolysis 1,2-quinone derivative **6** is formed that subsequently isomerizes to more stable quinone **7.** X-ray crystallography confirmed the structure of quinone **7** as *p*-quinone derivative.



Analysis of the bond lengths indicates that molecular structure of **7** is not trivial. Presenting schematically this molecular structure as two mesomeric forms, one can infer that the specific weight for the **7B** form is higher than

that for the **7A** form:



7A **7B**

The X-ray structure analysis of **7** shows an ethanol crystallization molecule in the crystal structure. In the crystal structure there are intermolecular hydrogen bonds of type OH•••N between ethanol molecule and nitrogen atom of N5 with the length of 2.848(3) Å (H•••N = 2.04(3) Å, O–H•••N = 171(2)°). At the same time "phenol" hydroxyl group forms strong intermolecular hydrogen bonds of OH•••O type with oxygen atom of ethanol. The hydrogen bond length is equal 2.595(3) Å (H•••O = 1.78(3) Å, O−H•••O = 156(2)°).

Acknowledgment: Support for this work was provided by the Riga Technical University through the Scientific Research Project Competition for Young Researchers No. ZP-2014/12.

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PP 19. 5-AMINOTETRAZOLE IN THE SYNTHESIS OF 6-Ar-3,5-DIAMINO-1,2,4-TRIAZINES. LAMOTRIGINUM AND ITS ANALOGUES

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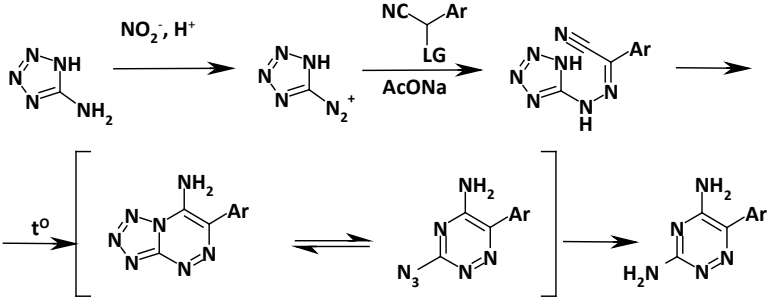
A derivatives of 6-aryl-3,5-diamino-1,2,4-triazines occupy a unique place in medicinal chemistry and possess remarkable biological properties such as anticonvulsants reagents, for example, the *Lamotriginum* is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. Our research group has developed new synthetic methodologies – *reconstruction* of heterocycles, which included, at first step, construction of fused azaindolizines on the base nitrogen containing heterocycles and next step destruction of basis heterocyle.



Ar = a-Py, benzimidazolyl-2; LG = H; Ar = Ar, LG = COR', CO_2H

A tetrazolyl hydrazones were prepared by azo coupling of tetazolyl-5-diazonium and α-pyridyl- or benzimidazolyl acetonitriles with good yields. Aryl derivatives of acetonitrile were activated by acyl functional before `Japp-Klingemann reaction with diazo compound. A tetrazolotriazines were destruction by copper or PPh_3 to 3,5-diamino-1,2,4-triazines.

This method is superior to the reported methods in all aspects such as short reaction times and excellent yields of 6-aryl-3,5-diamino-1,2,4-triazines. For example, the proposed method of preparation of *Lamotriginum* has 45%

yields for finished compounds. Also the method of activation for aryl derivatives of acetonitriles in Japp-Klingemann reaction can be used to synthesized of several new 6-aryl, -hetaryl and -alkyl derivatives of 3,5-diamino-1,2,4-triazine.

We thank the Russian Foundation of Basic Research grant 13-03-00867 A and State task of Russian Ministry of Education (projects code 2458).

PP 20. NITROCYANACETIC ESTER AS THE PERSPECTIVE SYNTHON IN SYNTHESIS OF NITROAZOLO[1,5-c][1,2,4]TRIAZINES

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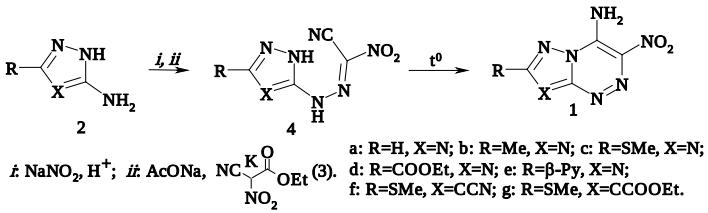
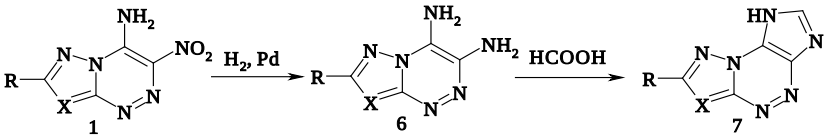
Synthesis of heterocyclic compounds similar in structure to the natural purines traditionally attracted interest in terms of search receptors inhibitors of natural purine nucleosides, e.g. the adenosine and guanosine. These inhibitors can be used in the treatment of numerous diseases, from Parkinson's and Alzheimer's deseages to malignant tumors. The perspective target in the wide area of azoloazines is 6-nitro-7-aminoazolo [5,1-c] [1,2,4] triazines (1). It is already known that some of those compounds possesses of medicinal action. A method of synthesis of compounds (1) consists in reacting 3-diazoazoles with nitroacetonitrile (2). Significant limitation of the method is the instability of compound (2), which is the obstacle in the synthesis of nitroaminoazolotriazines. Now we have developed an effective and simply method 6-nitro-7-aminoazolo [5,1-c] [1,2,4] triazines (1) synthesis using suitable nitrocyanacetic ester potassium salt (3), prepared by oxidation isonitrosocyanacetic ester. One can receive azolylhydrazones of nitriles of 2-nitroglyoxylic acid (4) in good yields by azo coupling 3-diazotriazoles or 3-diazopirazoles with nitrocyanacetic ester in aqueous solution. 6-nitro-7-aminoazolo [5,1-c] [1,2,4] triazines (1) are obtained by reflux hydrazones (4) in DMF.



Reduction of compounds (1) leads to the heterocyclic diamines (6). Azoloazapurines (7) are received by refluxing compounds (6) in formic acid.



Thus, we have upgrade method for the synthesis aminoazolo [5,1-c][1,2,4] triazines and azoloazapurines as potential receptors inhibitors of natural purine nucleosides.

Acknowledgment. We thank the Russian Foundation of Basic Research grant 13-03-00867 A and State task of Russian Ministry of Education (projects code 2458).

PP 21. TRANSFORMATIONS OF 2-AZIDO-5-NITROPYRIMIDINE IN REACTIONS WITH PYRIDINIUM YLIDES

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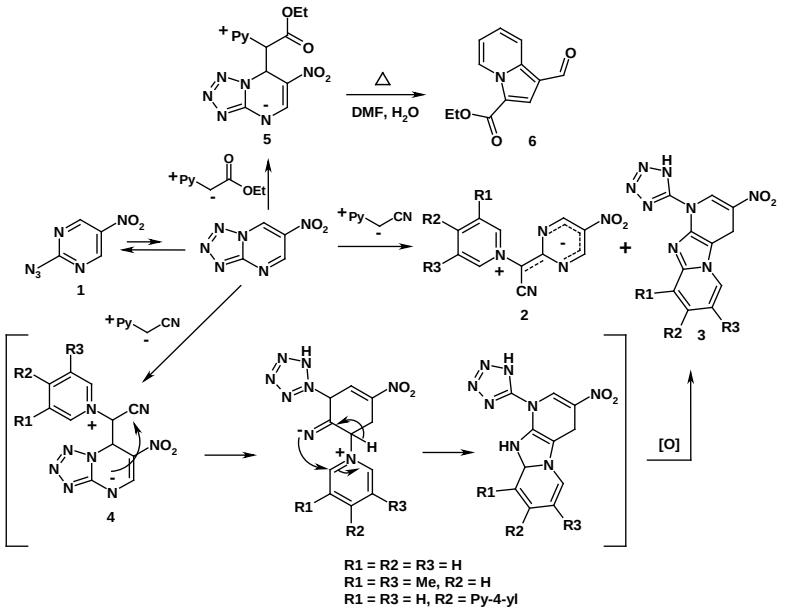
Nitroazines are well known to be the objects of functionalization based on the direct nucleophilic attack of unsubstituted C(sp^2)-H of heteroaromatic ring. Nitroazines are prone to react with ring opening and recyclization with creation of new and versatile heterocyclic systems.



The interaction products of 2-azido-5-nitropyrimidine **1** with nitrogen ylides appeared to depend on the reaction conditions and the structure of ylide. The result of coupling of **1** with pyridiniumcyanmethylylide derivatives are the products of *ipso*-substitution of azide group **2** and recyclization of **3,** the latter goes through the formation of unstable intermediate σ^H-product. The

ratio of **2** and **3** products is variable depending on the conditions.

The reaction of **1** with pyridiniumethoxycarbonylmethylylide brings to the stable σ^H-adduct **5**. The product can be further thermally transformed in DMFA (aq) into indolizine **6**.

Acknowledgments. The work was financially supported by the Russian Foundation for Basic Research (grants no. 14-03-01017_A, 14-03-31385_mol_a, 13-03-90606_Arm_a), Nsh-3656-2014.3.

PP 22. SUGAR-DERIVED CYCLIC IMINES: ONE-POT SYNTHESIS AND DIRECT FUNCTIONALIZATION

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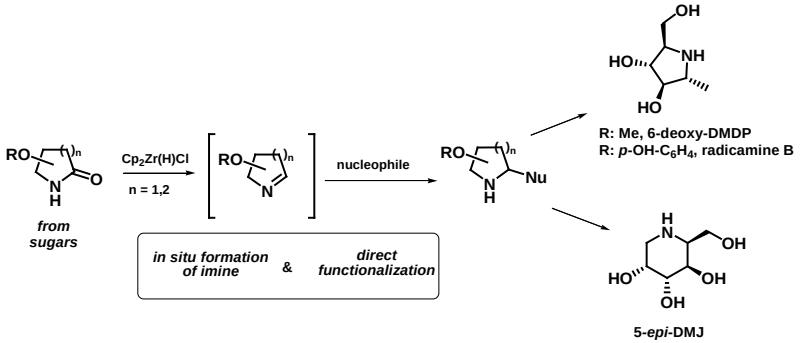
A simple method of synthesis sugar-derived imines[1] by Schwartz's reagent reduction of easily available sugar lactams[2] has been described. A direct addition of nucleophiles to the generated *in situ* cyclic imines and subsequent deprotection of hydroxyl function allows to convert sugar lactams in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



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PP 23. THE KINUGASA REACTION AS A USEFUL METHOD FOR THE SYNTHESIS OF β-LACTAMS FROM BASIC RESEARCH TO PRACTICAL APPLICATIONS

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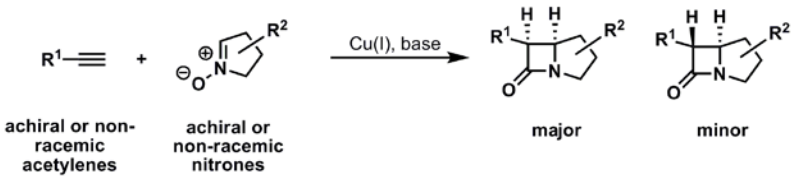
The copper(I) mediated reaction of nitrones and terminal acetylenes, known as Kinugasa reaction, represents an attractive method of direct formation of the β-lactam ring [1,2]. Herein, we present our studies on Kinugasa reaction involving cyclic nitrones readily available from hydroxy acids or amino 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].



Acknowledgment. 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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J. Antibiot. **2013**, *66*, 161-163

PP 24. NEW DERIVATIVES OF PYRANOPYRIDONES WITH TRYPTAMINE FRAGMENT: SYNTHESIS AND BIOLOGICAL ACTIVITY

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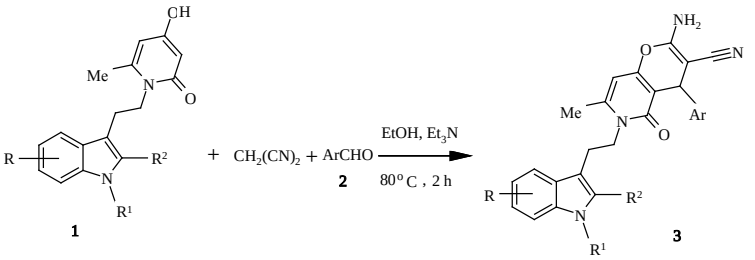
Previously, we reported that the method of multicomponent reactions can be use for preparation biological active heterocyclic analogues of podophyllotoxine [1, 2]. Continuing research we have synthesized the library of derivatives of pyranopyridones **3** with tryptamine fragment at the nitrogen atom.



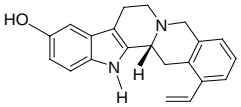
R=H, alkyl, halogen, O-alkyl, O-aryl; R^1= H, CH_2Ph; R^2=H, Me; Ar=Ph, substituted Ph, hetaryl

A one-step three component reaction of pyridotryptamines **1** with malononitrile and various substituted aromatic aldehydes **2** in 1:1:1 ratio proceeds smoothly in refluxing ethanol containing small quantity of Et_3N. The product yields 45-80%. The structure of compounds **3** was proved by ^1H NMR and confirmed by elemental analyses. Pyridones **1** have been prepared by treating commercially available 4-hydroxy-6-methyl-2*H*-pyran-2-on with tryptamine [3].

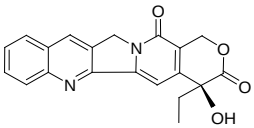
The pyranopyridones **3** contain voluminous lipophilic aryl group in the position 4 of pyrane cycle and fragment of tryptamine at the nitrogen atom of pyridone ring. These compounds, as we believed, must have potent cytotoxicity, because it repeats the structure of indolisinochinolin and iochimbin alkaloids (10-hydroxyaugustine and camptothecin).

The calculation of the energies of the molecules **3** identified the most

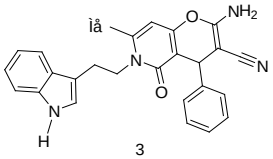
profitable conformations. The superimposition these conformations upon camptothecin detect the maximal overlap between the two structures.



10-Hydroxyaugustine



Camptothecin



3

The pyranopyridones **3** (24 samples) were tested for cytotoxic activity using cell line acute myeloid leukemia MV-4-11. The cells were treated with respect compounds for 72 h and cell viability was assessed through measurements of mitochondrial dehydrohenase activity using MTT method. It was found cytotoxic activity of number compounds (R=H, 7-Cl, 5-Me; Ar= C_6H_2-3-OCH_3-4-Oac-5-Br, C_6H_3-3-OH-4-OCH_3), but less than the camptothecin.

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PP 25. 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].

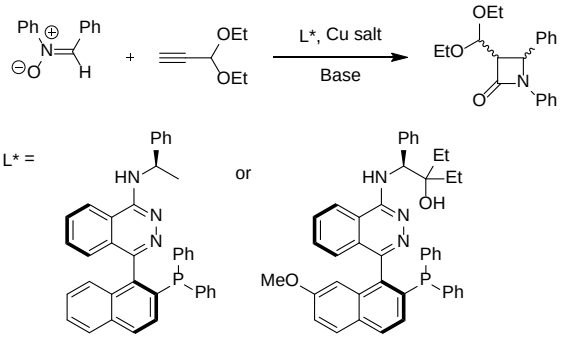
Scheme 1. *Kinugasa reaction*

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*

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

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PP 26. STEREOCHEMISTRY OF OXAZOLONE RING FORMATION IN THE SYNTHESIS OF ACETYLATED DERIVATIVE OF CYCLIC N^6-THREONYLCARBAMOYLADENOSINE (ct^6A)

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N^6-Threonylcarbamoyladenosine (t^6A), a universally conserved hypermodified nucleoside located at the position 37 (position adjacent to the 3'-end of the anticodon) of several tRNA molecules, is known for more than forty years. It has been well documented that t^6A is a very important modification for precise decoding of genetic information and accuracy of protein synthesis in the cells [1-3]. Recently it has been found by Suzuki and coworkers [4] that in several subspecies of bacteria, fungi and plants, the native structure of t^6A is a nucleoside with the threonine residue cyclized to the structure of the oxazolone ring (cyclic-t^6A or ct^6A) (Fig. 1a). The discovery of cyclic t^6A nucleoside indicates that many previous reports regarding the biological functions of the open t^6A form should be reconsidered.

Recently, we have elaborated the simple procedure for the efficient synthesis of acetylated derivative of ct^6A by dehydratation of the open nucleoside under acetic anhydride treatment[5] and we have shown that the oxazolone ring in ct^6A structure is more stable than the typical oxazolones derived from N-acyl or N-alkoxycarbonyl amino acids (Fig. 1 b). Additionally, it is also well known from peptide chemistry that during the typical oxazolone ring formation the epimerization at C-α carbon of amino acid residue is often observed [6,7].

In this context, the study on stereochemistry of oxazolone ring formation during the cyclization of chiral L-threonyl residue of t^6A nucleoside were undertaken.

For this purpose, we synthesized model 2',3',5'-*O*-acetylated derivatives of cyclic N^6-threonylcarbamoyladenosine from the open 2',3',5'-*O*-acetylated t^6A substrate bearing natural L-amino acid (L-Ac_3t^6A) as well as the racemic DL-threonine (DL-Ac_3t^6A). The synthesis was performed under the same

conditions, with acetic anhydride as dehydrating agent (Fig. 2a). ^{1}H NMR technique was used to recognize the situation of threonine stereochemistry and the spectra of obtained L-Ac$_3$ct^{6}A and DL-Ac$_3$ct^{6}A taken in D$_2$O or DMSO were compared.

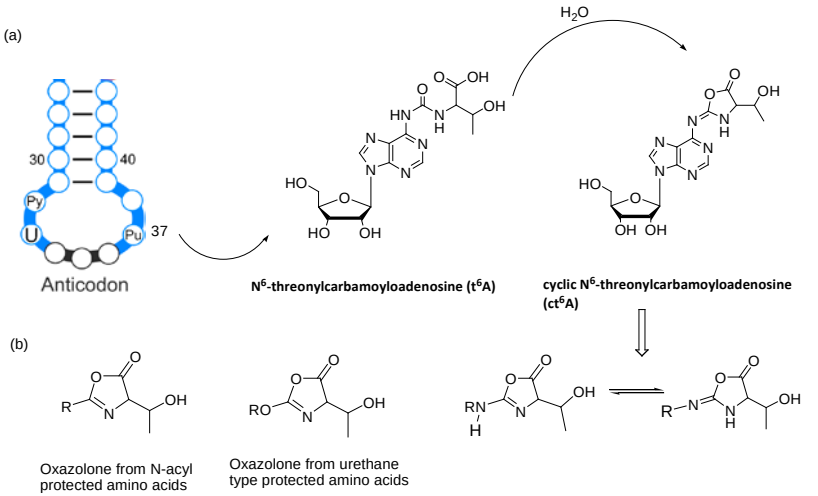

Figure 1. *(a) Structure of t^{6}A and ct^{6}A, modified nucleosides located at 37 position in tRNA anticodon loop (b) Structures of oxazolone ring from different types of N-protected amino acids.*

Analysis of ^{1}H NMR spectrum recorded for Ac$_3$ct^{6}A in D$_2$O bearing DL-threonine revealed splitting of H2', H3' sugar protons and Hα, Hβ protons of threonine residue, while in DMSO-d$_6$ the differentiation of purine H$_2$ and threonine C14-OH protons were observed. The corresponding signals in ^{1}H NMR spectra of Ac$_3$ct^{6}A obtained from open nucleoside with L-threonine were non-splitted. These results indicate that we are able to observe diastereoisomers differentation with ^{1}H NMR technique and confirm that there is no epimerization at the α-carbon on L-threonine residue in L-Ac$_3$ct^{6}A during oxazolone ring formation under acetic anhydride treatment.

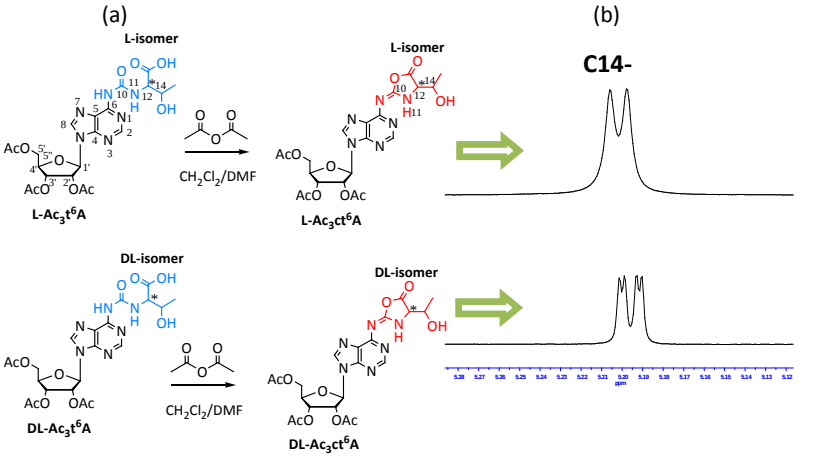

Figure 2. *(a) Synthetic procedure for cyclic 2',3',5'-tri-O-acetyl-N^6-threonylcarbamoyladenosine synthesis with "open" Ac$_3$t^{6}A bearing L-threonine or DL-threonine residue, respectively. (b) An example of 1H signals differentiation: C14-OH signal of L-Ac$_3$t^{6}A (upper) and C14-OH of DL-Ac$_3$t^{6}A (lower) from the ^{1}H NMR spectrum taken in DMSO.*

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PP 27. SYNTHESIS AND CYTOTOXIC EVALUATION OF 4,4-DISUBSTITUTED 3-METHYLIDENECHROMAN-2-ONES AND 5-SUBSTITUTED 4-METHYLIDENEPYRAZOLIDIN-3-ONES

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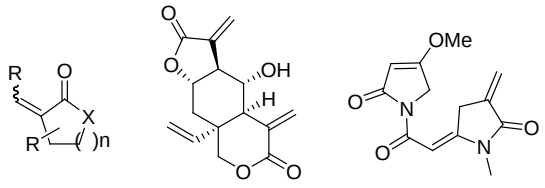
For some time we synthesize in our laboratory analogues of α-alkylidenelactones andα-alkylidenelactams of general structure **1** (Figure 1)[1]. These compounds constitute a class of natural and synthetic products with high biological activity, especially cytotoxic. For example, Vernolepin **2**, isolated from *Vernonia hymenolepis*, or Pukeleimide E **3**, isolated from cyanobacterium *Lyngbya majuscula*, exhibit significant cytotoxic activity [2]. This is mainly due to their ability to act as excellent Michael acceptors towards bionucleophiles containing mercapto groups, e.g. L-cysteine. In a search for new, biologically promising analogues we apply a Horner-Wadsworth-Emmons methodology for the construction of the *exo*-alkylidene bond. Many compounds obtained in our laboratory turned out to be highly potent against various cancer cell lines.



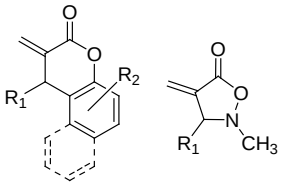
1 2 3

X = O, NR; n = 1, 2

Figure 1

Recently, we carried out synthesis of variously substituted 3-methylidenechroman-2-ones **4** bearing various aromatic rings condensed with α-alkylidenelactone ring (Figure 2). We also obtained 4-methylideneisoxazolidinones **5** containing additional nitrogen atom in the lactone ring. Some chromanones **4** and isoxazolidinones **5** prepared in our laboratory proved to

be very potent against several cancer cell lines (e.g. HL-60, NALM-6, MCF-7) [3].

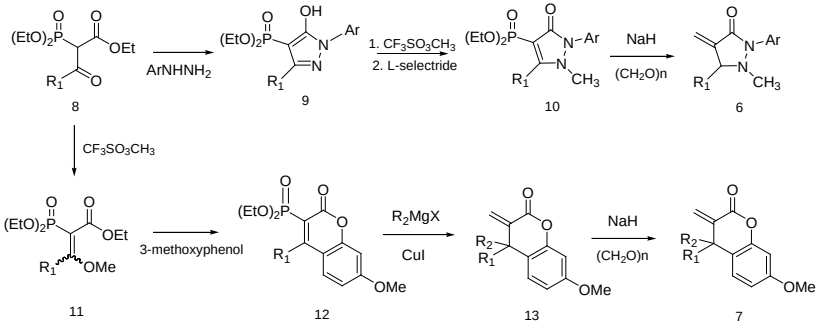


4 5

Figure 2

Encouraged by these results we decided to develop the synthesis of, so far unknown, 5-substituted 4-methylidenepyrazolidin-3-ones **6** which have additional nitrogen atom in the lactam ring and 4,4-disubstituted 3-methylidechroman-2-ones **7** (Scheme 1). To gain access to pyrazolidinones **6** we decided to prepare substituted 1-aryl-4-diethoxyphosphoryl-1*H*-pyrazol-5-ols **9** from various ethyl 2-acyl-2-diethoxyphosphorylacetates **8** and arylhydrazines. N-methylation of pyrazolols **9** using methyl triflate followed by reduction with L-selectride gave Horner-Wadsworth-Emmons reagents **10** which were next used for the olefination of formaldehyde to provide final 5-substituted 4-methylidenepyrazolidin-3-ones **6** in good yields.

3-Methylidenechroman-2-ones **7** were also obtained from ethyl 2-acyl-2-diethoxyphosphoryl-acetates **8**, which were converted into corresponding ethyl 3-alkyl-3-alkoxy-2-diethoxyphosphoryl acrylates **11** by the alkylation with methyl triflate. Reaction sequence consisting of Friedel-Crafts alkylation of 3-methoxyphenol using acrylate **11** followed by the Michael addition of Grignard reagents to the obtained phosphorylated chromenones **12** gave 4,4-disubstituted 3-diethoxyphosphorylchromanones **13**. Olefination of formaldehyde using Horner-Wadsworth-Emmons reagent yielded target 3-methylidenechroman-2-ones **7**.



Scheme 1

Cytotoxic activity of the obtained compounds was tested at the Medical University of Lodz.

Acknowledgement. This project was financed by the National Science Centre, Poland (decision No. DEC-2012/07/B/ST5/02006) and by Young Scientists' Fund at the Faculty of Chemistry, Lodz University of Technology, Grant W-3/FMN/11G/2013.

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PP 28. THE INVESTIGATION OF ALKYLLATION REACTION OF DIBENZOMETHANE AND MALONODINITRILE WITH 1,3-DIPHENYLPROPENONE

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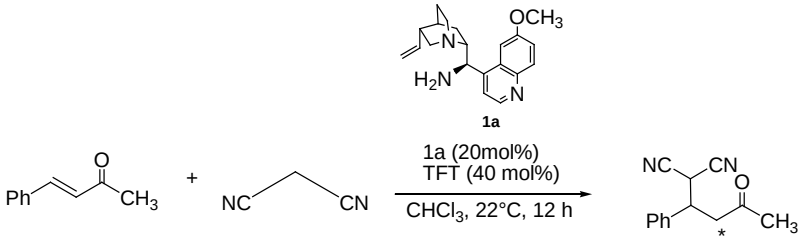
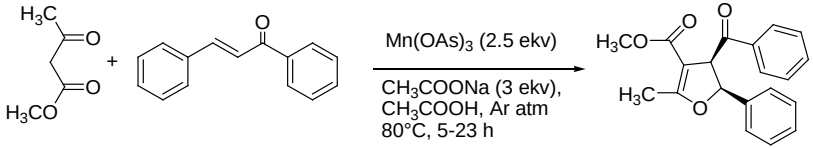
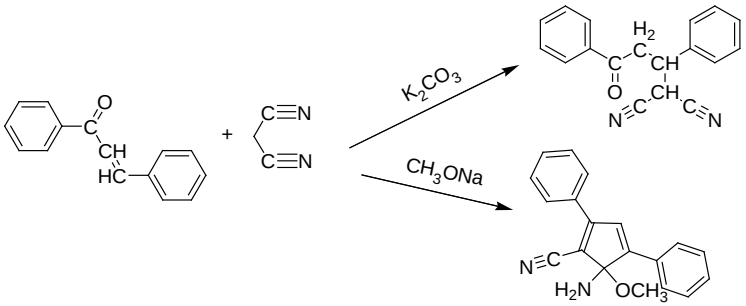
It has been investigated the Michael addition reaction of malononitrile to acyclic and cyclic α,β-unsaturated ketones with high enanthioselectivity by Xuefeng Li and others [1]. In this Michael addition reaction the primary amine obtained from quinine works as catalyst:



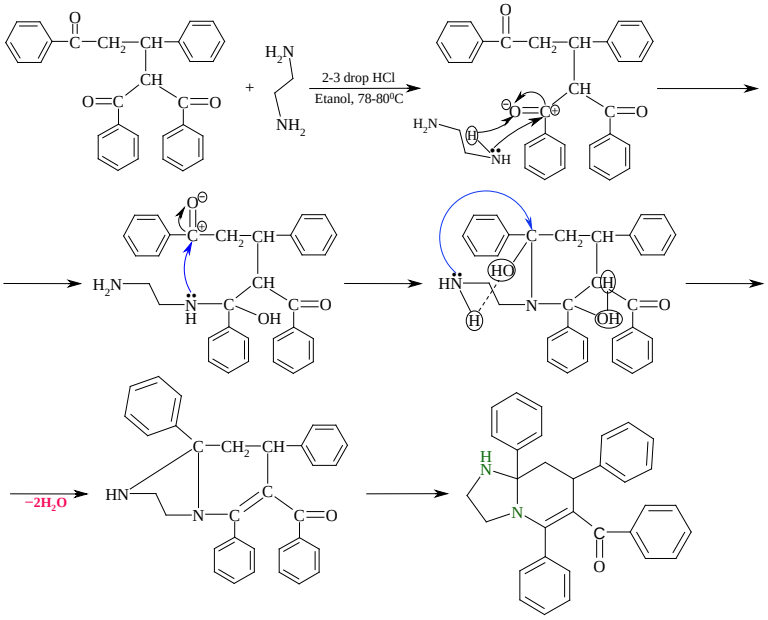
Pachiappan and others carried out the alkyllation reaction of chalchone with 1,3-dicarbonyl compounds in the presence of Mangan triacetate, sodium acetate, and acetic acid, in the argon media. The reaction takes place in the direction of obtaining of alkylation's product with high yield [2]:



But we carried out the Michael addition reaction of malonodinitrile to chalchone in the presence of sodium methylate. It was established that when carry out the reaction by using 15% solution of potassium carbonate, we obtained the corresponding compound with opened structure. But by using equimol quantity of alcoholate the reaction product is compound with cyclic structure:



It was established that by interacting of Michael's addition reaction adduct obtained from reaction of chalcone with dibenzoilmethane in etanol media and by using HCl with ethylenediamine, we can obtain heterocyclic compound. The proposed mechanism of reaction is:



Phenyl-(5,7,8a-triphenyl-1,2,3,7,8, 8a-hexahydro-imidazo[1,2-a]pyridin-6-yl)-methanone

The structures of synthesized compounds were established by IR, ^{1}H, ^{13}C NMR spectroscopy and by X-Ray investigation .

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PP 29. SYNTHESIS AND X-RAY INVESTIGATION OF N-(4,6-DIMETHYLPYRIDYN-2-YL)-1H-BENZIMIDAZOL-2-AMINE

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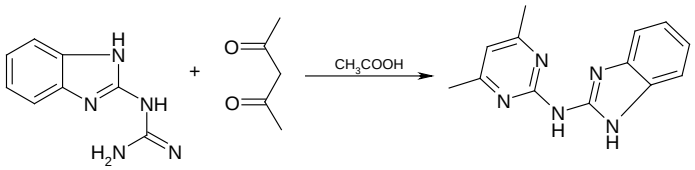
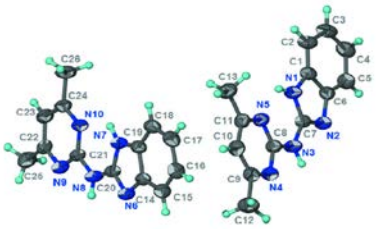
Benzimidazole derivatives have found application in medicine thanks to their broad spectrum of pharmacological activities such as antimicrobial, antiviral, anti-diabetic and anticancer activity [1]. By heating of 1H-benzo[d]imidazol-2-yliminomethanediamine with acetylacetone in the presence of catalytic quantity of acetic acid during 1 hour has been synthesized N-(4,6-dimethyl-piridyne-2-yl)-1H-benzimydazole-2-amine [2]. Title compound has been reported earlier [3]. The present synthesis is a more convenient synthesis that uses acetylacetone as one of the reactants.



The reaction was monitored by TLC until completion. After completion of reaction, the solid that formed on cooling was collected and recrystallized from ethanol to give the title compound in 80% yield.



X-ray investigation of this compound showed that an amino N atom in the approximately planar $C_{13}H_{13}N_5$ molecule is connected to a benzimidazoyl fused-ring and a pyrimidyl ring; the amino N atom of the fused ring forms an

intramolecular N–H···O hydrogen bond to a pyridmidyl N atom. There are two independent molecules; each molecule is connected to an inversion-related molecule by an N–H···O hydrogen bond

This compound crystallized in the triclinic space group and has following hydrogen-bond geometry (A˚, º):

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···N5	0.86 (1)	2.05 (2)	2.664 (2)	128 (2)
N3—H3···N2^{i}	0.87 (1)	2.05 (1)	2.912 (2)	170 (2)
N7—H7···N10	0.87 (1)	2.10 (2)	2.695 (2)	125 (2)
N8—H8···N6^{ii}	0.87 (1)	2.05 (1)	2.908 (2)	170 (2)

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PP 30. AMINO ALCOHOLS - A VERSATILE COMPOUNDS FOR THE SYNTHESIS OF THIAZOLIDIN-4-ONE DERIVATIVES IN THREE COMPONENT REACTION PROTOCOL

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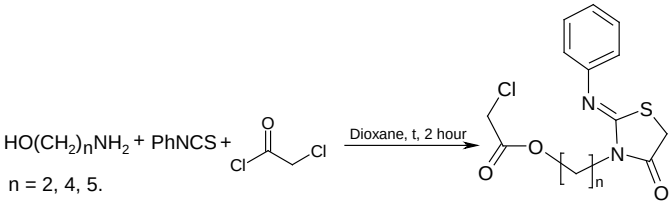
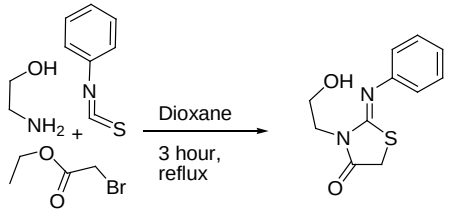
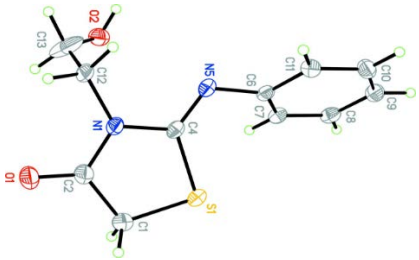
Thiazolidines and their derivatives have been reported to have fungicidal, local anesthetic, anti-seizure, antitubercular, anti-bacterial, anti-amoebic, anti-diabetic, and anti-inflammator activities [1]. Compounds incorporating the thiazolidinone moiety has established as one of the biologically important scaffolds [2,3]. Herein we report the facile synthesis of the tiazolidyne-4-one derivatives in three component condensation reactions. These reactions take 2-3 hours in the dioxane media in the boiling point of solvent. In the reaction system, chloroacethyl chloride was taken in excess amount, which lead acylation of hydroxyl group on side chain:



In the presence of ethyl bromoacetate in reaction medium has been synthesized 3-(2-hydroxyethyl)-2-phenyliminothiazolidin-4-one [4].



Structures of the synthesized compounds were determined by ^{1}H, ^{13}C spectrums. In X-ray investigations of 3-(2-hydroxyethyl)-2-phenyliminothiazolidin-4-one structure was used APEX2 diffractometer:



In the title compound the thiazole and phenyl rings are inclined at 56.99 (6) to one another. The presence of the phenylimine substituent is confirmed with the C-N distance to the thiazole ring of 1.2638 (19) A˚. The molecule adopts a Z conformation with respect to this bond.

The reactions were monitored by TLC until completion. The crude product was recrystallized from ethanol. Synthesized compounds were tested for their bactericide and fungicide properties and demonstrated good biological activity.

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PP 31. A FACILE AND PRACTICAL APPROACH TO NOVEL 6-HYDROXY-2,3,4a,5,6,7-HEXAHYDROBENZO[*f*]PYRAZINO[1,2-*a*]AZEPINE-1,4-DIONES

S. A. Guerrero[1], L. M. Acosta[1], J. Cobo-Domingo[2], M. Nogueras[2], A. Palma[1]
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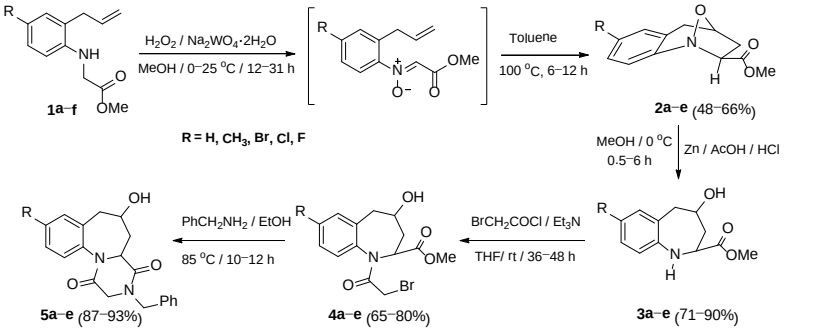
The tetrahydro-1-benzazepinesystem has been targeted in synthetic investigations for their knownbiological and pharmacological properties [1–6]. Consequently, it is not surprising that a significant number of methodologies have been developed for the synthesis of new derivatives of this heterocyclic system [7–10]. Taking into account that the tetrahydro-1-benzazepine nucleus is a good scaffold for the development of novel molecules with privileged bioactivities, we have reported a practical an expeditious approach for the stereoselective synthesis of new series of 2-aryl(alkenyl)-1,4-epoxytetrahydro-1-benzazepines and their reduced analogues, namely *cis*-2-aryl(alkenyl)tetrahydro-1-benzazepin-4-ols, starting from available *ortho*-allylanilines[11,12]. The potential utility of such compounds as anti-Chagasic and anti-leishmanial agents was also demonstrated [13].

Although a large number of synthetic routes to tetrahydro-1-benzazepine derivatives are described in the literature, there is very few information about hexahydrobenzo[*f*]-pyrazino[1,2-*a*]azepines [14,15], which may be due to lack of general methods for the synthesis of such derivatives. In order to improve the utility of our method, and as part of a program to identify structurally novel anti-parasitic compounds against both *T. cruzi* and *L. chagasi* parasites, we are now describing the synthesis of a new series of hexahydrobenzo[*f*]pyrazino[1,2-*a*]azepine-1,4-diones **4a–e**, starting from synthetically available methyl 2-((2-allylphenyl)aminoacetates **1a–e**.

As shown in Scheme,the preparation of the 1,4-epoxycycloadducts **2a–e** was carried out in the first step of our approach, and involvesthe selective oxidation of the precursors **1a–e** in methanol with an excess of H_2O_2 (aqueous, 30%) in the presence of sodium tungstate as catalyst, to give thecorresponding nitrones, which in situ suffer an1,3-dipolar cycloaddition

across the pendant allylic fragment connected to the *ortho* position.

In the next step, we conducted the reductive cleavage of **2a–e** by the treatment with excess of zinc powder in a mixture of glacial acetic acid and concentrated hydrochloric acidat 0 °C. In the conditions employed, the reductive cleavage of the N-O bridged bond proceeded very easy withthe formation of the expected 4-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*b*] azepine-2-carboxylates **3a–e**, which were isolated by silica gel column chromatography in good yields. When compounds **3a–e** were subjected to the usual conditions for N-acylation (1.5 equiv. $BrCH_2COCl$/1.5 equiv. Et_3N/dry THF/rt), the products isolated were the expected methyl 1-(2-bromoacetyl)tetrahydro-1*H*-benzo[*b*]azepine-2-carboxylates **4a–e**, which were further cyclized with an excess of benzylamine to obtain the desired6-hydroxyhexahydrobenzo[*f*]-pyrazino[1,2-*a*]azepine-1,4-diones **4a–e**in excellent yields.



Scheme 1. *Synthesis of novel6-hydroxyhexahydrobenzo[f]pyrazino[1,2-a]azepine-1,4-diones 4a–e*

Acknowledgement. AP,LMA and SAG acknowledge for the financial support due by the Colombian Institute for Science and Research (COLCIENCIAS, grant No 1102-521-28229) and the Universidad Industrial de Santander (Vicerrectoría de Investigación y Extensión). LMA also thanks COLCIENCIAS for her doctoral fellowship. JC and MN thank "Centro de Instrumentación Técnica" of Universidad de Jaén and the staff for data collection and supporting. The financial support from the Consejería de Economía,

Innovación y Ciencia (Junta de Andalucía) and Universidad de Jaén for financial support are also thanked.

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PP 32. SYNTHESIS OF NEW RIGID A-AMINO-ACIDS IN THE DIHYDRODIBENZO[*b*,*e*]AZEPINEAND TETRAHYDRO-1-BENZAZEPINE SERIES

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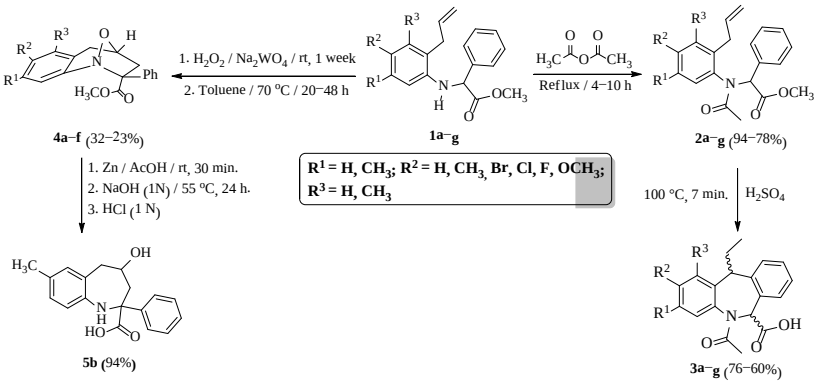
The partially reduced dibenzo[*b*,*e*]azepine and 1-benzazepine systems are important pharmacophores in drug discovery and many of their derivatives exhibit a broadspectrum of biological activities [1–8]. This fact has fuelled research, which focusesmainly in the development of methodologies for the preparation of new bioactive derivativesbearingthese heterocyclicsystems [9–15]. Lately, our attention has been focused on studying boththe intramolecular Friedel–Crafts alkylation [16] anddipolar 1,3-cycloaddition reactions [17,18] as key transformations inthe construction of several seven-membered nitrogen-containing heterocycles. To broaden the scope of these two classical reactions, and incontinuation of our research programme on the preparation ofnew potentially bioactive molecules containing the dihydrodibenzo[*b*,*e*]azepineand tetrahydro-1-benzazepine nuclei,we have been testingthe chemistry of several substituted methyl 2-((2-allylaryl)amino)-2-phenylacetatesin both acidic and oxidative conditions to obtain rigid α-amino-acids of the type 5-acetyl-11-ethyl-6,11-dihydro-5*H*-dibenzo[*b*,*e*] azepine-6-carboxylic acids and 4-hydroxy-2-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-2-carboxylic acids, compounds thathave not been reported up to now in the literature.

As depicted in Scheme, title compounds **3a–g** and **5b** were synthesized starting from the appropriately substituted methyl 2-((2-allylaryl)amino)-2-phenylacetates **1a-g**, compounds that were previously prepared in excellent yields (90–77%) by the treatment of the corresponding *ortho*-allylanilines with methyl bromophenylacetate in DMF at 60 °C. Initially, precursors **1a–g** were reacted with acetic anhydride at reflux to give the *N*-acetylated derivatives **2a–g.** Cyclization of **2a–g**was performed via intramolecularFriedel-Crafts alkylation in strong acidic conditions to give the expected 5-acetyl-11-

ethyl-6,11-dihydro-*5H*-dibenzo[*b*,*e*]azepine-6-carboxylic acids **3a–g** as mixture of two diastereomers, which were individually separated by silica gel column chromatography.



Scheme. *Synthesis of the target α-amino-acids 3a-g and 5b*

Additionally, precursors **1a–f** were subjected to selective oxidation with an excess of H_2O_2 (30 %) in the presence of sodium tungstate as catalyst, to give the corresponding nitrone intermediates, which in situsuffer an intramolecular 1,3-dipolar cycloaddition. This sequence of reactions affords only one of the two possible cycloadducts, which were identified by means of 1D and 2D NMR spectroscopy as the (1*S*,2*S*,4*R*)-methyl 2-phenyl-2,3,4,5-tetrahydro-1,4-epoxybenzo[b]azepine-2-carboxylates **4a–f**. The desired α-amino-acid **5b** was obtained in excellent yield via the stereospecific reductive cleavage of the N-O bond of the 1,4-epoxycycloadduct **4b**, by the treatment with an excess of zinc powder in a mixture of glacial acetic and concentrated hydrochloric acids, and subsequent hydrolysis of the formed α-amino-ester. All final compounds and intermediates were fully characterized by the usual spectroscopic methods.

Acknowledgements. CMS, ALL and APacknowledge for the financial support due by the Colombian Institute for Science and Research (COLCIENCIAS, grant No 1102-521-28229) and the Universidad Industrial de Santander (Vicerrectoría de Investigación y Extensión). JC and MN thank “Centro de Instrumentación Técnica” of Universidad de Jaén and the staff for data collection and supporting. The financial support from the Consejería de

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PP 33. UTILITY OF PIVALOATE ESTER FOR SYNTHESIS OF VARIOUSLY 5-SUBSTITUTED (-2-THIO)URIDINE DERIVATIVES

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5-Substituted (2-thio)uridines are frequently located at the position 34 ('wobble position'), of tRNA/mt-tRNA anticodon arm domains. Wobble (2-thio)uridines strongly influence the various functions/activities of those biopolymers in the cells cycles and their absence can result in serious diseases, *e.g.* MERRF, MELAS miopathies [1]. Synthetic, hypermodified tRNA fragments and/or their analogues have been successfully utilized for the model studies on the mechanism of ribosomal protein biosynthesis [2]. The superior hybridization of oligoribonucleotides modified with 5-substituted (2-thio)uridines encourage their use for the development of potential therapies based on selective gene silencing [3].

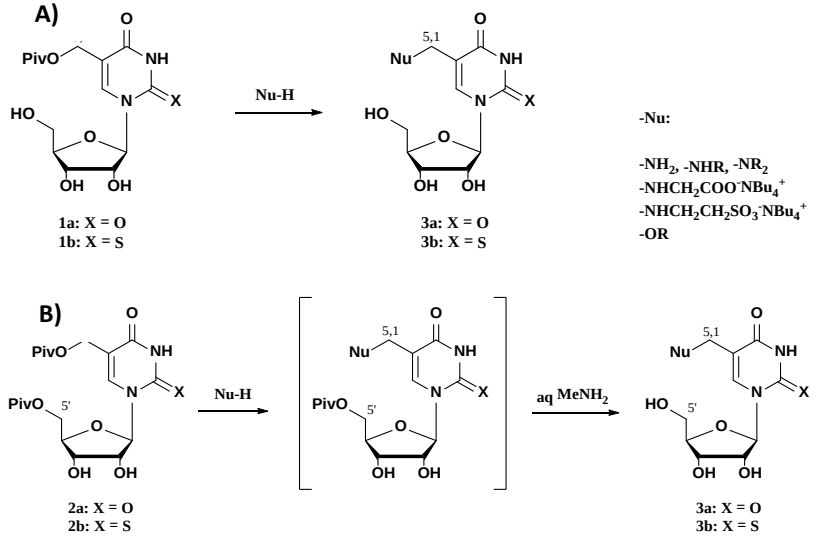
Here we report the new method for the synthesis of 5-substituted uridines (xm^5U, 3a) and 2-thiouridine derivatives (xm^5s^2U, 3b) *via* efficient nucleophilic substitution of pivaloyloxy group (Pivo) located at the position C-5,1 of nucleosides 1a,b and 2a,b (Scheme 1).

Nucleosides 1a,b and 2a,b were obtained by the pivaloilation of 5-hydroxymethyl-2',3'-O-isopropylidene(-2-thio)uridine and the subsequent removal of isopropylidene group, which resulted in the mixture of monopivaloyloxy derivative 1a,b (Pivo group only at C-5,1 position) as the main product and the minor bispivaloyloxy derivative 2a,b (Pivo groups at C-5,1 and C-5' positions). However both nucleoside substrates 1a,b and 2a,b can serve as the precursors for the synthesis of 5-substituted (2-thio)uridines.

The previously reported methods utilized 5-chloromethyl(-2-thio)uridine or quaternary ammonium salt of 5-pyrrolidinomethyl(-2-thio)uridine derivatives as substrates for the nucleophilic substitution at position C-5,1 [4]. However, these methods are not convenient due to instability of the substrates and moderate yields of the final 5-substituted (2-thio)uridines.

The application of monopivaloyloxy derivatives 1a,b allowed to perform the substitution reaction with various nucleophiles such as ammonia, primary and secondary amines, amino acids and alkoxides under anhydrous condition as well as in aqueous solution to obtain nucleosides 3a,b in 60-90% yield (Scheme 1A).

On the other hand different reactivity of pivaloyloxy group at C-5,1 position and at C5' position enabled the preparation of 3a,b also from bis-pivaloyloxy derivatives 2a,b utilizing two-step reaction, which includes nucleophilic substitution at the allylic position under anhydrous condition and then selective removal of 5'-O-pivaloate ester (Scheme 1B). 5'-O-Pivaloate ester of (2-thio)uridine 2a,b was stable under anhydrous condition, whereas the aqueous condition aq. 40% $MeNH_2$ caused its deprotection.



Scheme 1. *Synthesis of 5-substituted (2-thio)uridines 3a/3b via 5-pivaloyloxymethyl(-2-thio)uridine 1a/1b (A) or 5'-pivaloyl-5-pivaloyloxymethyl(-2-thio)uridine 2a/2b (B).*

The use of pivaloyloxy group for activation the C-5,1-position of (2-thio)uridine in nuclophilic substitution has advantages such as stability of the

substrate, no detectable reaction side-products and the possibility to use different reaction conditions, including those in aqueous solutions.

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PP 34. AN ENTRY TO CARBAPENEM ANTIBIOTICS SCAFFOLD *VIA* ASYMMETRIC KINUGASA REACTION

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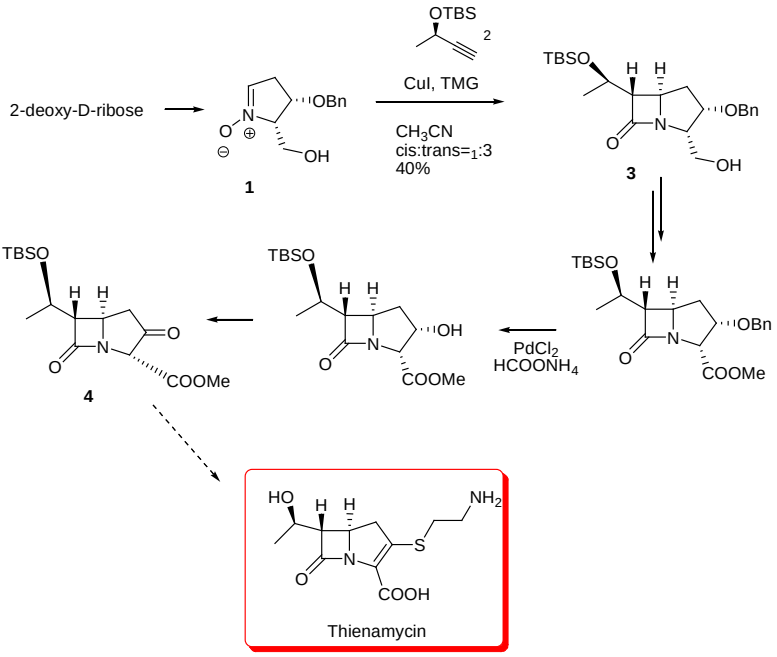
The copper(I) mediated reaction of nitrones with terminal acetylenes, which is known as Kinugasa reaction, represents an interesting method of direct formation of the β-lactam ring. We have shown that the cyclic nitrone **1**, readily available from 2-deoxy-D-ribose, is particularly attractive as a substrate in the synthesis of carbapenem antibiotics. Reaction of nitrone **1** with acetylene **2** derived from D-lactic acid, in the presence of tetramethylguanidine, provides the adduct **3** having thienamycin skeleton with the same configuration at three stereogenic centers (the β-lactam fragment and the side chain) as the parent antibiotic.



The stereochemical pathway of the reaction depended on the hydroxymethyl group next to the double bond of the nitrone, whereas the trans configuration of hydrogen atoms of the four membered ring was induced by the base used. Subsequent standard transformations provided the ketone **4**, which offers an entry to a variety of carbapenems.

Acknowledgments. Financial support by the European Union within European Regional Development Fund, Project POIG.01.03.01-14-036/09

PP 35. ONE-POT SYNTHESIS OF NOVEL 2-ARYLPYRROLO[2,3,4-kl]ACRIDIN-1(2*H*)-ONES

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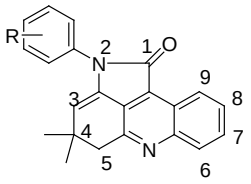
Pyrroloacridines and pyrroloacridones are of particular interest because they have a variety of interesting biological activities. Significantly, members of this family are active in assays for antihelmintic, 1 antitumor [1, 2], antifungal [3], and DNA binding [4–6]. These abilities are specifically important in inhibiting the growth of cancerous cells, making these compounds ideal for developing novel anticancer drugs.

Plakinidines and alpkinidine are pyrroloacridines that have been obtained from marine sources [1, 8]. Only a few reports are available for the synthesis of pyrroloacridines and therefore the synthetic versatility of these compounds needs to be explored.

As a result of their significant potential as therapeutics, a considerable synthetic attention has been directed at the development of efficient methods toward the construction of pyrroloacridine moiety. So, in this research we wish to introduce a new method for the synthesis of 4,5-dihydro-4,4-dimethyl-2-arylpyrrolo[2,3,4-kl]acridin-1(2H)-one as a new class of pyrroloacridin.



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PP 36. ADSORPTION OF FLUBENDIAMIDE IN TWO INDIAN SOILS VARYING IN PHYSICOCHEMICAL PROPERTIES

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Present study reports adsorption-desorption behavior of flubendiamide in two different Indian red soil and black soil varying in their physico-chemical properties. The soil sorption coefficient *K* and the soil organic carbon normalized sorption coefficient *K*oc are the two basic parameters used for describing adsorption-desorption of the insecticide. The adsorption data for the insecticide fitted well the Freundlich equation. Adsorption and desorption rates were calculated from kinetic studies. These values varied depending on the soil type and physicochemical properties. Freundlich adsorption equation described that the calculated K values from red soil was 2.13 and from black soil was 1.07. The distribution coefficient based on clay content *K*c values were 3.04 from red soil and 1.78 from black soil. The *K*oc values were 560.5 in red soil and 345.2 in black soil. Organic matter also played a significant role in adsorption and desorption of flubendiamide. Adsorption was lower at acidic pH and gradually increased towards alkaline pH, except in the range of pH 6-8. The study indicated that absorption of the insecticide was higher in red soil than black soil, which may be attributed due to different physico-chemical properties and thus contributing a significant role in flubendiamide adsorption and desorption.

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PP 37. HYDRAZONOYL HALIDES AS PRECURSORS FOR SYNTHESIS OF BIOACTIVE THIAZOLE AND THIADIAZOLE DERIVATIVES

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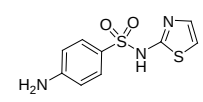
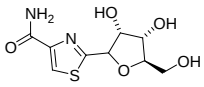
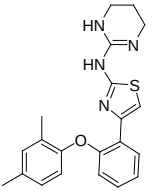
Thiazoles are important class of heterocyclic compounds, found in many drugs such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug) (Chart 1). In addition to that the thiazole moiety is a crucial part of vitamin B1 (thiamine), many derivatives of it possesses interesting biological activity such as antimicrobial [1,2], anti-HIV [3], anti-inflammatory [4], anti-Alzheimer activity [5] and anti-cancer [6] activities.



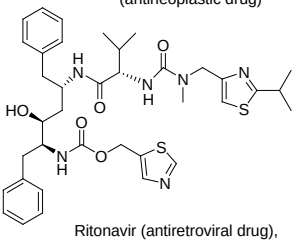
Sulfathiazol (antimicrobial drug)



Bleomycine and Tiazofurin (antineoplastic drug)



Abafungin (antifungal drug)

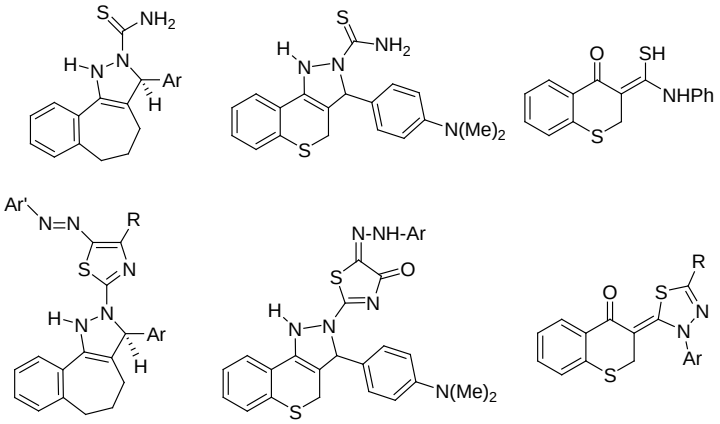


Ritonavir (antiretroviral drug),

From all of the above finding and in continuation of our work on the utility of hydrazonoyl halides in synthesis of bioactive heterocyclic ring systems [8-13], we interested herein to synthesis a new thiazoles and 1,3,4-thiadiazoles incorporated with benzo[6,7] cyclohepta[1,2-*c*]pyrazole and 1-benzothiopyran-4-ones *via* reaction of hydrazonoyl chlorides with each of 3-(4-fluorophenyl)-1,3a,4,5,6,10b-hexahydrobenzo[6,7]cyclohepta[1,2-]pyrazole-2(3*H*)-carbothioamide, 3-(4-(dimethylamino) phenyl)-3,4-dihydrothiochromeno[4,3-c]pyrazole-2(1*H*)-carbothioamide and 2-(thiochroman-4-ylidene)

hydrazinecarbothioamide. Our aim after such synthesis is to study the antitumor activity of the newly synthesized compounds and to illustrate the structure activity relationship (SAR).

The structure of all the newly synthesized compounds was established by elemental and spectral analyses. All of the synthesized compounds were tested for anticancer activity against colon cancer cell line HT29, human breast cancer cells MCF-7 and human hepatocellular carcinoma cell line HepG2. Many derivatives of the tested compounds showed moderate to high anticancer activity. Also, their structure activity (SAR) was studied.



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PP 38. SYNTHESIS AND STRUCTURE ETHYL-2,7,7-TRIMETHYL-5-OXO-4-PHENYL-1,4,5,6,7,8-HEXAHYDROQUINOLINE-3-CARBOXYLAT

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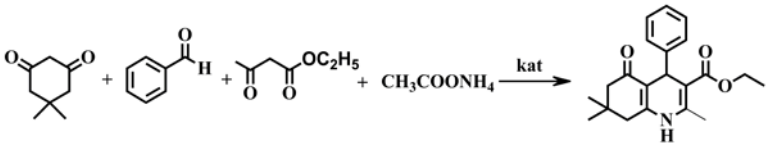
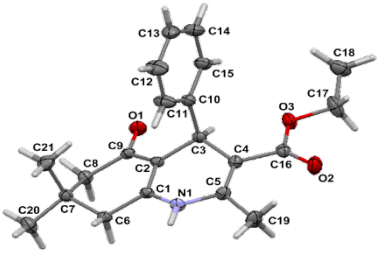
1,4-DHPs and their derivatives have recently attracted the attention of synthetic and medicinal chemists because of their wide range of biological and pharmaceutical activities such as diuretic, analgesic, myorelaxant, anticoagulant, anticancer, anti-tumor, and anti-HIV.

Based on a modified Hantzsch reaction were synthesized ethyl 2,7,7-trimethyl-5-oxo-4-phenylsubstituted-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates. It has been investigated the optical properties of ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1, 4,5,6,7,8- hexahydroquinoline -3-carboxylate (I) synthesized in the presence of chiral organic catalysts L-glutamic acid and S-proline.



cat = L- glutamic acid; S- proline



Sturucture of ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylat determined with method X-ray. Crystal ($C_{21}H_{25}NO_3$,M = 339.42) yellow, 0.20x0.20x0.20 mm^3, triclinic: a=7.3523 (4) Å, b=9.6349 (5) Å, c=13.9495 (7) Å, α=98.370 (1)°, β=91.778 (1)°, γ=106.291 (1)°, V=935.70(8) Å, Z=2, D_x=1.205q/sm^3, μ=0.08mm^{-1}, R_{int}=0.016.(6).

PP 39. SYNTHESIS AND STURUCTURE OF 9-(2-HYDROXY-4,4-DIMETHYL-6-OXOCYCLOHEX-1-EN-1-YL)-3,3-DIMETHYL-2,3,4,9-TETRAHYDRO-1*H*-XANTEN-1-ONE

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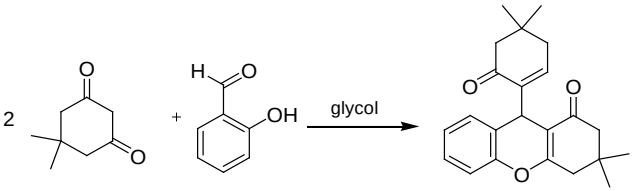
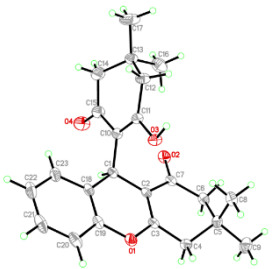
The great biological importance of the 1,4-dihydropyridine nucleus has over the years prompted the development of new improved methodologies, including solid- phase synthesis and activation. Alternatively, microwave irradiation represents an important improvement in the transformation and has also been applied for the direct synthesis of pyridines. Hence, direct microwave heating can reduce chemical reaction times from days or hours to minutes or even seconds, and therefore suppress undesired side reactions, increase chemical yields, and improve reproducibility. Based on a modified Hantzsch reaction were synthesized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanten-1-one by using microwave irradiation. The reaction scheme is following.



Sturucture of 9-(2-hydroxy-4,4-dimetyl-6-oxo-cyclohex-1-en-1-yl)-3,3-dimethyl-2,3,4,9-tetra-hydro-1H-xanten-1-one determined with method X-ray. Crystal ($C_{23}H_{26}O_4$,*M* = 366.44) colorless, 0,3x0,2x0,2 mm^3, orthorhombic: a=15.3583 (5) Å, b=11.3833 (4) Å, c=22.2070 (7) Å, V=3882.42(8) Å, Z=8, D_x=1.254q/sm^3, μ=0.09mm^{-1}, R_{int}=0.035.



PP 40. A FACILE AND EFFICIENT SYNTHESIS OF IMIDAZOPYRAZOLOPYRIDINES,PYRAZOLOPYRIDOTRIAZINES AND INVESTIGATING THEIR ANTI-TUMOR ACTIVITIES

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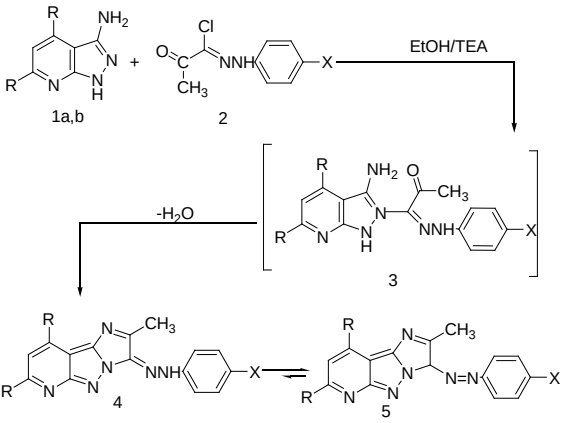
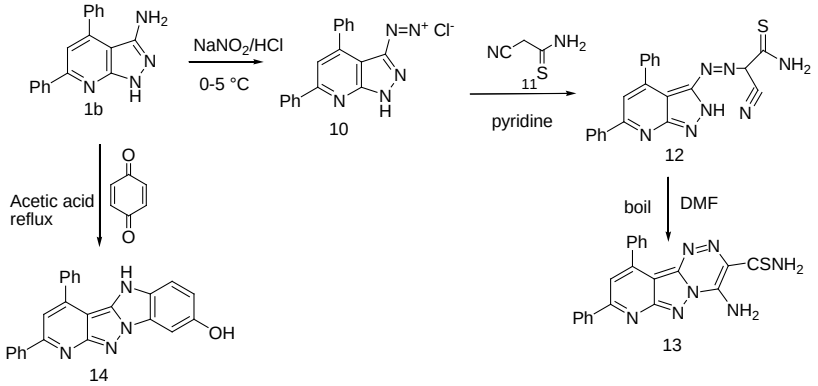
The intensive demand for constructing polyaroamtic heterocyclic systems and their analogs reflected the importance and vitality of such compounds in human life either economically or in health care products. Among the various synthesized compounds with such importance are pyrazolopyridines that built up of two highly interesting heterocycles. Pyrazolopyridines consist a unique of pharmacophores that are included in various therapeutic agents and antibiotics. These compounds were known to have antimalarial [1] anti-proliferative [2] antimicrobial [3-5] inhibition of cyclin-dependent kinases [6] and cardio-vascular [7,8] antiviral [10,11] and antileishmanial [12] activities. They also exhibit antitubercular, anxiolytic activities [13].

Generally, pyrazoplopyridines have been prepared through two alternative routes, either from building up pyrazole moiety first and reacting with activated nitriles [14]; the second route involved constructing polyfunctional pyridine nulcleus followed by reaction with various electrophilic reagents [15].

Starting from aminopyrazolopyridine derivatives **1** as a key intermediate, a number of annulated heterocycles is synthesized; compound **1** reacted with a wide range of hydrazonyl halides in ethanol in the presence of triethyl-amine to furnish compounds **5a-l** as a result of removal of a molecule of HX as well as a molecule of water. Alkylation of compound **1b** with α-haloketo-nes such as chloroacetone and phenacyl bromide in basic medium resulted in heterocyclization and afforded the tricyclic compounds **9a,b**. When com-pounds **9a,b** were coupled to benzene daizonium chloride, they delivered the imidazopyrazolopyridine derivatives **5a,f**; this could be considered as a chemical evidence of the products obtained fro reaction of **1b** with hydrazonyl halides. The building up of triazine nulcleus from the precursor **1b** was also possible through conversion of **1b** into its daizonium salt **10**;



Comp	R	X	comp.	R	X
a	CH_3	H	g	Ph	H
b	CH_3	Me	h	Ph	Me
c	CH_3	Cl	i	Ph	Cl
d	CH_3	OMe	j	Ph	OMe
e	CH_3	Br	k	Ph	Br
f	CH_3	NO2	l	Ph	NO2



coupling **10** with active methylene compounds such as cyanothioacetamide **11** furnished compound **12**. Boiling **12** in DMF for 1h yielded the bifunctional triazine derivative **13**. Cyclocondensation of compound **1b** with benzoquinone in acetic acid furnished the tetracyclic compound **14**. The structures of the prepared compounds were elucidated from their elemental analyses and spectral data and the biological activity is under investigation.

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PP 41. DEVELOPMENT OF VISIBLE FLUORESCENCE LASER PRINTING INK WITH BENZOXAZOLIC COUMARIN DYE

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Fluorescent inks have long been used for the certification of security documents, such as passports, bills, checks and coupons. Governments worldwide issue a large number of certificates and various security documents in local document offices using laser jet printer [1, 2]. Toner is a powder mainly composed of polymer and colorant that is used as ink in laser jet printing [3]. In this research, the emulsion aggregation method [3] used to synthesize the fluorescence toner that is visible under normal daylight. 0.5% of benzoxazolic coumarin dyes were employed as fluorescence dyestuffs for preparing the printing toner [4]. The resultant color toner composites were printed in a controlled environment [23°C, 50% relative humidity (RH)] using a monochrome laser-jet printer (HP 1100, Laser-jet printing machine). This printer was changed to only have a hot roll fusing system containing two metal rolls covered with silicone rubber and was heated from inside the rolls (Figure1).

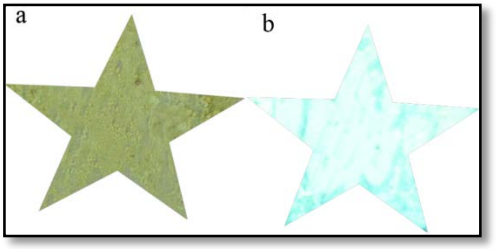

Figure 1. ***P****rinted fluorescent toners under visible light (a) and UV light (365nm) (b).*

Toner characteristics were examined using a fluorimetry, particle size analyzer, scanning electron microscopy, and differential scanning calorimetry. Fluorescent toners show appropriate characteristics compared to toners of original equipment manufacturer. The emission and reflectance spectra of

printed toner are shown in Figure 2.

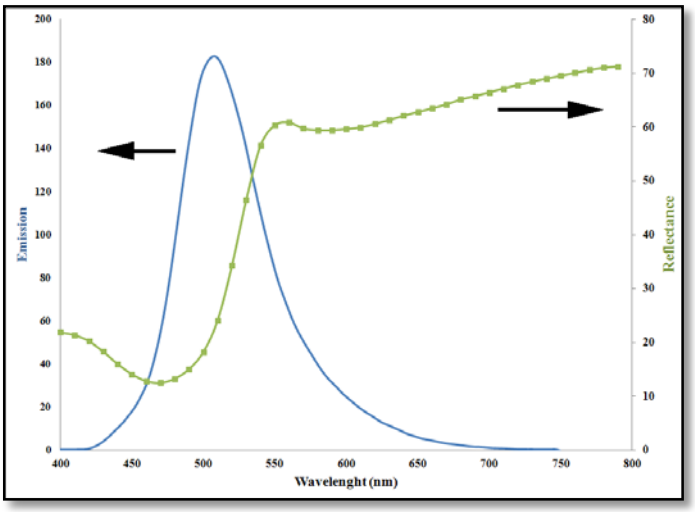

Figure 2: *Emission and reflectance spectra of printed toner*

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[4] F. Talebnia, F. Nourmohammadian, S. Bastani, Development of Novel Fluorescent Offset Ink based on Coumarin dyes: Synthesis and Properties, Progress in Organic Coatings In Press, Accepted Manuscript, (2014)

PP 42. SYNTHESIS OF NOVEL BISAZO-SPIROPYRAN PHOTOSWITCHS AND INVESTIGATION ON THEIR PHOTORESPONSES TO NANO LANTHANIDES

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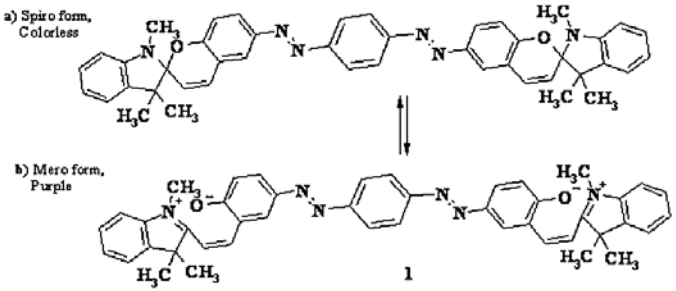
Spiropyrans, as well known photochromic compounds are considered which are usually colorless in ring close forms (spiro forms) and make colored ring open forms (merocyanine forms) under exposing to UV light. Also, they are subject of some investigation to declare their somerization in the presence of metal ions even under dark condition. Although, in the investigation of spiropyrans, synthesis of few bis-spiropyrans have been reported. The development of such bis-spiropyrans has led to the development of bifunctional chromophores in one molecule as highly sensitive molecular switches.



Scheme 1. *Synthesis pathway of the symmetric bis-azospiropyran dye 1, and colorless spiro (a) to merocyanine (b) forms*

The two provided zwitterionic merocyanine units, which had a more sensible system, developed higher sensitivity and molar capacity than the mono-spiropyran. Moreover, to the best of our knowledge, bis-azospiropyran systems have been introduced by authors only recently. Consequently, in

keeping with our earlier research on synthesis and properties of bis-azo-spiropyrans dyes, we decided to spectroscopic study of the optical behaviour of the produced photochromic dye in the presence of lanthanide salts.

Considering our latest studies, if *BASP* expose to 366 nm UV light for less than 2 minutes at r.t., it changes from colorless spiro (Sp) to merocyanine (Mc) form (Scheme 1). The maximum color created after producing of Mc-form under exposing to UV light. In this regard, the molar absorption coefficient of a non-substituted spiropyran in Mc form is $0.31\times10^4\ M^{-1}\ cm^{-1}$, it increases in the presence of an azo moiety in the Mc form of monoazospiropyran to $1.35\times10^4\ M^{-1}.cm^{-1}$. It is well-known that the higher molar absorption coefficient leads to higher sensitivity and resolution, and distinguishes the spiro form from the mero ones in photochromic applications; we found that the molar absorption coefficients of the constructed bis-azospiropyrans astonishingly surge to $3.8\times10^4\ M^{-1}cm^{-1}$ [1-2].

As expected, the presence of negatively charged phenolic oxygen in the zwitterionic open form and produced phenolate anion can act as a chelating site for effective the metal binding. Hence, during addition of aqueous solution of lanthanide salts [3] to the colorless (spiro) form of dye **1** color of solution changed.

The dependence of the absorbance on concentration of lanthanide salts was examined to investigate the composition of the complexes.

The binding constant K value for the complexes following the modified Benesi-Hildebrand was determined using the absorbance intensities recorded at different lanthanide salts concentrations.

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PP 43. COLORIMETRIC RESPONSES AND ANTIBACTERIAL EFFECTS OF AZOBENZOTHIAZOLE-POLYENE DYES IN DIFFERENT ORGANIC MEDIA

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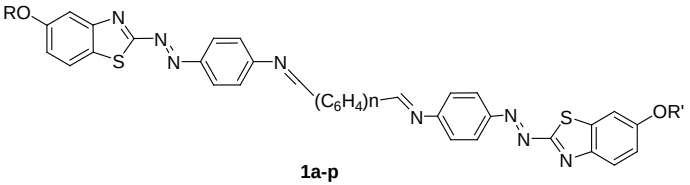
Aminobenzothiazole based dyes are considered to be the successful commercial developments of heterocyclic amines in the production of organic dyes [1]. Further to the continuous interest on benzothiazole dyes for textiles dyeing, a diverse range of non-textile applications such as liquid crystal technology, reprography, nonlinear optics, and corrosion inhibitors have been developed, and recently their biological activities such as antibacterial activity, antitumor activity, and antiviral activity have also been investigated [2].

In addition, more attention has paid to synthesis and properties of dicationic dyes as bifunctional molecules.

Therefore, the current study, in continuation of our recent investigations on novel hemicyanine dyes and due to growing interest in the synthesis of benzothiazole-based dyes with wide applications, was designed to synthesize a new series of aminobenzothiazoles-based dichromophoric azo dyes, and their electronic absorption and emission properties, as well as their solvatochromic behavior were studied. The color of the novel dyes were cover range of red to blue color**,** with high molecular extinction coefficient between 2.6 - 4.7× 10^4 ($LM^{-1}cm^{-1}$). Solvathochromic effects of ten different solvents on these dyes have been. All of dyes were showed fluorescence emission at a broad range i.e., 409–494 nm. The fluorescence quantum yield values were calculated for the selected dyes and the energy yields of the fluorescence for the selected dyes were studied [2-4].

Antibacterial effects of the synthesized cationic dyes were achieved against four bacteria; S. epidermidis and S. aureus (as gram positive bacteria) and E. coli, and *P. aeruginosa* (as gram negative bacteria), according to the standard methods (ATCC: 12228, 25922, and 27853 resspectively). The antibacterial activity was established via the diffusion plate method. Paper disks (r =2.5

mm) containing a serial dilutions of the samples, was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) which was heavily seeded with suspension of the selected bacterial strains. After 24 hours incubation at 37°C, the zone diameter within which the inhibition of the bacterial growth occurred by the influence of the dyes, was evaluate as a measure of the inhibitory power of the dyes against the particular test bacteria. The reference antibiotic; penicillin, ampicillin and ciprofloxacin were used as references to evaluate the relative potency of the given compounds under the same conditions (Table 1).



1a-p

Scheme 1. *The molecular structure of synthesized dichromophoric benzothiazole-based dye 1.*

Table 1. *The in vitro antibacterial activities of the selected bichromophoric dyes*

		Zone of inhibition[1] (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
Dye	Conc. (μg/ disc)	S. aureus ATCC 25923	S. epidermidis ATCC 12228	E. coli ATCC 25922	P. Aeruginosa ATCC 27853
1g	60	15.0	11	0.0	0.0
	30	13.0	8.0	0.0	0.0
	15	8.0	0.0	0.0	0.0
1i	60	11.0	0.0	0.0	0.0
	30	12.0	0.0	0.0	0.0
	15	9.0	0.0	0.0	0.0
1m	60	9.0	7.0	0.0	0.0
	30	8.0	0.0	0.0	0.0
	15	0.0	0.0	0.0	0.0
Positive control		40 (Penicillin)	35 (Penicillin)	12 (Ampicillin)	12 (Ciprofloxacin)

[1] Distilled water has been used as negative control

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PP 44. MICHAEL ADDITION OF INDOLES AND PYRROLES TO MALEIMIDES USING MOLYBDATE SULFURIC ACID (MSA)

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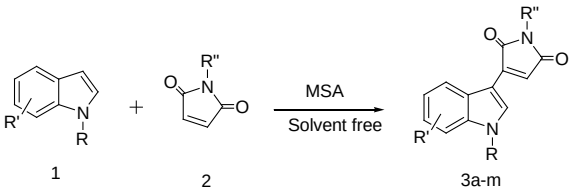
Indole derivatives are ubiquitous structural features of many alkaloid natural products and drug candidates. Among them, indolylsuccinimide rings are important building blocks in the synthesis of biologically active compounds and natural products. Their derivatives are important intermediates in organic synthesis and pharmaceutical chemistry [1].

Generally, indolylsuccinimides are prepared by the reaction of indoles with maleimides in acetic acid. However, the reaction requires long reaction times, and the products are obtained in low yields [2]. The acid-catalyzed conjugate addition of indoles requires careful control of the acidity to prevent side reactions such as dimerization or polymerization [3].

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents[4,5], we wish, herein, to report on the use of MSA as a more robust and efficient catalyst in the Michael addition of indoles and pyrroles to maleimides (**3a-m**) under a solvent-free condition (Scheme 1).



Scheme 1. *Synthesis of indoles and pyrroles maleimides using MSA*

In summary, the present methodology shows that MSA is an efficient catalyst in the one-pot synthesis of indoles and pyrroles maleimides derivatives . The main advantages of the presented protocol are mild, clean and environmentally benign reaction conditions, as well as the high yields.

Furthermore, this method is also expected to find application in organic synthesis due to the low cost of the reagent. It is believed that this method will be a useful addition to modern synthetic methodologies.

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PP 45. SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME HYDRAZONES OF 5α-ANDROSTANOLONE

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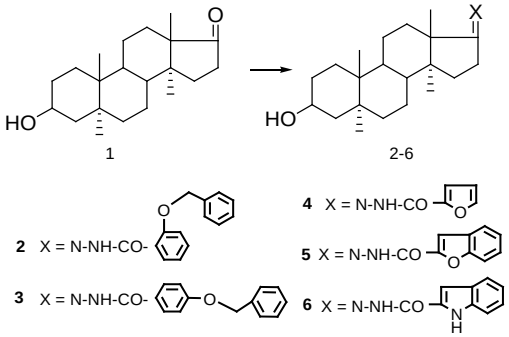
It is known, that steroidal hydrazones of the series of androstane and pregnane are characterized with high biological activity, including antimicrobial and anti-cancer activities [1, 2].

In order to study antiviral activities and establish relationship of structure-activity we synthesized some new hydrazones of 5α-androstan-3β-ol-17-one **1**.

By interaction of epiandrosterone **1** with hydrazides of various acids, such as hidrazides of o- and p-benzyloxybenzoic acids, furan-2-carboxylic acid, benzofuran carboxylic acid and indole-2-carboxylic acid, by boiling in ethanol solution in presence of catalytic amount of acetic acid, there were received corresponding 17-hydrazones **2-6** and were studied their antiviral activities. Starting ketone **1** was synthesized from tigogenine. The structures of steroids **2-6** were confirmed by IR- and NMR spectral data.



The antiviral activities of hydrazones **2-6** were studied at Utah State University National Institute of Allergy and Infectious Diseases (NIAID) (USA). On the basis of screening results on the Vero 76 cell line, it is shown, that compound **2** is highly active towards Polio virus (strain WM-3), whereas

hydrazones **3-5** and steroid **6** exhibit moderate and minor activity towards the same virus, correspondingly.

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PP 46. SYNTHESIS OF NOVEL MALEIMIDES BENZOTHIAZOLINONICS DERIVATIVES

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The benzothiazolinone and some of its derivatives have greatly been taken into consideration by many pharmacologists due to its capacity in the field of pharmacology [1].

Recent studies done on laboratories have shown the important antibacterial activity of various N-arylmaléimides derivatives substituted on the aromatic ring [2].

Among the possibilities of development done on laboratories of pharmacological chemistry, a particular focus was on maleimide derivatives and several compounds of the same type have been prepared, these are aromatic and hétérocyclic N-maléimides which shown a remarkable antibactirial property [3-8].

Starting from previous considerations it seems from the first time to associate benzothiazolinone pharmacophore where we know the potentialities in the field of analgesic [9-11] and antibacterial [12] to the imide pharmacophore into structure of maleimide type, which will lead us to synthetize these compounds.

Taking into consideration the interest presented by maleimide derivatives, it seems to widen the investigations of the analogue benzothiazolinonics caracterised by a grouping alkyl on the nitrogen atome of benzothiazolinonic hétérocycle to study the influence of nature on this latter concerning the chemical and pharmacological properties of the synthetises products.

Therefore, a series of maleimide benzothiazolinone derivatives and their corresponding maleamic acide has been synthetised in our laboratory following the concept of pharmacomodulation.

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PP 47. AN EFFICIENT SYNTHESIS OF 3-ARYLAMINO-5-ARYL-4*H*-1,2,4-TRIAZOLES

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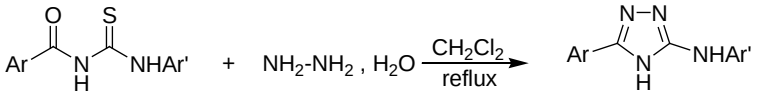
Over the years, a number of general synthetic methods have been developed for the preparation of the 1,2,4-triazoles [1-4]. Due to the diverse biological activity of 1,2,4-triazoles[5-7]. And our continuing interest in the development of new strategiestoward the synthesis of heterocyclic compounds We report a simple and efficient reaction, between*N*-aryloyl-*N'*-arylthioureas**1** and hydrazine hydrate, which leads to3-arylamino-5-aryl-4*H*-1,2,4-triazole derivatives**2** in good yields (Table 1).



1 2

Table 1. *Formation of 3-Arylamino-5-aryl-4H-1,2,4-triazole Derivatives 2*

Entry	Ar	Ar'	Product	Yield (%)
1	4-Et-C_6H_5	4-Me-C_6H_5	**2a**	92
2	4-Me-C_6H_5	4-Me-C_6H_5	**2b**	87
3	4-Cl-C_6H_5	4-Me-C_6H_5	**2c**	90
4	4-Cl-C_6H_5	4-Et-C_6H_5	**2d**	93
5	4-Cl-C_6H_5	4-Me-C_6H_5	**2e**	91
6	4-F-C_6H_5	4-Et-C_6H_5	**2f**	96
7	4-Et-C_6H_5	Ph	**2g**	93
8	Ph	4-Me-C_6H_5	**2h**	88
9	4-Et-C_6H_5	4-Me-C_6H_5	**2i**	86
10	4-Et-C_6H_5	4-Et-C_6H_5	**2j**	85

The structures of compounds **2a-j** were deduced from their elemental analyses and theirIR, ^{1}H and ^{13}C NMR spectra. The structure of product **2a** was supported by NMR spectroscopy. The ^{1}H NMR spectrum of product **2a** exhibit characteristic signals for the aliphatic, aromatic, and NH protons. Elemental analysis also gave satisfactory results for all the compounds. The ^{13}C NMR spectrum of compound **2a** showed thirteen signals in agreement with the proposed structure.The ^{1}H and ^{13}C NMR spectral data of product **2b-j** are similar to those of **2a**, except for the substituents, which show characteristic signals in appropriate regions.

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PP 48. NANO-TiO_2: A NOVEL, EFFICIENT AND RECYCLABLE CATALYST FOR THE SYNTHESIS OF 1,2,4,5-TETRASUBSTITUTED IMIDAZOLES IN SOLVENT-FREE CONDITIONS

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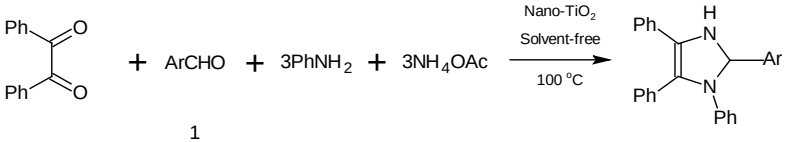
Imidazoles are an important group of five-membered nitrogen heterocycles that have attracted much attention because of the partipitation in the structure of biological active molecules [1-3]. The most well-known and classical method for preparation of this compounds involves four-component condensation of a benzil with aldehyde derivatives, primary amine, and ammonium acetate in refluxing HOAc, which is known to have poor yields and long reaction times [4]. Improvements occurred using other acidic conditions under microwave-irradiation, solvent-free or classical conditions. In this research we describe nano-TiO_2 as an efficient catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Table 1).



1 2

Table 1. *Synthesis of tetraarylimidazoles catalyzed by nano-TiO_2*

Entry	Ar	Time (min) Product	Yield (%)
1	C_6H_5	40	93
2	ρ-OHC_6H_4	55	86
3	ρ-BrC_6H_4	38	94
4	ρ-ClC_6H_4	36	94
5	ρ-$MeOC_6H_4$	44	90
6	ρ-MeC_6H_4	40	88
7	2-FC_6H_4	38	92
8	2-ClC_6H_4	44	86

Conditions: 1 mmol benzil, 3 mmol NH_4OAc, 3 mmol amine and 1 mmol aldehyde

All products were known and characterized by FT-IR, ^{1}H NMR and physical properties of those reported in the literature.

In summary, we described nano-TiO_2 as an efficient, eco-friendly and inexpensive catalyst for synthesis of tetrasubstitutedimidazoles.

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PP 49. SYNTHESIS OF NEW BENZIMIDAZOLYLINDOLOINDOLE

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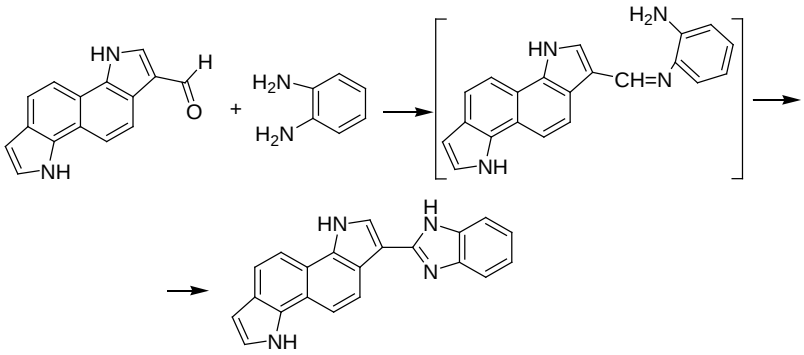
Indole and benzimidazole are biologically significant heterocyclic compounds.

In living organisms take place biosynthesis and metabolism of indole and its analogues. Also they are bilding blocks for other more complex bioorganic compounds.

In medicine indole compounds are used for curing cardiovascular diseases (Reserpine,Aimalin),malignancies(Vinblastine,Vincristine), mental illnesses (Indopan, Pirlindole, Inkazan). Indometacine is anti-inflammatory effective preparation and Arbidol-lense is new antiviral and immunostimulatory remedy.

In agriculture Indole compounds are used as pesticides and as plant growth regulators.



3(benzimidazol-2-yl)-1H.6H-indolo[7,6-g]indole

On the other hand, benzimidazole system is in composition of vitamin B_{12} . Its derivatives are chemiotherapic preparation, which have major usage in agriculture and medicine, e.g. Dibazol(2-benzylbenzimidazole) is used for lowering arterial pressure. Benzimidazolylcarbamates are anthelmintic

action drugs (Levamisole,Mebendazole,Albendazole) and benzimidazole containing fungicides (Carbendazim,Thiabendazole,Benomyl)inhibit fungal cell nucleus division process. They are widely used in cereals,fruit and vegetable crop protection.

In the present work our aim was to connect indoloindole ring with benzimidalole, in order to study their interconnection.

We synthesized new Benzimidazolylindoloindole by condensation of indoloindole aldehyde and o-Phenylendiamine and then carried out cyclization in glacial acetic acid area. Afterwards, purified on column chromatography and identified its probable structure with IR and proton NMR spectroscopy. This compound is perspective because of its unsubstituted Pyrrole rings and with these reaction centre we are going to synthesize other interesting compounds.

PP 50. THE SYNTHESIS OF SOME 4-NITRO-5-ALKOXY-2-(1-ADAMANTYL)BENZIMIDAZOLE DERIVATIVES

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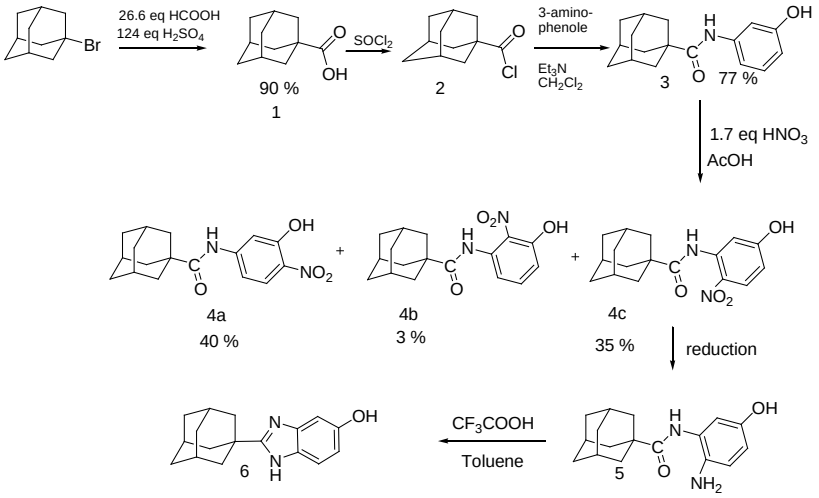
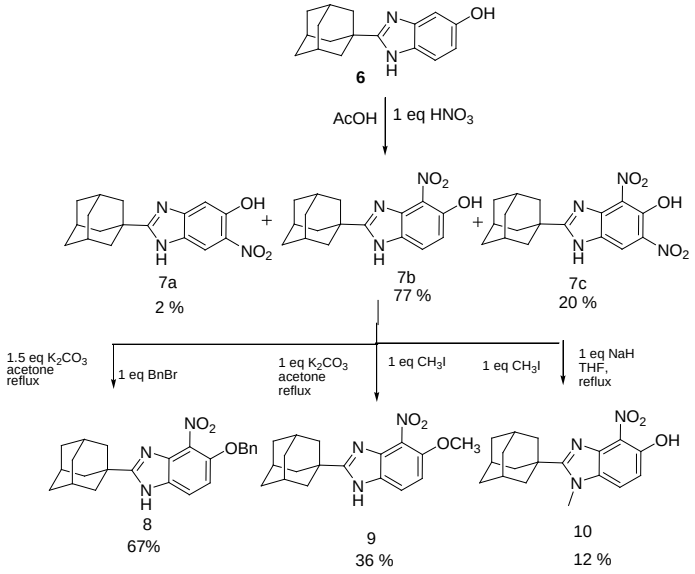
Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. This ring system is present in numerous antiparasitic, fungicidal, anthelmintic and anti-inflammatory drugs. Preparations created on their base are widely used in medicine, veterinary and agriculture [1-3].

It is well known that adamantane line preparations (Amantadine, Amantol, Simmetrel, Mantadix, Rimantadine, Paramantine, Protexin, Viregite, Betsovet, Neoride, Bromantane, Kemantane etc.) also display simultaneously antiviral, antimicrobial, cytotoxic, psychoneuro immunoregulatory and other actions. What is more, it is proved experimentally that including of adamantane fragment in a medication can fully change, or partially enhance its biological activity; often decreases toxicity, increases lipophilicity and creates favorable conditions for transportation through the biological membranes [4-7]. According to this information, the synthesis and studying of adamantane fragment containing new structures of benzimidazole is perspective and actual.

We developed a synthetic method for some 4-Nitro-5-alkoxy-2-(1-adamantyl)benzimidazole derivatives. Initially, was studied carboxylation of 1-Bromo adamantane to obtained Adamantane carboxylic acid. Afterwards, converting of carboxylic acids to acyl chlorides made easier condensation of 3-Aminophenole with Adamantane carboxylic acid chloride and gave N-(3-Hydroxyphenyl) adamantane-1-carboxamide (3). Subsequently, were studied nitration conditions of obtained amide. As it was expected, there were isolated three isomers – Ortho and Para isomers toward hydroxyl group of compound 3 in the ratio 40/35/3. After isolation and subsequent reduction and cyclisation of desired N-(5-Hydroxy-2-nitro-phenyl) adamantane-1-carboxamide (4c) isomer was gained 5-Hydroxy-2-(1-adamantyl)-benzimidazole (6) (Scheme 1).



Scheme 1



Scheme 2

The nitration of synthesized Benzimidazole (**6**) gave Mono - and Di - nitro compounds (**7a-7c**). Isolated target 4-Nitro-5-hydroxy-2-(1-adamantyl)benzimidazole (**7b**) underwent alkylation reaction with some alkyl halides to gave 4-Nitro-5–alkoxy–2–(1–adamantyl)benzimidazole derivatives (**8-10**) (Scheme 2).

Thus, there was synthesized 4-Nitro-5-alkoxy-2-(1-adamantyl)benzimidazole derivatives by six steps starting from 3-Aminophenole. All obtained compounds were characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, DEPT, HMQC, HMBC, Mass spectroscopy and Elementary Analysis.

Acknowledgments: 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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PP 51. DETERMİNATİON OF BİNDİNG PROPERTİES OF BUTACLAMOL İN COMPLEX WİTH A MEMBRANE-BOUND HUMAN Gİ-COUPLED D_{2L} DOPAMİNE 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 Syndrom. Here, homology modelling, explicit solvent molecular dynamics (MD), and MM-PBSA methods were applied to determine the effect of butaclamol, an inverse agonist of $D_{2L}R$, as well as dopamine, an agonist of $D_{2L}R$ binding on tertiary structure changes in Gi-coupled $D_{2L}R$ in complex. It was determined that dopamine as an agonist stabilizes active-state conformation of $D_{2L}R$ by leading to specific interactions between $D_{2L}R$ and Gi, enabling Gi interactions with its effector. On the other hand, butaclamol favors inactive-state conformation of $D_{2L}R$ by weakening specific interactions between Gα(i) and $D_{2L}R$, which possibly prevents inhibition of its effector.

PP 52. CATECHIN HYDRATE ANTIBACTERIAL ACTIVITY AGAINST MULTI-DRUG RESISTANT *ACINETOBACTER BAUMANNII* ISOLATES

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Antibacterial activity of herbal extracts is well known and confirmed by many authors. It is reported, that this activity is due to extracts chemical composition [1]. The compounds of plant extract influence and determine the antibacterial activity. Among compounds active against bacterial cell are flavonoid heterocyclic compounds such as quercetin, catechin and its derivates. Catechins and great deal of flavornoids are synthesized by plants to fight against bacterial infections. Therefore it is no surprise that they exhibit *in vitro* antimicrobial activity [3]. Catechins exert antibacterial effects *via* DNA gyrase inhibition. Specific binding of selected catechins was demonstrated for the N-terminal fragment of gyrase B, i.e. by interaction with its ATP binding site [3]. Furthermore, catechins are able to restore the susceptibility of bacterial antibiotic resistance to antibiotics such as tetracycline, beta-lactams and beta-lactamase inhibitors [4,7,8]. Such activity of the catechin and its derivates is of the grate importance because of the increasing bacterial resistance to the conventional antibiotics. *Acinetobacter baumannii* is an opportunistic pathogen with increasing prevalence, causing nosocomial infections in imunocompromised and imnunoincomepetent patients. *A. baumannii* is well known by its resistance to a majority of commercially available antibiotics (penicillins, aminoglycosides, cephalosporins, quinolones), raising an important therapeutic problem [5, 6]. The aim of the study was to determine the antibacterial activity of the heterocyclic compound of plant extracts - catechin hydrate (Figure 1), against thirty multy-drug resistant *A. baumannii* wound isolates (Figure 2).

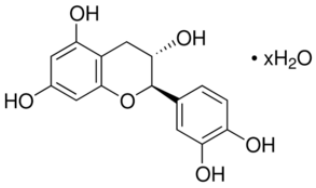

Figure 1. *Catechin hydrate chemical structure Figure*

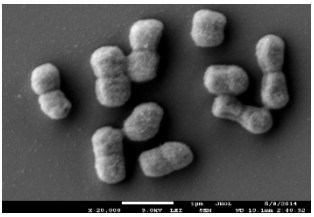

Figure 2. *A. baumannii cells electron micrograph*

Acinetobacter baumannii strains under investigation are previously identified by multiplex PCR technique and also characterized as multi-drug resistant. Among *A. baumannii* isolates three are refernce strains (ATCC 19606, ATCC BAA747, NCTC 13420), twenty clinical and outpatient wound isolates, and seven isolates from the environment.

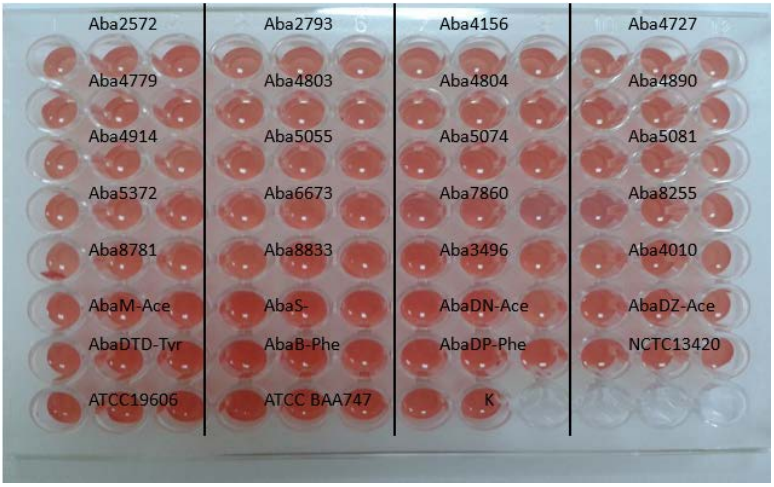

Figure 3. *The activity of catechin hydrate against multi-drug resistant A. baumannii isolates*

The minimal inhibitory concentrations (MICs) of catechin hydrate were determined by broth microdilution susceptibility testing method according to CLSI (2007) using 0.5 % DMSO as agent solvent. The tested concentrations

of catechin hydrate were two-fold serial dilutions ranging from 0.125 to 256 μgmL^{-1}. The bacteria without any treatment were used as control. The sealed microplates were incubated at 37 ^oC over night. After incubation, in order to determine the antimicrobial activity of the catechih hydrate, 10 µL of TTC solution was added to each well an incubated for 2 h at 37 ^oC. Bacterial cells which survived the treatment will express hydrogenase activity and the solution will became red. The concentration of the compound that completely inhibited bacterial growth will remain colorless and it will be determined as MICs. For minimal bactericidal concentration (MBC), 10 µL from wells without obvious bacterial growth was subcultured on nutrient agar plates to determine if the inhibition was reversible or permanent. MBC was determined as the highest dilution (lowest concentration) at which >99.9 % reduction of initial CFU was obtained. Each experiment was performed in triplicate.

The catechin hydrate was not exhibited bacteristatic or bactericidal activity against tested *A. baumannii* isolates, with MIC values above 256 μgmL^{-1} for all examined *A. baumannii* isolates (Figure 3). These results suggest that further investigation should be carried out in direction of examining the synergistic effect of catechin hydrate with other bioactive compounds and/or with conventional antibiotics.

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PP 53. VIRUCIDAL EFFECT OF *Allium* EXTRACTS AND QUERCETINE

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Bacteriophages are bacterial viruses which can be used as models for human and animal non enveloped viruses. The non-enveloped bacteriophages containing double stranded DNA (dsDNA) are good models for examination of effects of various agents on animal viruses, such as those from families *Adenoviridae* and *Papovaviridae*.

The aim of the study was to examine virucidal effect of three Allium species extracts (A. fuscum, A. paniculatum, A. rhodopeum and A.melantherum) containing significant content of heterocyclic compounds, as well as to examine virucidal effect of quercetin (Fig. 1), a phenolic heterocyclic compound.

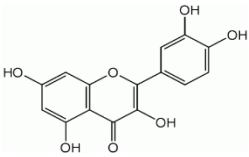

Fig. 1. Quercetin

The extract of various Allium species were prepared and total flavonoid content was measured by the aluminum chloride spectrophotometric assay [1], determined from the regression equation of the quercetin calibration curve, and expressed as quercetin equivalents in mg per g of dried extracts (Table 1). As a model viruses were used *Pseudomonas aeruginosa* specific phage delta and sigma-1, belonging to family *Podoviridae* and *Siphoviridae*, respectively. The phages were multiplied, concentrated and purified in CsCl gradient [2]. The virucidal activity was determined by estimation of PhI50 (inactivation of 50% of virions). For this purpose virus titration was carried out prior to and after exposure to corresponding agents, applied in various concentrations for 30 min. at 37°C [3].

None of the *Allium* extracts showed virucidal activity, since PhI50 was not obtained even when maximal examined concentration was applied (40 mg/ml). Similarly, quercetin in methanol did not show activity with the maximal examined concentration (2 mg/L). However, quercetin dissolved in DMSO showed considerable virucidal effect, with PhI50= 106.4 + 3.2 µg/ml. This difference is probably a result of its various solubility in methanol and DMSO. The dependence between quercetin virucidal activity and DMSO concentration have been observed by Gravina et al. (2010) [4] against EHV-1. Some studies showed better effect of quercetin derivatives than quercetin against RNA viruses, such as quercetin 3-rhamnoside [5] or isoquercetin [6] against influenza A virus, or quercetin 3-*O*-glycosides used as anti-Mayaro virus agent [7]. It is also interesting to notice that phage delta is more sensitive to quercetin, while sigma-1 is more resistant. The results are is in accordance with previously determined sensitivity of the phages to examined inorganic agents, i.e. silver nitrate and povidone-iodine (Knezevic et al, 2011).

Tabele 1. *Viruscidal activity of methanolic Allium extracts and quercetin*

Antiviralni agens (origin)	**Total flavonoid content** mg of quercetin equivalents g^{-1} of dw	**PhI50[1] (mg ml^{-1})** **Bakteriophage**	
		σ-1	**δ**
A. fuscum subsp. *fuscum* (Zaovine)	2.32 ± 0.38	> 40	> 40
A. paniculatum (Titelski breg)	4.40 ± 0.40	> 40	> 40
A. rhodopeum (Dimitrovgrad)	0.22 ± 0.01	> 40	> 40
A. melantherum (Čemernik)	1.15 ± 0.54	> 40	> 40
A. cepa (Neradin)	N.D.[2]	> 40	> 40
A. sativum (Šajkaš)	N.D.	> 40	> 40
Quercetin/MetOH	-	> 2	> 2
Quercetin/DMSO	-	> 2	0.108**

[1]PhI50- concentration exhibiting 50% of virucidal activity
[2]Not determined
**R=0.954; P=0.045; N=5

The results indicate that *Allium* did not show antiviral effect, while quercetin possesses potential to be used as virucidal agent. Accordingly, the vircudal effect of quercetin derivatives should be further examined against dsDNA viruses, using bacteriophages as models.

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PP 54. EFFICIENT ONE-POT SYNTHESIS OF THIAZOL-2-IMINE DERIVATIVES VIA THE REACTION BETWEEN PRIMARY AMINES, PHENYLISOTHIOCYANATE, AND A- CHLOROACETALDEHYDE

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The design of one-pot reactions is an important field of research in organic synthesis. These reactions afford good yields and ready operations. The thiazol-2-imine ring system has attracted considerable attention due to its presence in several drug candidates with different biological activities such as anti-inflammatory, analgesic and kinase (CDK1, CDK5, and GSK3) inhibition, antifungal, and skin whitening properties [1-2]. In this work we wish to report a simple one-pot procedure for the synthesis of thiazol-2-imine derivatives via the reaction of primary amines, α-chloroacetaldehyde, and phenylisothiocyanate in the presence of a catalytic amount base. Different bases were tested for this reaction and DABCO was found as the best catalyst among all bases tested. The structures of products were characterized by IR, ^{1}H NMR, ^{13} C NMR, and Mass spectroscopy.

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PP 55. 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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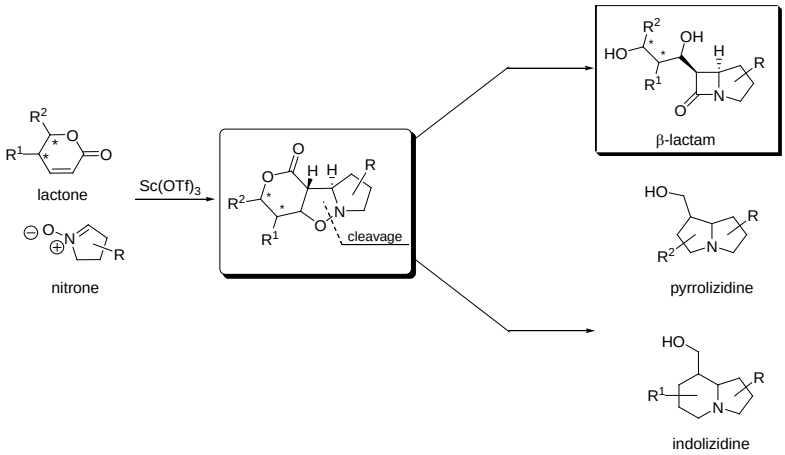
1,3-Dipolar cycloaddition reactions (1,3-DCA) are powerful tool for the synthesis of heterocyclic compounds. Their advantage is fact that, the cycloaddition of 1,3-dipole, such as a nitrone, to double bond, results in formation of up to three continuous stereogenic centers in single step [1]. Previously, 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 56. ACID CATALYZED REARRANGEMENT OF VINYL AND KETENE ACETALS – STEREOSELECTIVE SYNTHESIS OF *C*-GLYCOSIDES AND RELATED COMPOUNDS

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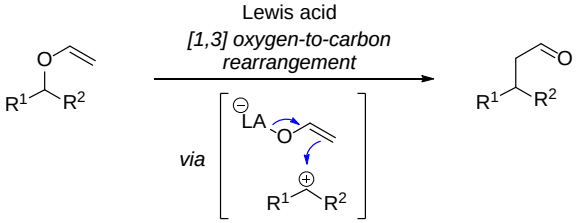
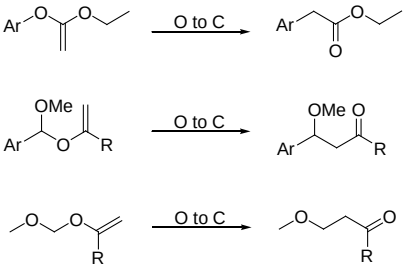
The reaction [1,3] rearrangements of vinyl ethers represent powerful method of construction of a new carbon-carbon bond by the breaking carbon-oxygen one.[1]



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.

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PP 57. 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 58. NOVEL MACROCYCLIC POLYAZOMETHINES

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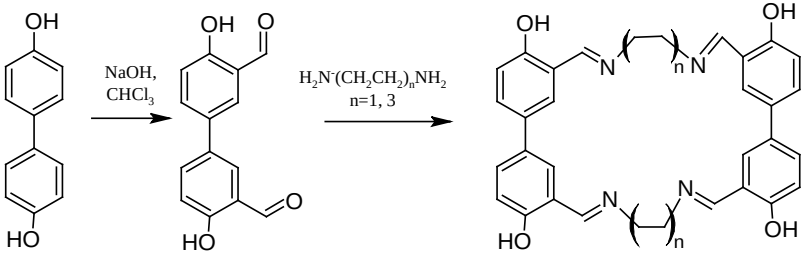
Nowadays azomethines are used as substrates to prepare a large number of industrial and biologically active compounds via ring closure, cycloaddition and replacement. Moreover azomethines are also known to have antimicrobial [1], antifungal [2], antitumor biological activities [3] and are used as herbicides.

We have reported the method of synthesis of 20-membered cyclic polyazomethine compounds [4]. Some chemical and physical properties of these macrocycles have been also investigated [5]. They are excellent azo partners and have ability to give tetrakis azo dayes via one-pot azo coupling reaction.

In the current research the synthesis rout of polyazomethine macrocycles with methylene spacers are presented. 28- and 32-membered cycles may be synthesized via two step conversion from bis-phenol by carbonylation and condensation with ethylene diamine or hexamethylene diamine.



Scheme.

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