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**“BIOACTIVE COMPOUNDS, ANTIMICROBIAL AND  
BIOMEDICAL PRODUCTS & MATERIALS FOR PROTECTION  
OF HUMAN AND ENVIRONMENT”**

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**BOOK OF ABSTRACTS**

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Ioseb Chikvaidze, Professor, Doctor of Chemical Sciences

**Executive secretary:** Khatuna Barbakadze, Doctor of Chemistry

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## PLENARY SESSIONS

### ENANTIOSEPARATION OF BIOLOGICALLY ACTIVE CHIRAL COMPOUNDS

#### B. Chankvetadze

Institute of Physical and Analytical Chemistry, School of Exact and Natural Science,  
Tbilisi State University, Chavchavadze Ave 1, 0179 Tbilisi, Georgia

This presentation summarizes the recent developments in analytical and preparative scale separation of enantiomers of chiral drugs. The techniques discussed include high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), nano-liquid chromatography (nano-LC) and capillary electrochromatography (CEC). Chiral drugs and drug-like compounds discussed include arylpropionic acid N. Beridze, E. Tsutsqiridze, N. Takaishvili, A. Mskhiladze, T. Farkas, B. Chankvetadze, Comparisson of chiral recognition ability of coated and covalently immobilized versions of two polysaccharide-based chiral selectors in high-performance liquid chromatography, *Chromatographia*, 81 (2018) 611-621. derivatives,  $\beta$ -blockers, imidazole and triazole derivatives, dihydropyridines, chiral sulphoxides, amino acid derivatives and others. Various fundamental and applied aspects will be discussed in each technique.

In HPLC part novel chiral selectors, mobile phases, mobile phase additives and inert carriers, as well as some unusual effects and approaches for a better understanding of the chiral recognition mechanisms will be summarized [1, 2]. This part of the presentation will highlight the efforts of our group with regard to separations of enantiomers in the liquid phase with the highest possible coverage of analytes, separation selectivity, plate numbers and shortest analysis time. In order to achieve this goal, the systematic optimization of the composition of polysaccharide-based chiral selectors, the structures of the studied analytes (chiral sulphoxides), composition of the mobile phases, mobile phase additives and separation temperature have been performed. In a parallel project, the particle size of the silica, its morphology (porosity and pore size), the nature of the chiral selector and its content in the chiral stationary phase were optimized in order to reach the highest possible column performance [3]. The nano-LC and CEC parts of the presentation will discuss the application of novel core-shell silica-based chiral stationary phases for separation of enantiomers of chiral drugs [4]. The CE part will focus on chiral recognition mechanisms with cyclodextrin-type chiral selectors [5, 6].

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## ULTRASENSITIVE MULITI-PROTON NONLINER LASER METHODS FOR BIOMEDICAL AND ENVIRONMENTAL APPLICATIONS

**W. Tong**

San Diego State University, Distinguished Professor, Head, Department of Chemistry and Biochemistry San Diego, California 92182, USA  
william.tong@sdsu.edu

We have developed and patented novel nonlinear multi-photon laser methods with zeptomole-level (10<sup>-21</sup> mole) or sub-parts-per-quadrillion-level detection sensitivity for a wide range of areas including biomedical and environmental applications. Laser wave mixing offers comparable or better detection sensitivity levels for biomolecules as compared to widely used fluorescence-based methods and yet our wave-mixing methods can detect both fluorescing and nonfluorescing molecules with excellent sensitivity levels. Hence, biomolecules could be detected label-free in their native form without using tags or labels (more convenient), with fluorophore tags (using existing labels and procedures) or with chromophore tags (more widely available). The laser probe is very small (picoliter) and it can be positioned precisely inside the analyte (e.g., a single bio cell) for 2D and 3D

spatial mapping. The input laser beams create dynamic laser gratings at the atomic or molecular scale and the resulting nonlinear optical effect produces a strong signal beam that propagates out of the analyte. Unlike currently available techniques such as fluorescence methods, our laser methods produce a strong coherent laser-like signal beam, and hence, it is easy to detect with excellent signal-to-noise ratios. Picoliter-level probe volumes offer effective interfacing to sensors, microchannels, microarrays, lab-on-a-chip, chip-based electrophoresis systems and microfluidic devices that are suitable for studying mechanisms and dynamics of important chemical and biological processes.

Our patented laser wave-mixing methods can distinguish not only large biomolecules but also small isotopes. Our laser-based detectors are more portable and less expensive than isotope-capable high-resolution mass spectrometers. Wave-mixing laser methods yield hyperfine profiles (atomic fingerprints), and hence, unambiguous isotope information from both stable and radioisotopes. Hence, one could use stable isotopes as biotracers instead of radioactive biotracer isotopes. We have also studied fast laser-induced diagnostic real-time monitoring of reaction rates, intermediate species and mechanisms of semiconductor materials. We use a wide range of lasers with wavelengths from UV (solid-state lasers) and visible (tunable external cavity diode lasers) to mid-IR (tunable quantum cascade lasers). Potential applications include earlier detection of diseases (Parkinson's, Alzheimer's, Multiple Sclerosis, etc.), more sensitive detection of biomarkers, cancer cells, heart cells and viruses (HPV, HIV), more sensitive detection of pollutants and chemicals both inside the human body and in the environment, remote standoff detection of chem/bio agents, and even authentication of paintings and art objects.

## COMPUTER-AIDED APPROACHES TO DRUG DESIGN & DISCOVERY

**V.V. Poroikov, D.A. Filimonov, D.A. Druzhilovskiy, A.A. Lagunin, T.A. Gloriozova,  
A.V. Rudik, A.V. Dmitriev, O.A. Tarasova, P.V. Pogodin, S.M. Ivanov,  
V.M. Bezhentsev, K.A. Murtazalieva, M.I. Semin, P.I. Savosina, D.A. Veselova**

Institute of Biomedical Chemistry (IBMC)  
10, Pogodinskaya Street, Bld. 8, 119121, Moscow, Russia  
E-mail: vladimir.poroikov@ibmc.msk.ru

Computer-aided prediction of the biological activity of pharmacological agents significantly decreases the financial and time expenses at the stage of discovery and optimization of lead compounds and reduces the risk of negative results during the investigation process [1, 2].

For more than 25 years [3], we are developing the ligand-based methods of drug design. For analysis of structure-activity relationships, we developed novel chemical descriptors that reflect the peculiarities of ligand-target interactions.

The algorithm of creating models represented structure-activity relationships is based on naïve Bayes estimations [4, 5]. The building of quantitative structure-activity relationships is based on self-consistent regression [6]. It was shown that our methods deliver the reasonable estimates despite the incompleteness of information in the training set [7] and provide some advantages in comparison with the other techniques [8-10].

We created an open-source platform Way2Drug (<http://www.way2drug.com>), which provides web-services for prediction of the biological activity of drug-like organic molecules.

Computational components of the platform allow to estimate the probability of several thousand biological activities, including pharmacotherapeutic and adverse effects, interaction with the molecular targets [11], acute rat toxicity for four routes of administration [12], action on tumor and non-tumor cell-lines [13], metabolism [14, 15] and some other characteristics necessary to estimate the prospects of studying particular molecules and potential drug-candidates [16].

One purpose of our studies is the analysis of predicted biological activity spectra for the launched medicines, which may help to identify new indications for known medicines. For instance, we predicted nootropic effect for several antihypertensive drugs, angiotensin-converting enzyme inhibitors, which was confirmed on experimental animals and, later, in clinical trials [10].

In the framework of Russian-Indian project RSF-DST, we predicted antidiabetic properties of some known medicines. Prediction for two antimalarial drugs (hydroxychloroquine and colchicine) was confirmed by known published data. According to the prediction, two other antimalarial (lumefantrine and clindamycin) and two anti-inflammatory drugs (acetylsalicylic acid and ketorolac) may also be considered as “candidates” for treatment of diabetes. Currently, our Indian collaborators are carrying out the appropriate research in clinics.

In the framework of Russian-American project RFBR-NIH, we perform the analysis of the big chemical library SAVI (Synthetically Accessible Virtual Inventory), included over 283 mln of potentially synthesizable compounds. Using the sophisticated approach combined similarity assessment, machine learning, and molecular docking, we identified ten compounds as potential inhibitors of HIV-1 protease.

Way2Drug web-resources are used by more than 18 thousand researchers from 90 countries; they obtained over 6000 thousand predictions and published about 500 papers with the description of the results. Informational-computational platform Way2Drug provides the tool for selection of the most promising hits for synthesis and testing of biological activity, as well as identify novel indications for known medicines.

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## BIODEGRADABLE POLYMERS FOR NUMEROUS BIOMEDICAL APPLICATIONS

**R. Katsarava**

Institute of Chemistry and Molecular Engineering, Agricultural University of Georgia  
Research Center for Medical Biotechnology and Bioengineering, Georgian Technical University  
r.katsarava@agruni.edu.ge, kats@gtu.ge

Proteins are one of the most appropriate biomaterials for a variety of biomedical applications including resorbable surgical and pharmaceutical devices owing to their innate affinity to tissues, enzymatic biodegradability with releasing  $\alpha$ -amino acids ( $\alpha$ -AAs), which could be assimilated by the organism promoting in that way tissue regeneration. However, the proteins have some serious shortcomings among which the most important is *immunogenicity* that is connected with their molecular architecture. We have developed a new generation of synthetic  $\alpha$ -AAs based biodegradable (AABB) polymers having a new macromolecular architecture less recognizable by the immune system of living organism [1-6]. The key monomers to build up the macromolecules of the new architecture are diamine-diester monomers made of  $\alpha$ -AAs and diols. Several classes of AABB polymers both regular [1-5] and functional [6] ones having the widest range of material properties have been designed. The AABB polymers, similar to proteins, release  $\alpha$ -AAs upon the biodegradation and could be considered as pseudo-proteins showing from low to zero immunogenicity. The new polymers are highly suitable materials for numerous applications in regenerative medicine, pharmacy, etc.

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## INTEGRATED STUDIES IN THE FIELD OF ARILINDOLES, PYROLOINDOLES, AND BI- AND TRIINDOLES

**I. Chikvaidze\*, Sh. Samsoniya**

Ivane Javakhishvili Tbilisi State University, Faculty of E&NS, Department of Chemistry  
3, Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia  
iosebc@yahoo.com

The report focuses on one of the directions of the scientific problem "Novel nitrogen-containing heterocyclic systems". It shows the stages of its development, progress, difficulties and the ways of their solution.

As a result of the investigations of several years, in the Chair of the organic chemistry and Department of heterocyclic compounds at the Institute of organic chemistry there are obtained symmetric and asymmetric bi- and triindoles, aril- and diarilindoles, condensed isomeric pyroloindole and five-ring pyridazinoindole systems, isomeric bis-tricyclic pyridazindoles. The principles of the key systems and general preparation methods of their synthesis have been developed. Their physico-chemical and chemical properties as well as quantum-chemical parameters of the obtained compounds were studied; derivatives with various functional groups are synthesized, among them were plant growth regulators, antiseptics, substances with cytostatic, biocidal, luminescent properties, intercalators and markers of biomacromolecules, substances with curare-like activity and other useful properties.

Some new reactions have been discovered: unusual chlorination of the indole ring, deformylation of heterocyclic aldehydes, 1,7-migration of the benzyl group; probable mechanisms of these reactions are proposed; the effect of substituents on the main stage of the mechanism of the reaction of indolisation of arylhydrazones (Fischer reaction) has been investigated

## CHEMICAL REGULATION OF ADAPTATION MECHANISMS IN LIVING SYSTEMS

**R. Gakhokidze**

Ivane Javakhishvili Tbilisi State University, Faculty of E&NS, Department of Chemistry  
3, Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia  
rgakhokidze@gmail.com

Growth is a very complicated physiological process. It consists of numerous separate reactions going in cell. Integrity of every living organism is maintained by management and regulation systems. By application of the systematic approach to the management of living cell we worked out

a new methodology and on this base developed the methods, which are enabling to control endogenous (self) regulatory systems of living cell.

There are two ways of adaptation of human with environment. The first – improvement of environmental preservation, the second – increase the stability of organisms towards the action of harmful factors. Adaptation of living organisms to the different conditions is possible through the usage of bioenergyactivators. Due to them plants are more resistant against diseases, pests and unfavourable influence of weather.

Bioenergyactivators enable to receive ecologically pure, high quality crop without polluting the ground with poison. They significantly accelerate growth, stability and productivity of plants and animals, improve environmental preservation and life quality by receiving healthy food with curative prophylactic effects.

Bioenergyactivators easily penetrate into the plant cell, play a role of inductors of general unspecific durability and stimulate the protection function of the plant by activating the reserve mechanism. They enable preservation of homeostasis through activation of physiological regulatory mechanisms, providing adaptation to the extremal conditions. They influence on the various system of metabolism: breath, photosynthesis, biosynthesis of proteins, carbohydrates and secondary substances. They cause sharp increase an activity of some enzymes, for example katalases, peroxidases, change mineral and chemical properties of protoplasm and penetrability of cellular membranes for water, mineral and organic substances. Bioenergyactivator stimulates the nitrate assimilation and protein levels in the been primary leaves by using nitrate as single nitrogen source at the early stages of vegetation.

The agricultural products obtained by the use of Bioenergyactivators due to their ecological purity and high nutrient content (protein, limited amino acids, vitamins, microelements) are valuable for baby nourishment. Based on current research of physicians and hygienists the crop obtained with bioenergyactivators is a good means for preventing goitre, cardiovascular and other diseases.

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## MOLYBDENUM ISOTOPE SIGNITATURE OF ROSEBAY WILLOWHERBPLANTS – A PROMISING INDICATOR OF ANTROPOGENIC POLLUTION

**D. Malinovskiy<sup>1†</sup>, N. Kashulin<sup>2</sup>**

1: Division of Applied Geology, Luleå University of Technology, S-97187 Luleå, Sweden;

<sup>†</sup>currently at LGC Limited, Queens Road, Teddington, TW11 0LY, UK

2: Institute of North Industrial Ecology Problems, Apatity, 184209, Russia

dmitriy.malinovskiy@lgcgroup.com; nikolay@inep.ksc.ru

It is well known that molybdenum is an important micronutrient in all kingdoms of life. Despite having very low concentrations in most biological systems the element play an important role in many biochemical redox reactions, including nitrogen assimilation, sulphur metabolism, phytohormone biosynthesis and stress reactions. Molybdenum exhibits biochemical activity only when it is complexed with certain types of proteins, forming macromolecular biological catalysts known as enzymes [1]. A useful probe for investigating mechanisms of Mo reactions and distribution in all types of systems is natural variations in the isotopic composition of the element. Multi-collector inductively coupled plasma-mass spectrometry (MC-ICPMS) and thermal ionisation massspectrometry (TIMS) are the techniques in routine use which can measure Mo isotope ratios with a precision sufficient to resolve isotopic fractionation concomitant with chemical reactions involving molybdenum.

As typical Mo concentrations in plants are low and range from 0.1 to 1.0  $\mu\text{g}\cdot\text{g}^{-1}$  of dry weight, high precision Mo isotopic analysis in plants is a significant analytical challenge. Research performed at Luleå University of Technology, Sweden, and Institute of North Industrial Ecology Problems, Russian Academy of Sciences, led to development of a method for precise and accurate Mo isotope ratio measurements by MC-ICPMS[2]. Among other things, this study showed that *Rosebay willowherb*, which is a common plant genus in Northern Hemisphere, did not fractionate Mo isotopes during uptake and transport of the element within the plant. This finding prompted a follow-up study with sampling and Mo isotopic analysis of *Rosebay willowherb* from the areas affected by anthropogenic pollution to test the hypothesis that natural variations in the isotopic composition of Mo can be a useful tool for discriminating individual sources of anthropogenic pollution. The following two observations suggest that such discrimination is possible. First, it is the fact that atmospheric precipitation makes a significant contribution to molybdenum pool dissolved in soil pore water which is uptaken by plants. Second, as noted above, *Rosebay willowherb* seems not to alter the isotopic signature of molybdenum during migration of the element from roots to other anatomical parts of the plant. The results show that the isotopic composition of Mo in *Rosebay willowherb* do vary in different locations subject to pollution, supporting the working hypothesis and opening up a new application of Mo isotope ratio data.

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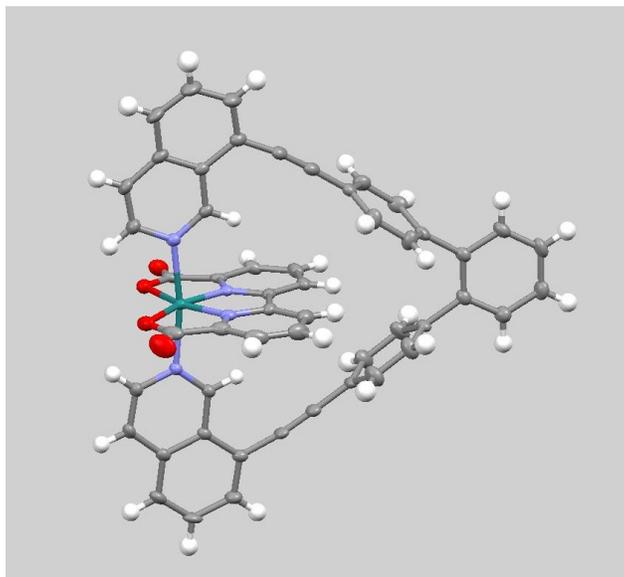
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## **BIFUNCTIONAL CATALYSIS FOR ORGANIC CHEMISTRY AND ENERGY**

**D. Grotjahn**

Department of Chemistry and Biochemistry, San Diego State University  
5500 Campanile Drive, San Diego, CA 92182-1030, USA

Nature's enzymatic catalysts often rely on exquisite control of proton transfer or hydrogen bonding to accelerate reactions. Organometallic catalysts can benefit in a similar manner, helping reactions which enzymes cannot accomplish. Our laboratory focuses on metal complexes with ligands containing nitrogen bases or their conjugate acids, starting with bifunctional systems with one pendant organic group to help the metal during catalysis, but more complex systems can be imagined. Rate accelerations of as much as 1,000 to 10,000 have been achieved thanks to pendant bases. In this presentation, both published and ongoing work from our group in the areas of catalysis for organic synthesis and energy will be discussed.



## **A GENERAL OVERVIEW OF THE DATA IN GEORGIA ABOUT ENVIRONMENT AND HEALTH**

**E. Bakradze**

LEPL National Environmental Agency, Tbilisi, Georgia

According to the World Health Organization, "Environment" means not only pathological impact on the human body from Physical, chemical and biological factors and natural environment components but also (often indirectly impacted) habitats, such as: buildings, Work

and entertainment places. Environmental risk factors for human health include: air, water and soil polluted with chemical and biological reagents; Ultraviolet ionizing radiation Noise and electromagnetic field; Risks associated with professional wedding; Climate change caused by human impact; Ecosystems and others.

Observation of atmospheric air pollution in Georgia is made on the following contaminants: dust, sulfur dioxide, carbon dioxide, nitrogen oxide and dioxide, manganese dioxide and lead. The following contaminants of carbon dioxide, nitrogen dioxide, nitrogen oxides, ozone, PM<sub>2,5</sub> and PM<sub>10</sub> is measured in automatic mode from September 2016, three automatic air pollution stations started operation. Where carbon dioxide, sulfur dioxide, nitrogen oxides, ozone, PM<sub>2,5</sub> and PM<sub>10</sub> is measured.

Surface water is monitored on the river basins of the Black Sea and Caspian Sea, as well as on lakes and reservoirs. In water samples are measured physical and chemical parameters, the main ions, biogenic compounds, biological Oxygen demand, pH, heavy metals etc.

Soil pollution monitoring on measured copper, zinc, lead, manganese, cobalt, cadmium, nickel, arsenic and iron concentrations. Expository dose capacity measurements of  $\gamma$ -radiation are carried out in 15 settlements of Georgia, seven of which are in continuous automatic mode at the earliest private system.

On the basis of the statistical data is defined the influence human health of pollutant substances for certain regions of Georgia.

## **FROM ARSENIC TO MEDICINAL CHEMISTRY: SYNTHESIS, CHARACTERIZATION AND EVALUATION OF BIOLOGICAL ACTIVITY**

**L. Arabuli**

University of Georgia, Faculty of Health sciences and Public health, Department of Pharmacy  
77a, M. Kostava Str., 0171, Tbilisi, Georgia; l.arabuli@ug.edu.ge

Our interest was concerned to the stabilization of reactive arsenic-chlorine center by arsenic-sulfur bond formation and attachment of phenyl and 2-mercaptobenzothiazole. The new compounds showed low toxicity, but as they contain many different atoms (arsenic, sulfur, nitrogen), would be showed antimicrobial activity and they serve as good complex-forming ligands for preparation of metal coordination compounds. The 10-chloro-5,10-dihydrophenar-sazine thio-ethers were obtained in the two ways: in neutral environment using BuLi, but because they are stable in the air and are not sensitive toward moisture, we prepared these compounds also with potassium hydroxide; the second way was easier and faster. The new compounds were characterized using various spectrometric techniques.

On the other hand, the most advantage of the macrocyclic polyamines is their unique capacity to bind some biologically important metals (Zn, Cu, Co, Fe) and their role was dramatically increased as behavior models for enzymes and other metalloproteins. The modification of macrocyclic polyamine receptor molecules with additional ligands (arms) enables to interact with nucleobase, sugar and other biomolecules moieties for a more efficient “multipoint”

recognition, as well as for thermodynamic stabilization of the ternary complexes in aqueous solution.

Cyclen, cyclam, their derivatives and metallocomplexes are proposed as good candidates to cross blood-brain barrier and with low toxicity as potential neuroprotective or neurorescue agents in the treatment of Alzheimer's disease. In addition, cyclen derivatives showed antibacterial, anti-HIV and anti-malarial activities. On the other hand, polyphenolic compounds, like coumarins and its derivatives are able to bind transition metal ions and inhibit hydroxyl radical and hydrogen peroxide formation produced by Fenton's reactions. Polyphenol derivatives (or metabolites) found numerous therapeutic applications, such as central nervous system stimulants, antitumor and anti-HIV therapy, antibacterial, anticoagulants etc.

We prepared cyclencarboxymethylen and 3,4-dihydroxyphenylalanine (L-DOPA) derivatives with His-rich dipeptides (cyclen-HisHis, cyclen-AspHis, cyclen-GluHis, Dopa-HisHis, Dopa-AspHis, Dopa-GluHis, Dopa-HisHis-Dopa, Dopa-AspHis-Dopa, Dopa-GluHis-Dopa, Dopa-GluHis-Dopa and Dopa-cyclen) via solid-phase synthesis strategy and identified using <sup>1</sup>H-NMR and MALDI TOF MS-spectrometry.

The new DOPA and 1,4,7-10-(carboxymethyl)-tetraazacyclododecane – oligopeptide derivatives were tested for their biological activity evaluation, such as antioxidant, antimicrobial, anticancer, antidiabetic etc. activities using their different concentration levels. The cytotoxicity and genotoxicity of new compounds were also studied.

## ANTIMICROBIAL HYBRID MATERIALS AND STRATEGIES OF THEIR TARGETED MODIFICATION

**Kh. Barbakadze<sup>1,2</sup>, N. Lekishvili<sup>1\*</sup>**

<sup>1</sup>Tbilisi State University, Department of Chemistry, Faculty of Exact and Natural Sciences, Institute of Inorganic-Organic Hybrid Compounds and Non-traditional Materials

3 Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia; \*nodar@lekishvili.info

<sup>2</sup>Tbilisi State Medical University, 33, Vazha Pshavela ave., 0186, Tbilisi, Georgia

The effects of pathogenic microorganisms constitute global hazards for humanity and environment. These microorganisms appear in natural systems and form complicated aggregates on the surfaces of various natural and synthetic polymer materials resulting in irreversible deterioration and non-controlled biodegradation that cause significant economic losses to industry and pose serious threats to cultural heritage (historic monuments, archeological patterns, museum exhibits, etc.) as well [1, 2].

An important option to mitigate biodegradation is formation of polymer-based hybrid materials, taking advantage of the best properties of each component, decreasing or eliminating their drawbacks, and achieving synergic effects. Low scratch and wear resistance and also environmental degradation have hindered many important applications and long-term performance of polymer materials [3, 4]. Thus, it is essential to achieve prolonged maintaining of their physical and mechanical properties (isothermal aging stability, strength, tribological characteristics, etc.) in operational conditions. Improved features will allow widened applications

of hybrid materials as functional coatings, adhesives, membranes, optics, fuel and solar cells, sensors, medical products and materials, etc. [4].

The main concept of the following research consisted in creation of bioactive hybrid materials against wide spectrum of biodestructors. Polyurethanes and organic polyepoxide as a base of polymeric matrix were used for creation of antimicrobial inorganic-organic hybrid composites and materials. Silicon-organic oligomers with functional groups at silicon atoms act as plasticizers and modifiers, providing improvement of elasticity and thermal stability as well as formation of homogeneous films and hydrophobicity of the obtained polymer composites and coatings. As a bioactive component coordination compounds of some biogenic metals (Fe, Co, Ni) based on organic and organometallic ligands were chosen [5].

Tribological properties of hybrids are related to their composition. The sliding wear of the samples was determined by multiple scratching along the same groove at a constant force using a micro scratch tester. The modification mainly causes gradual decrease of sliding wear with respect to pure polymers, improvement of viscoelastic recovery (75-90%), lowering of dynamic friction and also increasing of hydrophobicity. By progressive scratch testing performed with linearly increased load (1.0N-30.0N) was shown improvement of scratch resistance of researched materials depending on the modifier type and quantity. The study of surface morphology confirmed obtained results. Thus, lower friction and higher scratch resistance of obtained composites and coatings with targeted modification was achieved.

Created antimicrobial polymer materials show improved mechanical, tribological and thermophysical properties and provide prolonged exploitation of the protected materials and wares what will economize material resources. Herewith, elimination of unfavorable factors which affect on the operational characteristics and surface morphology of the hybrid materials will reduce the risk of bio-damaging caused by biodestructors and effectively will provide inhibition of growth of harmful microorganisms on materials surfaces. Thus, developed antimicrobial, fungistatic/fungicidal (antimycotic) hybrid coatings of multi-vectorial and directional action have real perspective for protection of synthetic and natural polymeric materials from bio-deterioration and non-controlled biodegradation as well as for human, cultural heritage and environmental protection.

**Acknowledgement:** One of us (Dr. Kh. Barbakadze) would like to thank Fulbright Foundation (CIES/IIIE; Washington, DC) for financial support in the form of Research Scholarship, also to Professor W. Brostow for helping to test of tribological properties of the coatings.

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**SECTIONS:****“Synthesis and Study of Bioactive Compounds;  
Antimicrobial and Biomedical Products and Materials”****SEPARATION OF ENILCONAZOLE ENANTIOMERS IN CAPILLARY  
ELECTROPHORESIS AND INVESTIGATION OF STRUCTURE  
OF SELECTOR-SELECTAND COMPLEXES BY USING NUCLEAR-  
MAGNETIC RESONANCE SPECTROSCOPY**

**L. Chankvetadze<sup>1</sup>, A. Gogolashvili<sup>1</sup>, E. Tatunashvili<sup>1</sup>, T. Sohajda<sup>2</sup>,  
J. Szemann<sup>2</sup>, A. Salgado<sup>3</sup>, B. Chankvetadze<sup>1</sup>**

<sup>1</sup>Institute of Physical and Analytical Chemistry, Faculty of Exact and Natural Sciences,  
3, Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia

<sup>2</sup>Cyclolab Ltd., Illatos út 7, 1097 Budapest, Hungary

<sup>3</sup>Centro de Espectroscopía de RMN (CERMN), Faculty of Pharmacy, University of Alcalá,  
Madrid, Spain

**Introduction**

The enantiomer migration order (EMO) of enilconazole in the presence of various cyclodextrins (CDs) was investigated by capillary electrophoresis (CE). Opposite EMO of enilconazole were observed with  $\beta$ -CD and heptakis(2-di-O-methyl-3,6-O-sulfo)- $\beta$ -CD (HMDS- $\beta$ -CD) were used as the chiral selectors. Nuclear Magnetic Resonance (NMR) spectroscopy was used to study the mechanism of chiral recognition.

**Materials and Methods**

All CE experiments were carried out on a CE system from Agilent Technologies (Germany). Fused-silica capillaries were provided by Polymicro Technologies (USA). A Varian NMR System (USA), was used for all NMR experiments. The spectrometer resonance frequency for <sup>1</sup>H was 499.61 MHz.

Racemic enilconazole, deuterium oxide (D<sub>2</sub>O), sodium deuterioxide (NaOD, 40% wt.), phosphoric acid (85%), 85% deuterated phosphoric acid were from Sigma-Aldrich (Germany). Native  $\beta$ -CD was kindly provided by Cyclolab (Budapest, Hungary). Heptakis(2,3-di-O-acetyl)- $\beta$ -CD (HDA- $\beta$ -CD) was synthesized in our laboratory according to ref. [1].

**Results**

On the basis of rotating frame nuclear Overhauser (ROESY) experiments, the structure of an inclusion complex between enilconazole and  $\beta$ -CD was postulated, in which (+)-enilconazole seemed to form a tighter complex than the (-)-enantiomer. These correlates will with the migration order of enilconazole enantiomers observed in CE. No evidence of complexation between enilconazole and HMDS- $\beta$ -CD could be gathered due to lack of intermolecular NOE interactions. Most likely the interaction between enilconazole and HDMS- $\beta$ -CD leads to formation of shallow external complex that is sufficient for separation of enantiomers in CE but cannot be evidenced based on ROESY experiment.

## Conclusions

Opposite affinity of enilconazole enantiomers was observed to native  $\alpha$ -CD and its single component derivative HMDS- $\alpha$ -CD based on CE experiment. 1D ROESY experiments showed the formation of an inclusion complex of both enilconazole enantiomers with  $\beta$ -CD. On the other hand, no interaction of enilconazole with HMDS- $\beta$ -CD could be detected from 1D- and 2D-ROESY data, although based on the results of CE experiments these interactions are definitely there.

**Acknowledgement:** This study was supported by a grant of Shota Rustaveli National Science Foundation (Project № 217642)

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## STUDY OF BIOLOGICAL ACTIVITY OF PEPTIDE DERIVATIVES OF CYCLENCARBOXYMETHYLEN AND 3,4-DIHYDROXYPHENYLALANINE

**L. Arabuli<sup>1\*</sup>, R. Jezek<sup>2</sup>, P. Lovecka<sup>2</sup>, T. Macek<sup>2</sup>, T. Ruml<sup>2</sup>, J. Viktorova<sup>2</sup>, E. Nikoleishvili<sup>1</sup>**

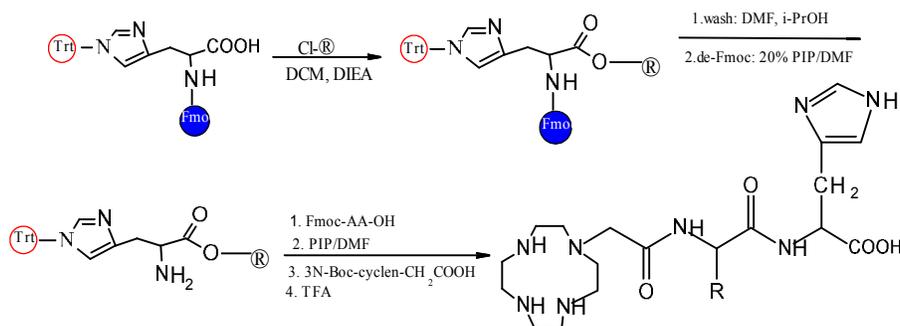
<sup>1</sup> University of Georgia, School of Health Sciences and Public Health, Department of Pharmacy  
\*l.arabuli@ug.edu.ge

<sup>2</sup> University of Chemistry and Technology, Department of Biochemistry and Microbiology,  
Technická 5, 166 28 Prague, Czech Republic

The most advantage of the macrocyclic polyamines is their unique capacity to bind some biologically important metals (Zn, Cu, Co, Fe) and their role was dramatically increased as behavior models for enzymes and other metalloproteins. The modification of macrocyclic polyamine receptor molecules with additional ligands (arms) enables to interact with nucleobase, sugar and other biomolecules moieties for a more efficient “multipoint” recognition, as well as for thermodynamic stabilization of the ternary complexes in aqueous solution. Cyclen, cyclam, their derivatives and metal complexes are proposed as good candidates to cross blood-brain barrier and with low toxicity as potential neuroprotective or neurorescue agents in the treatment of Alzheimer’s disease. In addition, cyclen derivatives showed antibacterial, anti-HIV and anti-malarial activities. On the other hand, polyphenolic compounds, like coumarins and its derivatives are able to bind transition metal ions and inhibit hydroxyl radical and hydrogen peroxide formation produced by Fenton’s reactions. Polyphenol derivatives (or metabolites) found numerous therapeutic applications, such as central nervous system stimulants, antitumor and anti-HIV therapy, antibacterial, anticoagulants etc.

We prepared cyclencarboxymethylen and 3,4-dihydroxyphenylalanine (L-DOPA) derivatives with His-rich dipeptides (cyclen-HisHis, cyclen-AspHis, cyclen-GluHis, Dopa-HisHis, Dopa-AspHis, Dopa-GluHis, Dopa-HisHis-Dopa, Dopa-AspHis-Dopa, Dopa-GluHis-Dopa, Dopa-GluHis-Dopa and Dopa-cyclen) via solid-phase synthesis strategy and identified using <sup>1</sup>H-NMR

and MALDI TOF MS-spectrometry. The new DOPA and 1,4,7-10-(carboxymethyl)-tetraazacyclododecane – oligopeptide derivatives were tested for their biological activity evaluation, such as antioxidant, antimicrobial, anticancer, antidiabetic etc. activities using their different concentration levels. The cytotoxicity and genotoxicity of new compounds were also studied.



Scheme. Stepwise reaction of functional derivation of tri-N-Boc-Cyclen-CH<sub>2</sub>COOH with dipeptide (HH, DH, EH)

## MODIFICATION OF POLYPROPYLENE YARN BY METAL NANOPARTICLES FOR GIVING THEM ANTIMICROBIAL PROPERTIES

**N.P. Prorokova<sup>1\*</sup>, S.Yu. Vavilova<sup>1</sup>, O.Yu. Kuznetsov<sup>2</sup>**

<sup>1</sup>G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, ul. Akademicheskaya 1, 153045 Ivanovo, RF

<sup>2</sup>Ivanovo State Medical Academy, Sheremetevskii pr. 8, Ivanovo, RF

\*npp@isc-ras.ru

A very urgent task is to create fibrous materials (fabrics, including nonwoven fabrics) with barrier antimicrobial properties which inhibit the vital functions of microorganisms falling on them. The use of such fibrous materials for the manufacture of medical clothes and linen will help minimize the likelihood of hospital-acquired infections.

It is possible to make the antimicrobial effect an inherent property of modified yarn that does not depend on the terms of its operation by the immobilization of metal nanoparticles with biocidal properties not on the surface of the fiber material, but in its entirety. The good antimicrobial properties of polymer composites based on polypropylene distributed in the polymer matrix of copper nanoparticles were reported in the papers [1 - 4]. However, it should be noted that the authors of these papers received massive undirected polymeric materials, whose submolecular is significantly different from that of yarns. Therefore, the data presented in them on the biological activity of polypropylene, filled with metal-containing particles, cannot be automatically extended to the same polypropylene yarn with analogous fillers. The antimicrobial properties of the latter can be

affected by the structural features of polypropylene yarn that is formed not by spherulites, but by fibrils, characterized by a very high degree of orientation and anisotropy. It should be also noted that in prior studies, silver- and copper-containing nanoparticles were used as biocides for immobilizing polymers in the structure, although the use of other metal-containing nanoparticles with antimicrobial properties is also of interest.

The authors of this paper firstly obtained polypropylene yarns modified with metal-containing nanoparticles, prestabilized by immobilization in polyethylene [5, 6]. The preparation and properties of such composites containing highly dispersed metals and their oxides in inert polymer matrix (so-called composite materials such as klaspol) are firstly described in detail in papers [7 - 9]. One important property of these nanocomposites is that metal-containing nanoparticles in them are tightly bound to the polymer matrix [9]. As we have shown in [5], during the preparation of the modified yarn, low density polyethylene due to intensive mixing in an extruder is uniformly distributed in polypropylene. It provides high uniformity of distribution of metal-containing nanoparticles firmly bound to the polymer matrix throughout the yarn, including its surface layer. Modification of polypropylene yarns with stabilized metal-containing nanoparticles leads to a significant increase in strength and a significant reduction in the surface electric resistance of the fibrous material.

It is found that, as a result of modification, polypropylene yarn acquires the ability to inhibit the life activity of pathogenic microorganisms [28]. The level of biological activity of modified yarns depends on the type of metal-containing nanoparticles and the type of test microorganisms. Thus, nanoparticles of transition metals (manganese, iron, and nickel) have a very good antimicrobial effect when expose to *gram*-positive bacteria *S. aureus* and fungi of *Candida* genus (*C. albicans*), but lead only to a slight reduction in the number of colonies of *gram*-negative bacteria of test strain of *E. coli*. The nanoparticles of noble metals (gold and palladium) have little effect on pathogenic bacteria, but a good antimicrobial effect in contact with yeast fungi of *Candida* genus (*C. albicans*).

It is demonstrated in the context of iron-containing nanoparticles that the form of polyethylene matrix stabilizing nanoparticles has a significant effect on the antimicrobial properties of modified polypropylene yarn. Yarns modified with nanoparticles in the matrix from low-density polyethylene have preferably good and very good effects on *S. aureus* and *C. albicans*, while having little effect on the vital activity of *E. coli*. On the contrary, the yarns containing nanoparticles in a matrix of high-density polyethylene cause an excellent antimicrobial effect in contact with *E. coli*, from good to excellent upon reacting with *S. aureus*, and slightly reduce the amount of colonies of fungi *Candida* genus (*C. albicans*). Thus, the selectivity of the antimicrobial action of polypropylene yarn modified with nanoparticles depends on the polymeric matrix stabilizing metal-containing nanoparticles.

The antimicrobial activity of nanoparticles increases with their concentration in the polymer structure. This relationship appears especially clearly for nanoparticles stabilized with high-density polyethylene.

The antimicrobial properties of polypropylene yarns modified with metal-containing particles stabilized by polyethylene appear only in direct contact of yarns with pathogens. Thus, it is found that polypropylene yarns as a result of their modification with metal-

containing nanoparticles, stabilized by polyethylene matrix, acquire antimicrobial properties, which are of the barrier type. This means that the fibrous material made of them will prevent the penetration of pathogens through it by inhibiting the vital functions of the latter in contact with it.

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## THE NEW GENERATION OF TEXTILE MATERIALS FOR MEDICAL CARE

**Moryganov A.P., Dymnikova N.S., Erokhina E.V.**

G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences,  
1, Akademicheskaya, 153045 Ivanovo, RF

The development and application of modern medical dressings and bondage materials attracts an ample attention over the last decade. The main reason of such an interest to aged bandage technology is due to its availability, efficiency and low cost. In contrast to traditional gamgee tissue, cotton wool, roller bandages and various types of

first aid kits, the new generation of first aid kits and bandages for treatment of the variety of wounds and injuries must meet many requirements. Such products are required to act in a complex fashion providing effective healing of wounds with different etiology.

At the Institute of Solution Chemistry of RAS we have a 15 year experience in study and development of modern technologies for production of a new generation medical materials for health care and general purpose antimicrobial treatment products composed from cellulose fibers.

1. Flax fibers demonstrate significant advantages over traditional cellulose/cotton fibers in production of health care dressings and other bandage materials. Morphology, structure and composition of flax fibers and their natural counterparts result in much better hygienic, medical, biological, and medicinal properties compared to traditional cotton and hydrocellulose fibers. We have developed a new technology of chemical modification including purification and bleaching of short flax fibers. The technology is based on an efficient treatment of flax fibers with various liquid mixtures containing highly potent chemicals and activators. The designed methods of treatment result not only in excellent bleaching grade and high quality characteristics of medical wadding but also help to retain significant portions of natural components of flax fiber (polysaccharides, lignin, and other important cellulose components) responsible for its medical and biological properties.

Our new technology has been tested at “LenOm” facility (City of Kalachinsk, Omsk region). The “LenOm” company is the first industrial facility in Russia built for production of flax wadding. It has been shown that our technology together with specially designed equipment allows mass production of high quality flax wadding with the following characteristics: bleaching – 72%, capillarity – 80-85 mm, absorption (at least) – 19 g per one gram of fiber, and high purity with negligible amounts of unwanted additives.

Currently “LenOm” factory is the only facility in Russia which uses eco-safe technology for production of bleached flax fiber for medical purposes and medical surgical hygroscopic flax wadding, both sterile and non-sterile: WSFS-“ISC” (registration certificate № ФСР 2011/10244 issued March 05, 2011) [1].

2. We have developed the technology for production of “BioLen” line of medical bandage products from flax fibers which includes eight different product types (TY 9393-008-17777359-2007). Various state-approved antiseptic medicals, including the newest drugs, have been employed for the treatment of bandage products made of flax fibers.

Atraumatic, antimicrobial and high-sorption medical dressings and bandages “BioLen” have been developed for the first aid needs, treatment of infected and granulated wounds of various etiologies. Such medical dressings and bandages exhibit excellent adhesion to wounded area regardless of its localization on the patient body, and provide high sorption of wound exudate; also, our products tend to normalize vapor interchange inside the wound, exhibit prolonged antimicrobial action, and can be safely removed when changed.

3. Another point of interest covers production of bioactive medical dressings and bandages with combined antimicrobial and anesthetic effects. As a part of the first aid

procedures it can be very important for bandages to deliver an anesthetic action, which significantly reduces pain and allows medical personnel to avoid a neurogenic shock. We have developed a new technology for production of pilot bandage samples derived from flax fibers with inclusion of local anesthetics.

Laboratory medical tests of such combined dressings revealed that inclusion of lidocaine anesthetic drug into the bandage increases anesthetic threshold from 2.13 mA (control samples) to 2.47 mA (nonwoven flax fabric, treated with 4% lidocaine solution) after 5 min of treatment on an actual patient. In case of nonwoven medical dressings made of modified mixture of flax fibers with viscose and treated with 5% lidocaine solution, the anesthetic threshold went up to 2.73 mA.

4. We have developed the technology for production of nonwoven cellulose materials for various medical purposes. Applying theoretical models and experimental methods we have found proper raw material mixture compositions for production of diverse nonwoven medical dressings. Our findings will help to simplify the technological process and provide the ability to achieve the required medical properties. Function modeling has been used to design and make the original structures of nonwoven atraumatic flax fabrics and hygienic materials with high absorption capability, retaining ability, porosity and antimicrobial properties.

Actual clinical trials of our products (bandages, tampons, absorption towels, medical dressings treated with medicine) demonstrated their excellent hygienic and functional (antimicrobial, atraumatic, and wound healing) properties.

5. Currently, our research group conducts study and synthesis of a new class of high potent drugs preliminary called “NanoTex” composed of silver nanoparticles. Also, we research various techniques for the treatment of textile materials with such particles [2, 3]. To improve the therapeutic and preventive qualities of synthesized silver nanoparticles another composite medicine has been developed. It incorporates special polymers into stabilization shell of silver nanoparticle. Such polymers possess antimicrobial activity and allow us to regulate autonomy of silver nanoparticles with relation to cellulose. In contrast to silver ions, silver nanoparticles reveal much higher antimicrobial activity at silver concentrations of only  $1.9 \cdot 10^{-3} \text{ mol} \cdot \text{l}^{-1}$ , and this ability retains after many washing cycles. Besides that, with a new drug we are able to regulate silver migration rate from textile material to outside media, thus controlling the required level of antifungal or antimicrobial activity.

All required procedures and activities for implementation of NanoTex” chemical for the treatment of hosiery garments has been started. The treated garments are very effective for prevention and rehabilitation of fungal infections and related diseases for prolonged period of time, even after many washing cycles. Providing wide assortment of such agents for consumers will expand development and production of the effective protective chemicals for the treatment of products we use everyday (bedding fabric, lingerie, etc.) for military personnel, travelers, hospital patients, etc.

The technologies described above can be successfully applied for the production of a new generation medical and consumer materials and products with prolonged antifungal and/or antimicrobial effects as well as materials intended for short-term usage (i.e. disposable). These materials can be used for production of everyday use

merchandise and medical products for health care centers, hospitals, fitness centers, spas, in transportation and during public events such as festivals, Olympic games, etc.

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## SEQUENTIAL EXTRACTION AND ANALYSIS OF VALUABLE COMPOUNDS FROM ORANGE AND TANGERINE POMACE

**M. Tsitsagi<sup>\*</sup>, K. Ebralidze, M. Chkhaidze, M. Buzariashvili, M. Khachidze, I. Jinikashvili**

Petre Melikishvili Institute of Physical and Organic Chemistry,  
Iv. Javakhishvili Tbilisi State University  
31, A.Politkovskaia Str., Tbilisi, 0186, Georgia; <sup>\*</sup>mziatsitsagi@yahoo.com

Tangerine and orange are important agricultural crops in Georgia. As the statistical data for year 2016 manifest, the total harvest exceeds 100 thousand tons. Tangerine and orange pomace, agro-industrial waste of production of juice concentrates and jams present rich sources of valuable bioactive compounds. Citrus pomace is usually treated as by-products or waste, resulting in environmental pollution. Citrus peel is promising source of essential oil, carotenes, natural flavanones such as hesperidin and pectin. Stepwise, sequential utilization of tangerine and orange peel provides an opportunity for selective extraction of the aforementioned bioactive compounds and allows one to manage nonstandard citrus (amounting to a third of the harvest) in a rational manner. Hence, the present study is undertaken to elaborate a feasible and effective method of sequential extraction of above mentioned bioactive compounds from citrus pomace.

The first step is supercritical CO<sub>2</sub> extraction of essential oil. It was found that at subcritical conditions yield of oil is lowest, but most selective. As the temperature, pressure and extraction time increases, yield of oil increases, but selectivity drastically reduces. The extracted oil found to extract carotenoids and imparting orange color to the extract. Optimal conditions for  $\beta$ -carotene free tangerine oil are 100 atm pressure and 35<sup>o</sup>C temperature and 15 min equilibrium time. The yield of the carotene free oil varies from 0.8%wt-0.9%wt.

Optimal conditions for  $\beta$ -carotene free tangerine oil are 100 atm pressure, 35C<sup>o</sup> temperature, and 15 min equilibrium time. The principal compound in Citrus Unshiu peel and orange essential oil is d-limonene. Stepwise extraction requires correct extraction sequence of target products. Acetone (7%) was used as co-solvent in the second step of extraction. The  $\beta$ -carotene is soluble

in acetone, whereas hesperidin is not. Optimal parameters are 150 atm, 40°C and 1h equilibrium, and 1h extraction time in dynamic conditions.

The chromatographic conditions were determined by optimizing the system operational parameters: the wavelength for detection, the gradient program of mobile phase, the composition of mobile phase, the flow rate, the nature of stationary phase and the injection volume. The system suitability parameters: theoretical plates, tailing factor, peak purity was checked.

Ethanol (7%) was used in the third step of extraction. Optimal parameters were: 250 atm pressure, 60°C temperature, 1h equilibrium and 30min dynamic extraction time. At least pectin was extracted from residue of tangerin and orange waste.

Stepwise supercritical fluid extraction of bioactive compounds from agro-industrial waste materials is simple, effective, eco friendly separation method, which provides high quality of target products and needs one standard technological equipment.

## THERMOPHYSICAL INVESTIGATION OF ECO-SUSTAINABLE HYBRID MATERIALS

**N. Lekishvili<sup>1\*</sup>, Kh. Barbakadze<sup>1,2</sup>, N. Kokiashvili<sup>1</sup>, M. Tatarishvili<sup>1</sup>, A. Fainleib<sup>3</sup>**

<sup>1</sup>Tbilisi State University, Department of Chemistry, Institute of Inorganic-Organic Hybrid Compounds and Non-traditional Materials, Faculty of Exact and Natural Sciences  
3 Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia; \*nodar@lekishvili.info

<sup>2</sup>Tbilisi State Medical University, 33, Vazha Pshavela ave., 0186, Tbilisi, Georgia

<sup>3</sup>Institute of Macromolecular Chemistry of National Academy of Sciences of Ukraine  
48, Kharkiv Highway, 02160, Kyiv, Ukraine

Novel hybrid inorganic-organic multifunctional composites and coatings targeted for protection of cultural heritage (archeological patterns, museum exhibits, etc.), also various natural and synthetic materials and wares, from non-controlled biodegradation provoked by the action of aggressive microorganisms have been developed.

By the methods of differential scanning calorimetry (DSC), differential-thermal (DTA) and thermogravimetric analysis (TGA) thermophysical properties of the selected polymeric matrices and corresponding hybrid materials have been studied.

The DSC measurements were performed with a differential scanning calorimeter from Netzsch, Selb, Germany, model DSC 200. All tests were conducted under dry nitrogen in the temperature range from -100°C up to +300°C at a heating rate 5°C/min. Samples of about 10 mg were enclosed in aluminium DSC capsules.

Thermogravimetric analysis was carried out using thermogravimeter – Perkin Elmer TGA 7; temperature range 30-700°C, heating rate 10°C/min. 10-20 mg of each dry sample were tested.

DSC results allowed identifying different glass temperature transitions ( $T_g$ ) for the different ratios. Small changes on the mass losses at high temperatures could be investigated by analyzing TGA results. Both DSC and TGA techniques are well explained by Menard [1].

The differential scanning calorimetric measurements show that endothermic peaks on the obtained curves correspond to the glass transition temperatures of tested samples ( $T_g$ ). It was

established, that the modification of chosen polymeric matrices causes decrease of glass transition temperature compared with non-modified basic polymer (PU). The glass transition regions on DSC curves are located at the higher temperature range than  $+50^{\circ}\text{C}$ . Herewith, they are amorphous (is not seen the exothermic peak characterized for crystallization) and optical transparent. This is important for the use of coatings for protection of museum exhibits since the optical clarity at room temperature and above is assured.

DSC diagrams show also phase transitions in the glassy state, so called  $\beta$ -transitions.  $T_{\beta}$  centered about  $-46^{\circ}\text{C}$  to one centered about  $-62^{\circ}\text{C}$ . Apparently, the internal cohesion of pure polymer matrix at the low temperature is perturbed by the presence of siloxanes. On the other hand, modification by bioactive components results the shift of values of  $T_{\beta}$  to the right. Thus, addition of bioactive components enhances the stability of the low temperature amorphous phase.

Thermogravimetric study was carried out to establish the initial degradation temperature (IDT), decomposition temperature ( $T_{\text{dec}}$ ) with corresponding weight loss (wt.%) and the temperature of maximum rate of degradation ( $T_{\text{max}}$ ), – temperature after what no changes are observed for researched samples. TGA results show that thermal stability of the modified hybrids increases with respect to the pure polymeric matrices. Herewith resistance to thermal degradation is enhanced and weight loss is shifted to higher temperatures as the amount of siloxane modifiers increase and further is improved by addition of bioactive components. In particular, hybrid coatings obtained based on modified polymers are stable at higher temperature than  $200\text{-}220^{\circ}\text{C}$  (there was observed only a little weight loss - 5-8 %). Above  $350\text{-}400^{\circ}\text{C}$  takes place the intensive destruction of the researched samples of polymeric matrices and coatings prepared on their basis (with a large weight loss in the range of 60-81 %).

Thus, modification of basic polymeric matrix by silicon-organic oligomers improves the thermal stability of corresponding composites; their weight loss is shifted to higher temperatures and further is improved by addition of bioactive components. The full thermal degradation of tested hybrids is observed above  $550\text{-}600^{\circ}\text{C}$ .

It has been established that by the purposeful selection of structure, bioactivity and ratio (wt.%) of basic components of hybrid composites and materials were improved their thermo physical and operational characteristics.

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## SYNTHESIS AND SOME TRANSFORMATION OF 5(6)-NITRO-[2-(3-ACETYLAMINOADAMANTYL-1)]-1H-BENZIMIDAZOLE

D. Zurabishvili, T. Bukia\*, M. Lomidze, I. Gogolashvili, T. Tabatadze,  
A. Vanishvili, Sh. Samsoniya

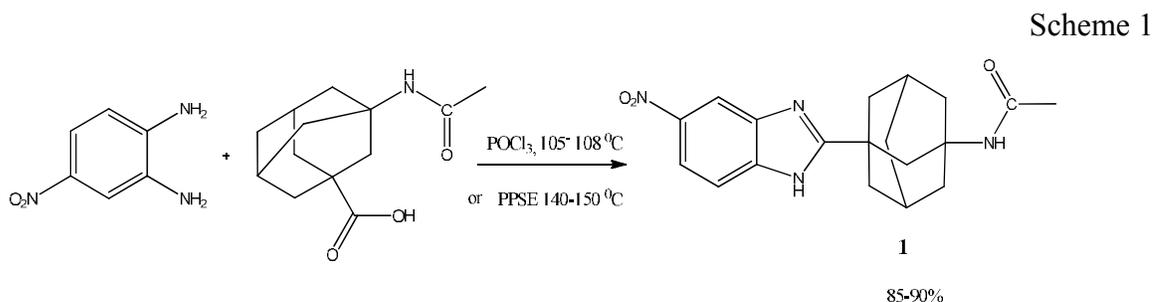
Institute of Organic Chemistry, Faculty of Exact and Natural Sciences,  
Iv. Javakhishvili Tbilisi State University, 3, I.Chavchavadze Ave., 0179, Tbilisi, Georgia

\*t.bukia@yahoo.com

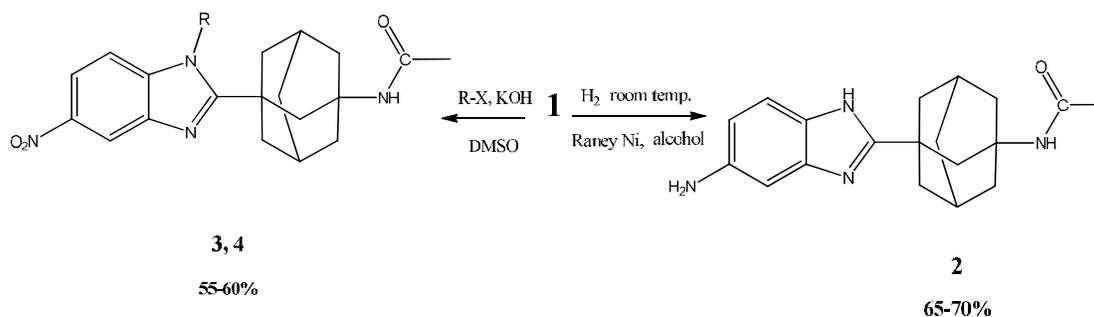
It is known that benzimidazole derivatives are characterized by biological activity. They are having a variety of therapeutic uses including antitumor, antifungal, antiparasitic, analgesics, antiviral, antihistamine, as well as use in cardiovascular disease, neurology, endocrinology, and ophthalmology [1]. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B<sub>12</sub>. The adamantyl group is present in several compounds in current clinical use for the treatment of neurodegenerative disorders, viral infections and type 2 diabetes, and in many more substances that are in development as potential therapeutics. In many cases the adamantyl group has been found to improve pharmacological properties of a parent compound, without increasing its toxicity. Incorporation of a bulky lipophilic adamantyl moiety into compounds increases their biological availability by inducing greater membrane permeability and/or decreasing the susceptibility to hydrolytic enzymes (amidases, esterases) [2]. Therefore, adamantane containing benzimidazoles are of interest in the search for new compounds with a broad spectrum of pharmacological action. Previously, we have synthesized 2-(1-adamantyl)-1H-benzimidazole and studied its some transformation [3]. The aim of present work was to synthesis of 5(6)-nitro-[2-(3-acetylaminoadamantyl-1)]-1H-benzimidazole (**1**) and study some of its transformations. Condensation of 5-nitro-*o*-phenylenediamine with 3-acetylaminoadamantane-1-carboxylic acid in POCl<sub>3</sub> or in PPES produces compound **1** in excellent yield (Scheme 1).

The preparation of 5(6)-amino-[2-(3-acetylaminoadamantyl-1)]-1H-benzimidazole (**2**) is described in scheme 2. The reduction of compound **1** with molecular hydrogen in the presence of Raney Ni was carried out in alcohol. Compound **2** was obtained with 65-70% yeald.

Compound **3** and **4** were prepared by the interaction of alkyl halogens with compound **1** in the area of DMSO in presence of KOH (Scheme 2).



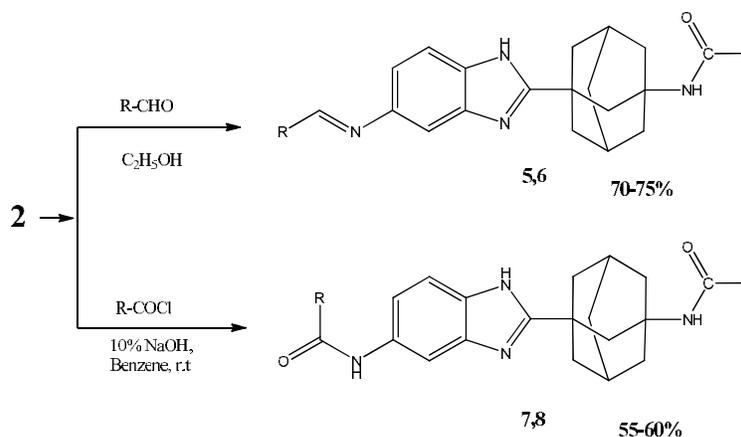
Scheme 2



R=CH<sub>3</sub> (**3**), C<sub>3</sub>H<sub>7</sub> (**4**).

In an attempt to prepare new derivatives of 5(6)-amino-[2-(3-acetylaminoadamantyl-1)]-1H-benzimidazole (**2**), the condensation of amine **2** with salicylaldehyde and benzaldehyde was carried out by heating in alcohol solution. The corresponding Schiff bases **5** and **6** were isolated in 70-75% yields (scheme 3). Condensation of amine **2** in absolute benzene with benzoylchloride or acetic anhydride in the presence of TEA led to the formation of the corresponding novel 5(6)-amino-[2-(3-acetylaminoadamantyl-1)]-1H-benzimidazole acyl derivatives **7, 8** (Scheme 3).

Scheme 3



R= C<sub>6</sub>H<sub>5</sub> (**5**) C<sub>6</sub>H<sub>4</sub>OH (**6**), CH<sub>3</sub> (**7**), C<sub>6</sub>H<sub>5</sub> (**8**);

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## NEW, $\alpha$ -AMINO ACID BASED UNSATURATED POLY(ESTER AMIDE)S

### E. Chkhaidze

Georgian Technical University, Department of Chemical and Biological Technology  
69, M. Kostava Ave., 017,5 Tbilisi, Georgia  
ekachkhaidze@yahoo.com

$\alpha$ -Amino acid based (AAB) poly(ester amide)s (PEAs) are a relatively new class of resorbable polymers [1-4]. Besides the diversity in material properties [1,5], they have shown good biocompatibility [6] and low inflammatory response [7], which makes PEAs highly attractive for biomedical applications. The lateral functional groups (e.g., -COOH) along the PEA chain makes it suitable for a wide range of chemical modifications [4]. Therefore, it is desirable to design new functional PEAs that could have pendant lateral functional groups along the backbones. One of the most convenient ways to render biodegradable polymer functional is the incorporation of unsaturated double bonds in the polymer backbone that could easily be derivatized [8].

Series of new biodegradable unsaturated polyesteramides (UPEAs) and co- polyesteramides (coUPEAs) were obtained by us in the Research Center of biomedical polymers and biomaterials at Georgian Technical University in collaboration with research group of Cornell University (USA) [9] Unsaturated UPEAs were synthesized using in solution active polycondensation di-*p*-nitrophenyl fumarate as a bis-electrophilic partner of di-*p*-toluenesulfonic acid salts of bic-( $\alpha$ -amino acid)- $\alpha,\omega$ -alkylene diesters – key monomers for preparing AAB-PEAs [10].

Fumaric acid – unsaturated dicarbonic acid was a key monomer of our work, by means of which we inserted unsaturated bonds into basic chain. The syntheses of three types of new unsaturated PEA polymers were explored – (I) Leu- and Phe- based unsaturated PEA homopolymers (UPEAs) composed of 100% of fumaric acid, (II) Leu-based unsaturated-saturated copolymers (USPEAs) composed of fumaric acid and saturated fatty diacids, and (III) Leu- and Phe-based UPEA copolymers composed of 100% fumaric acid (co-UPEAs).

Many of the targeted unsaturated polymers were soluble in common organic solvents and showed good film-forming property. The UPEAs were further chemically modified into functional derivatives as well as subjected to thermal and photochemical transformations (curing) that substantially expand material properties and, hence, the scopes of potential applications of  $\alpha$ -amino acid based biodegradable poly(ester amide)s as absorbable surgical devices and drug carriers.

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## **BIOCIDE PROPERTIES OF Co(II) AND Ni(II) COMPLEXES WITH META-NITROBENZALDEHYDE BENZOYL HYDRAZONE**

**Z. Lomtadze<sup>1</sup>, T. Shiukashvili<sup>2\*</sup>, I. Sharia<sup>1</sup>**

<sup>1</sup>Sokhumi State University

<sup>2</sup>Ilia State University, Institute of Botany

1, Botanikuri, 0115, Tbilisi, Georgia

\*shiukashvilit@gmail.com

Synthesis of physiologically active substances with different structure for economic purposes is very popular today [1,2]. According to literary data hydrazides, hydrazones and their metal salts are more toxic than the coordinated substances of the same metals. From this point of view the biocide properties of meta-nitrobenzaldehydebenzoyl hydrazone and its coordinated substances with Co(II) and Ni(II) chlorides towards some actinomycetes, and phytopathogenic bacteria *Xantomonascampestris* (pathogen of melons and gourds), has been studied in our experiments. Mentioned substances were obtained by G. Tsintsadze, T. Tsivtsivadze and I. Sharia from the dep. of general chemistry of Georgian Technical University [3, 4].

0.1g/l and 1g/l concentrations of test-substances were applied. Actinomycetes: *Actinomyces griseus*, *Actinomyces streptomycini*, *Actinosporangium violaceum*, *Streptomyces Albogriseolus*, *Streptomyces violaceus*, *Nocardiopsis dassonvillei* and phytopathogenic bacteria *Xanthomonas campestris* served as test-objects. Biocidity of substances was determined by Egorov' method (5), viability of spores - by Kuznetsov' method [6].

Obtained results clear the selective and different extent biocide effect of the tested substances, in particular of meta-nitrobenzaldehyde benzoyl hydrazone complexes with Co(II) and Ni(II) on

microorganisms – *Actinomyces griseus*, *Actinomyces streptomycini*, *Actinosporangium violacium*, *Streptomyces albogriseolus*, *Streptomyces violaceus*, *Nocardiopsis dassonvillei* and pathogenic *Xanthomonas campestris* growth and development. Among experimental substances especially high biocide properties revealed the coordinated complex of Co(II) with tested substances.

Complex of meta-nitrobenzaldehyde benzoyl hydrazone complexes with Co(II) inhibited the viability of spores of the tested microorganisms as well. Especially effective was its influence on *Actinosporangium violaceum* (number of viable spores 33.3%), *Streptomyces violaceus* and *Nocardiopsis dassonvillei* (number of viable spores 50.0%).

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## DEVELOPMENT OF WASTELESS TECHNOLOGICAL PROCESS IN DIARY INDUSTRY WITH USE OF COMPLEX MEMBRANE TECHNOLOGY

**R. Gotsiridze, N. Mkheidze**

Agrarian and Membrane Technologies Scientific Research Institute  
of Shota Rustaveli State University, Batumi, Georgia  
35/32 Ninoshvili/Rustaveli str., Batumi 6010

Whey, as a waste of cheese and cottage cheese production contains valuable components including milk sugar – lactose. It is also called “life sugar”, as it is a very important product. The medicines and foodstuffs produced with use of lactose cure many diseases and promote intellectual development. Objective of this work includes production of proteins and lactose from waste products of dairy industry with use of complex membrane technology.

In Georgia milk is used mainly for production of cheese and cottage cheese. It is known that whey, as a waste of cheese production makes 90% of processed milk and its discharge causes pollution of the environment. In our laboratory we have developed combined membrane technology of whey processing, namely technology of production of melted cheese and lactose from whey.

Our work in this stage is of experimental nature and for improving of separation processes we have used the various methods of membrane filtration: microfiltration, ultrafiltration, electrodialysis, reverse osmosis.

In the first stage we let whey through fluoroplastic microfiltration membrane (pores size 0.1 mcm), providing pasteurization of whey in this case, i.e. making it free of microbes. Before filtration we warmed whey up to 42-55°C, corrected pH up to 5.5–6.0. This moment we inactivated calcium phosphate which fouls membrane pores in filtration.

For production of proteins concentrate from whey we used ultrafiltration membranes made of polysulfone and polyoxadiazole (pores size 300-500A), workings pressure 2-5 Atm. After neutralization of concentrate we received the mass of cream consistence which nutritive value and taste were not worse than the same of the analogical product. The received product contained approximately 14-15% of dry residual containing 11.5–12.5% of proteins. The proteins received such way have high biological and nutritive value due to preservation of their initial nature and optimal content of calcium and phosphorus.

After ultrafiltration, filtrate gets free of colloids. Apart of lactose, the mineral salts are dissolved therein. For production of pure lactose in the next stage of the process we used electrodialysis with use of electromembranes (MA-40, MK-40). Resulted such process, we received water solution of lactose in dialysate and water solution of mineral salts in concentrate.

In the final stage we concentrated dialysate on the reverse osmosis membrane made of polyoxidiazole polymer. Further we let the received concentrate through spray dryer (LabPlant™ SD-BASIC) and received pure crystal lactose with max. humidity 4%. In the process of fractioning the membrane produced by us were used, as their thermo- and chemical stability allows membrane regeneration with use of alkali and sodium hypochlorite solution.

## **TRIBOLOGICAL AND OPERATIONAL PROPERTIES AND THERMOSTABILITY OF THE ANTIMICROBIAL COATINGS BASED ON NANO COMPOSITES**

**Kh. Barbakadze<sup>1,2,3</sup>, G. Lekishvili<sup>2</sup>, B. Arziani<sup>2</sup>, N. Lekishvili<sup>1\*</sup>,  
N. Hnatchuk<sup>3</sup>, W. Brostow<sup>3</sup>**

<sup>1</sup>Tbilisi State University, Department of Chemistry, Faculty of Exact and Natural Sciences, Institute of Inorganic-Organic Hybrid Compounds and Non-traditional Materials

<sup>2</sup>Tbilisi State Medical University, 33, Vazha Pshavela ave., 0186, Tbilisi, Georgia

\*nodar@lekishvili.info

<sup>3</sup>University of North Texas, Laboratory of Advanced Polymers & Optimized Materials (LAPOM), Department of Materials Science and Engineering and Department of Physics, University of North Texas, 3940 North Elm Street, Denton, TX 76207, USA

Antimicrobial composites and materials with specific properties based on polyurethane and nano-size biogenic metals and metal oxides (Ag, ZnO) have been created and studied. Thermo-physical characteristics, basic tribological (scratch resistance, dynamic friction) and surface properties of the obtained composites and materials have been studied. It was established that the

addition of silicon organic modifiers and bioactive components into polyurethane matrix modifies thermal, tribological and operational properties (isothermal aging, water absorption) of corresponding materials to the desired direction. To evaluate thermal stability and decomposition behavior of the neat and modified hybrid composites thermogravimetric study (TGA method) was carried out. Thermal stability parameters, namely, initial degradation temperature (IDT), decomposition temperature ( $T_{dec}$ ) with corresponding weight loss (wt.%) and the temperature of maximum rate of degradation ( $T_{max}$ ), have been determined. The water absorption resistance for modified hybrid polymer composites is better compared to the non-modified PU. As performed tests show, hydrophobicity increases by modification and  $W_{H_2O}$  does not exceed 0.03 wt.% during 720 hours in all cases. Hence, silicon-organic and bioactive inorganic modifiers act as barrier in polyurethane matrix, hindering effective path for the water molecules to travel, and accordingly lead to the increase of water absorption resistance.

The elaborated antimicrobial hybrid materials are characterized with good fixation on various samples and wares, good strength, elasticity and do not change the color during photo- and isothermal aging and have a number of applications.

## **COORDINATION COMPOUNDS OF SOME 3D-METALS OF TETRATHIOARSENATES(V) WITH ORTO-PHENYLENEDIAMINE**

**I. Didbaridze, B. Gogichaishvili, N. Bregadze**

Kutaisi Akaki Tsereteli State University  
59, Tamar Mefe Ave., Kutaisi, Georgia

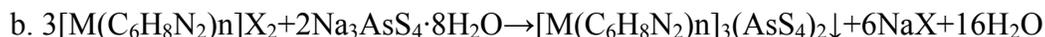
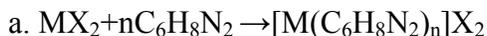
The use of the transformation products of the arsenic industrial waste for obtaining of new compounds with specific properties, under growing deficit conditions of raw materials, not only will promote the elaboration of new, commercially interesting forms of corresponding compounds, but also will introduction protect the environment from pollution by arsenic-containing waste. One of the most interesting ways to solve of this problem is obtaining new bioactive coordination compounds. As it is known from literature, polyelement coordination compounds manifest a lot of interesting properties that gives possibility for their wide practical application. In recent year among these types of compounds the points of special interest provoke the complex compounds which contain tetrathioarsenate(V) group along whir nitrogen and d-metals [1,2].

Goal of our research was obtaining and study of coordination compounds of Zn and Cu(II) with orto-fenilendiamine – one of the most prospective and accessible nitrogen-containing ligand received on the basis of products obtained via transformation of above mentioned production waste. These compounds will demonstrate the high bioactivity.

As the initial compounds we have used water soluble salts of abovementioned metals. Among arsenic-containing compounds, we have used sodium tetrathioarsenate  $Na_3AsS_4 \cdot 8H_2O$ , which was obtained in the following reaction [3].



Synthesis of d-metal orto-fenilendiamines occurs according to the exchange reaction via interaction of equimolar quantity of saturated solution of sodium tetrathioarsenate with the orto-fenilendiamines of 3d-metals salts (Scheme).



Where M=d-metals, Zn or Cu(II), X=anion of acid ( $CH_3COO^-$ ,  $1/2SO_4^{2-}$ ), n=2.

#### Scheme

Synthesized compounds are mildly crystalline substances of different colors. The composition and structure of compounds was established by elemental analysis (Table 1), IR spectroscopy and X-ray phase studies. IR spectra have been obtained on the spectrometer "SPECORD IR-75" in liquid paraffin. X-ray studies were carried out on diffractometer "DRON-3M", thermogravimetric studies were carried out on derivatograph "Q-1500" ("F. Paulik, J. Paulik, Erdey", Hungary), by heating of test specimen in the air up to 1000°C with the 10°C/min heating rate, reference substance – corundum [4].

As is seen in IR spectra of synthesized compounds, absorption bands of valence vibration characteristic for  $AsS_4^{3-}$  group are manifested at 420  $cm^{-1}$ , while absorption bands of deformation vibration are manifested at 470  $cm^{-1}$  area [5]. Besides as it is known [6], the value of absorption band in case of coordination of free ligand with the central atom are shifted by  $\sim 8-30 cm^{-1}$ . Then it is claimed that ortho-phenylenediamine is in a coordinated state with the metal through the nitrogen atoms.

Table 1. Elemental analysis data and output of synthesized complex compounds of  $[M(C_6H_8N_2)_2]_3(AsS_4)_2$  type

№	Coordination compound	color	Elemental analysis				Yield, %
			Calculated / found, %				
			M	As	N	S	
1	$[Zn(C_6H_8N_2)_2]_3(AsS_4)_2$	Brown	15,71/15,64	12,01/12,09	13,45/13,38	20,49/20,57	88,4
2	$[Cu(C_6H_8N_2)_2]_3(AsS_4)_2$	Hazel	15,41/15,34	12,04/12,11	13,48/13,39	20,55/20,62	86,6

The data of X-ray phase analysis of synthesized compounds on based on classification given in the literature [7] testifies that obtained compounds belong to the subgroup of sulfo-salts according to their structural nature. Cations' formed of crystal structure deserves special attention. For example, Zn and Cu(II) promotes of finely-crystalline phase which approaches to X-ray amorphous state [8].

The preliminary investigations showed that the synthesized compounds can be used for obtaining of antimicrobial coatings for protection of museum exhibits [2].

The individuality and structure of the studied compounds, in addition to elementary analysis, were established by physicochemical methods. Scattering of the IR absorption spectra of the complexes shows that ortho-phenylenediamine with central metal atoms is bound through nitrogen atoms to form chelate compounds. It was found that the resulting coordination compounds are cationic complexes, and the tetrithioarsenate ion is in the outer sphere. The thermal stability and decomposition of the compounds obtained is studied.

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## THE EFFECTS OF AIR POLLUTION ON THE PHENOL CONTENT IN BLACKBERRY (*RUBUS CAESUIS*) LEAVES

**N. Chaganava\*, B. Arziani**

Tbilisi State Medical University, Department of Medical Chemistry  
33, Vazha Pshavela Ave., 0186, Tbilisi, Georgia; \*nanat.chaganava@gmail.com

Increase in the levels of air pollution due to the development of industrial and agricultural technology has prompted investigation of the mechanisms that contribute to air pollution tolerance in plants.

According to the epidemiological studies the increased concentrations of atmospheric pollutants (SO<sub>2</sub>, NO, NO<sub>2</sub>, NO<sub>x</sub>, O<sub>3</sub>, CO, hydrocarbons and solid particles of dust) cause respiratory, cardiovascular, oncological, hypertensive and other diseases and the death rate increase accordingly [1-3]. Thus, regular monitoring of quality of atmosphere for any country in the world as well as for Georgia is necessary.

As recent researches have shown, atmospheric pollution in natural conditions provokes formation of definite compounds in the plants or the change their concentration. These compounds could be used as bio-indicators during monitoring of atmosphere purity. Defining of content of chemical compounds in the plants makes it possible to determine harmful influence of pollutants even in case of their small amount in the air.

Meanwhile, these researches are important as the plants do not render this service to the mankind without any serious deformities caused by the integrating pollutants and show diverse morphological, biochemical, anatomical and physiological responses [4, 5].

Phenolic compounds are secondary metabolites and play important role in growth and development of plant, in particular, during symbiosis, in bot stamen fertilizing, transporting of polar auxin. They are protectors of ultraviolet irradiation and take part in regulation of cell cycle.

The aim of presented study was to access the impact of air pollutants on phenolic compounds content of blackberry (*Rubus caesuis*) leaves.

In order to study quality of air pollution blackberry (*Rubus caesuis*) leaves were chosen as a control plant due to its widespread dissemination in most of Georgian regions. For the first step analyses leaves collected from three cities - Bakuriani, Zestaphoni and Batumi was selected.

Blackberry (*Rubus caesuis*) leaves were collected at the end of July, dried on air at room temperature in the dark space. Samples were extracted with hexane, chloroform and methanol. Total phenol content was determined using spectrophotometer V-2602 (absorption at 765 nm).

According to the conducted researches the least content of phenolic compounds was shown in Zestaphoni samples (596 mg/L), higher in Batumi samples (816 mg/L) and the highest - Bakuriani samples (1012 mg/L). Obtained results indicate probability of the higher degree of atmosphere pollution in Zestaphoni.

Thus, it is needful to continue researches to establish a certain correlation between the content of phenolic compounds in plants growing in natural condition and air pollution extent as used method is available (no need to use expensive equipments) and represents relatively cheap way to control the air purity.

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## SPECTROPHOTOMETRIC RESEARCH COMPLEXES OF CU(II) IN THE 3<sup>rd</sup> COMPONENT

**M. Qochiashvili<sup>1</sup>, M. Tsintsadze<sup>1\*</sup>, F.Chiragov<sup>2</sup>, T. Tusiashvili<sup>1</sup>, N.Bolqvadze<sup>1</sup>**

<sup>1</sup>Georgian Technichal University

77, M. Kostava St., 0175, Tbilisi, Georgia, \*m.tsintsadze@gtu.ge

<sup>2</sup>Baku State University, Azerbaijan

Complexation of copper(II) with 3-(2-hydroxy-3,5-disulphophenilazo) pentadion-2,4 in the presence of cationic surfactants has been studied by spectrophotometric method. Optimal conditions of their formation have been established, spectrophotometric characteristics are

calculated. Stability constants of complexes were calculated by spectrophotometric method. Complex compound for monoligand complexes is 1:2 and 1:2:1 for mixligand complexes. Influence of foreign ions to the complexation has been studied. The established method was applied for determination of copper in sea water.

The formation of solid compound-complexity of reagent copper (II) ions depends on pH. Maximum traction occurs when pH = 4. At this time, the maximum speed is 309 nm. In this case the sustainable complex Cu (II), which has a maximum light weight of 454 nm. The complex study of 3<sup>rd</sup> component in the pH's wide range showed that bacterial shifts in the absorption spectrum marked the third component and the optical density of the fluid increases significantly. Multilens complex is formed in a more acidic environment than in a binomial.

The maximum delocalization of the  $\pi$ -electron reagent system results in a bathochromic displacement of the absorption band of the associate formed, which is also associated with an increase in the negative inductive effect of the sulfo group under the influence of 3<sup>rd</sup> component.

The influence of foreign ions and masking substances on the photometric determination of copper in the form of mixed ligand complexes was studied. When comparing the selectivity of the copper reagents known from the literature, it is clear that the reagents used in the presence of the third component are more selective.

Data on selectivity allows us to apply the developed technique for photometric determination of copper in the form of different ligand complexes in sea water.

Table

Complex	pH <sub>opt</sub>	$\lambda_{max}$	$\epsilon \cdot 10^4$	lg $\beta$	component ratio	Linearity interval, mcg/ml
Cu - R	4	454	1.56	16,25 ± 0,05	1 : 2	0,25 – 3,07
Cu-R- ЦПICI	3	468	1.89	17,47 ± 0,05	1 : 2 : 2	0,18 – 2,56
Cu-R- ЦПIBr	3	471	1.96	17,28 ± 0,06	1 : 2 : 2	0,12 – 2,56
Cu-R- ЦTMABr	3	473	2.07	17,58 ± 0,05	1 : 2 : 2	0,12 – 2,56

## NEW 1,2,3-TRIAZOLE CONTAINING BIODEGRADABLE POLYMERS VIA CLICK STEP-GROWTH POLYMERIZATION

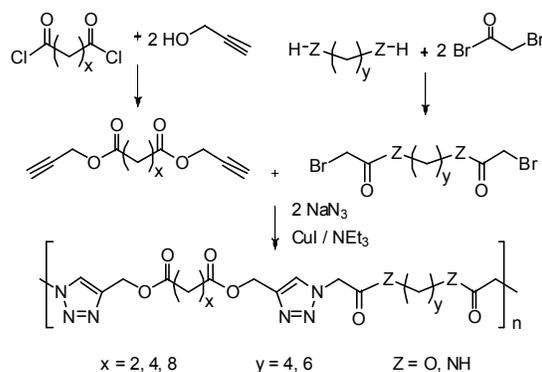
**Teng. Kantaria, Tem. Kantaria, G. Titvinidze, N. Kupatadze, N. Zavrashvili,  
D. Tugushi, R. Katsarava**

Institute of Chemistry and Molecular Engineering  
Agricultural University of Georgia  
Email: t.kantaria@agrni.edu.ge

The copper(I) catalyzed azide–alkyne cycloaddition (CuAAC) click reaction has already been exploited for the synthesis of numerous well-defined macromolecular structures including end-functionalized polymers, block copolymers, cyclic polymers, graft polymers, dendrimers, cross-linked materials, etc. Surprisingly, there are only few papers on the application of CuAAC click reaction in step-growth polymerization (SGP) as a chain propagation reaction, and there are limited publications on the synthesis of aliphatic triazole-linked AA-BB-type ester polymers by CuAAC click SGP.

In this work high-molecular-weight AA-BB-type aliphatic polyesters and poly(ester amide)s were synthesized *via* Cu(I)-catalyzed click SGP following a new synthetic strategy. The synthesis was performed between diyne and diazide monomers in an organic solvent as one pot process using three components and two stages. The di-propargyl esters of dicarboxylic acids (component 1) were used as diyne monomers, di-(bromoacetic acid)-alkylene diesters (for synthesizing polyesters) / di-(bromoacetic acid)-alkylene diamides (for synthesizing poly(ester amide)s) (component 2) were used as precursors of diazide monomers, and sodium azide (component 3) was used for generating diazide monomers. The SGP was carried out in two steps: at the Step-1 di-bromoacetates / di-bromoacetamides interacted with two moles of sodium azide resulting in diazide monomers which interacted *in situ* with diyne monomers at the Step-2 in the presence of Cu(I) catalyst. A systematic study was done on the example polyester for optimizing the multiparameter click SGP in terms of the solvent, duration of the both Step-1 and Step-2, solution concentration, catalyst concentration, catalyst and catalyst activator (ligand) nature, catalyst/ligand mole ratio, temperature and duration of the both steps of the click SGP. Comparing the click polyester's molecular weights and yields the best parameters for the click SGP were found as: a solvent - N-Methyl-2-pyrrolidone, a catalyst – CuI, a ligand – NEt<sub>3</sub>, a monomers concentration – 0.6 mol/L, duration of bis-azide formation step – 3 h (at room temperature), duration of SGP – 15 h, temperature of the click SGP reaction – 0° C. The established optimal conditions of the CuAAC-based SGP reaction was applied to the synthesis of a series of high-molecular-weight (Mw up to 73,000 Da) 1,2,3-triazole containing click polyesters and poly(ester amide)s (Scheme 1) which reveal improved thermal properties compared to their regular analogues.

The new polymers were found suitable for fabricating biodegradable nanoparticles, which are promising as drug delivery containers in nanotherapy. One of the important advantages of the developed CuAAC click SGP is the possibility of quaternization of 1,2,3-triazole rings of the resulting polymers which opens a way to cationic polymers – both water soluble ones and cross-linked cationic hydrogels promising for numerous biomedical applications.



**Scheme 1.** Synthesis of 1,2,3-triazole containing polyesters and poly(ester amide)s

**Acknowledgement:** This work was supported by Shota Rustaveli National Science Foundation of Georgia (SRNSFG) [FR17\_102, Elaboration of Biodegradable Nanocarriers for Ocular Drug Delivery].

## PREPARATION AND SURFACE MODIFICATION OF POLYMERIC NANOPARTICLES MADE OF AMINO ACID BASED POLY(ESTER AMIDE)S FOR MEDICAL APPLICATIONS

**Tem. Kantaria, Teng. Kantaria, S. Kobauri, D. Tugushi, R. Katsarava**

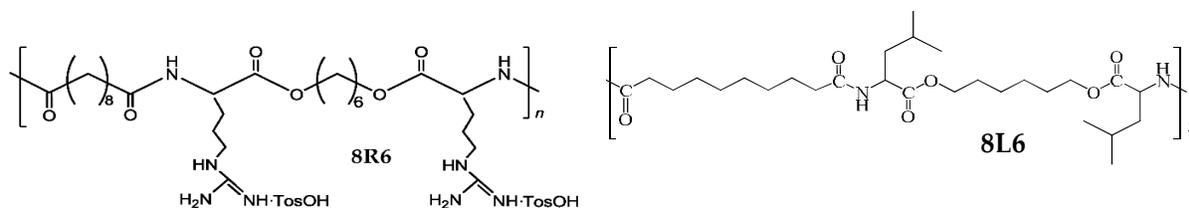
Institute of Chemistry and Molecular Engineering  
Agricultural University of Georgia, Georgia  
Email: tkant2015@agruni.edu.ge

The elaboration of nano- and microscale drug delivery vehicles is very actual nowadays since targeting drug delivery is one of the most important problems of the state-of-the-art drug therapy. The important technological advantages of nanoparticles (NPs) usage as drug carriers are their high stability, high carrier capacity, feasibility of encapsulation of both hydrophilic or hydrophobic substances, as well as a high variety of possible administration routes.

Various degradable and non-degradable polymers of both natural and synthetic origin have been used for NPs construction. The most used are synthetic biodegradable polymers such as poly(lactic acid), poly(epsilon-caprolactone), poly(glycolic acid), poly(lactic-co-glycolic acid) etc. These polyester classes of biomaterials, however, produce acidic products during degradation that are considered to be toxic and induce undesired phenotype modulation in cells. Hence, other class of hetero-chain biodegradable polymers – poly(ester amide)s (PEAs) which showed better biocompatibility compared to polyesters along with wider range of material properties, look more promising. In this work we have used the PEAs composed of naturally occurring and non-toxic building blocks such as  $\alpha$ -amino acids, fatty diols and dicarboxylic acids.

In our previous research we have performed a systematic study for the preparation of biodegradable NPs by cost-effective nanoprecipitation method using PEAs. The present work deals with the fabrication of the surface modified biodegradable NPs that includes the PEGylation (coating with polyethylene glycol, PEG) and imparting positive charge to the particulates.

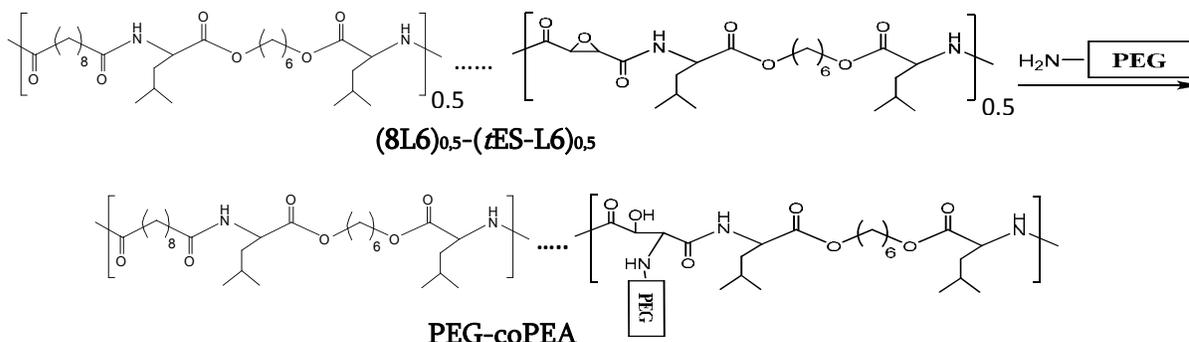
The PEGylation of NPs is important for improving their biocompatibility whereas positive surface charge (zeta-potential) is necessary for enhancing permeability through the biological barriers. The PEA composed of L-leucine, 1,6-hexanediol and sebacic acid (8L6) was used as a basic polymer for fabricating the NPs (Scheme 1), and the arginine based cationic PEA composed of L-arginine, 1,6-hexanediol and sebacic acid (8R6) was employed for imparting them the positive charge (Scheme 1).



TosOH = *p*-Toluenesulfonic acid

**Scheme 1.** Structure of the PEAs used for fabricating the NPs

An originally designed comb-like PEA, containing lateral PEG-2000 chains along with 8L6 anchoring fragments, was used as a PEGylating surfactant (**Scheme 2**). It has been established that depending on the fabrication conditions a size and zeta-potential of the NPs could be tuned within  $78 \div 161$  nm and  $+7.5 \div +23.2$  mV, respectively.



**Scheme 2.** Synthesis of new biodegradable surfactant

We can conclude that the obtained biodegradable PEGylated NPs based on poly(ester amide)s 8L6 and 8R6 are promising for application in medicine as drug delivery nanocarriers.

**Acknowledgments:** This work was supported by Shota Rustaveli National Science Foundation of Georgia (SRNSFG) [FR17\_102, Elaboration of Biodegradable Nanocarriers for Ocular Drug Delivery].

## THE SYNTHESIS OF ADAMANTANE RING CONTAINING BENZIMIDAZOLE, BENZOXAZOLE AND IMIDAZO[4,5-*e*] BENZOXAZOLE DERIVATIVES

**M. Soselia, D. Zurabishvili, I. Gogolashvili<sup>1</sup>, Sh. Samsoniya**

<sup>1</sup>Scientific-Research Institute of Organic Chemistry, Faculty of Exact and Natural Sciences  
Iv. Javakhishvili Tbilisi State University, 3, I. Chavchavadze Ave., 0179 Tbilisi, Georgia  
E-mail: marina.soselia001@ens.tsu.edu.ge

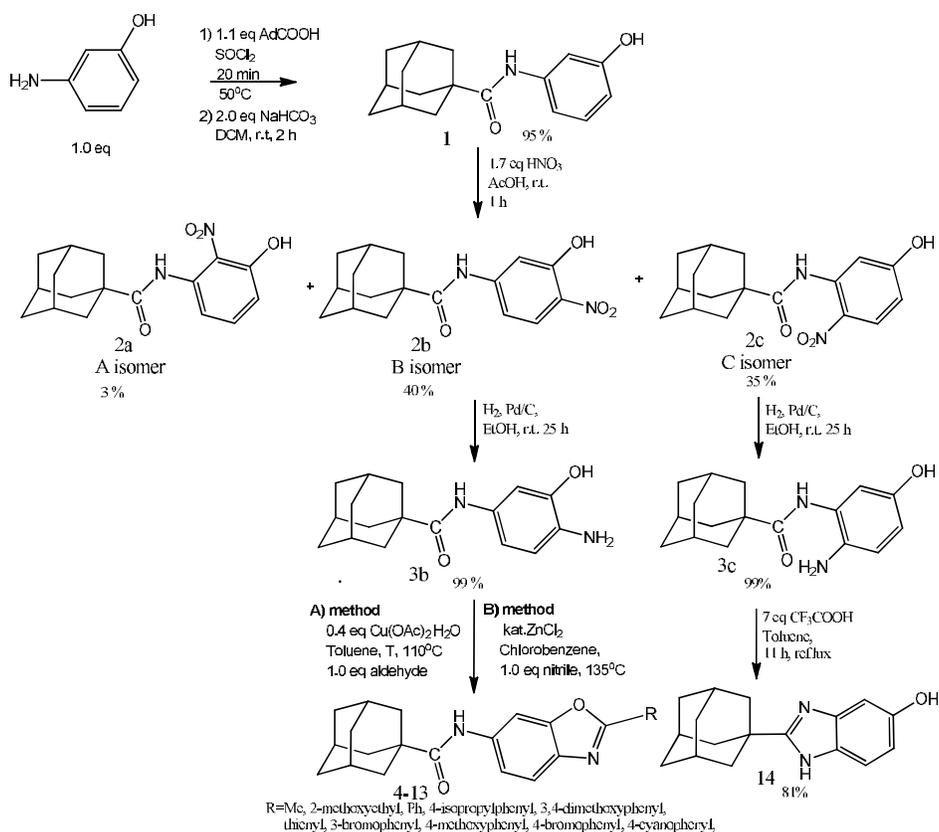
Benzimidazole and benzoxazole heterocycles derivatives are of wide interest because of their diverse biological activity and clinical applications. These ring systems are present in numerous antiparasitic, fungicidal, anthelmintic and anti-inflammatory drugs. Preparations created on their base are widely 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 [4-8]. According to this information, the

synthesis and studying of adamantane fragment containing new structures of benzimidazole and benzoxazole is perspective and actual.

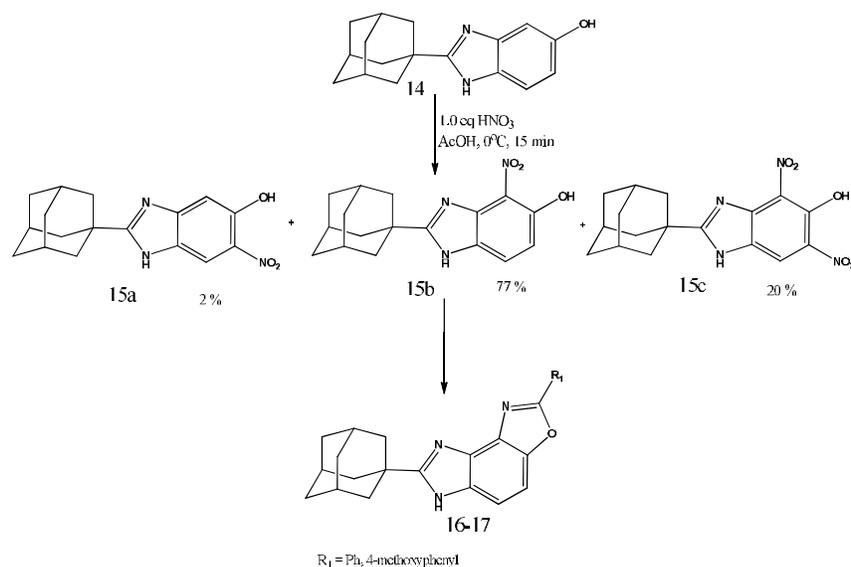
We developed a synthetic method for N-[alkyl(aryl)benzoxazol-6-yl]adamantane-1-carboxamide, 5-hydroxy-2-(1-adamantyl)benzimidazole and 7-(adamantan-1-yl)-2-(aryl)-8H-imidazo[4,5-e]benzoxazole derivatives. Initially, was studied condensation reaction of 3-aminophenol with adamantane carboxylic acid via converting of *carboxylic acids* to acyl chlorides to obtain N-(3-hydroxyphenyl) adamantane-1-carboxamide (**1**).

Afterwards, 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 **1** in the ratio 40/35/3. After isolation and subsequent reduction and cyclisation of obtained isomers were synthesized desired N-[alkyl(aryl)benzoxazol-6-yl]adamantane-1-carboxamides (**4-13**) from B isomer and 5-hydroxy-2-(1-adamantyl)-benzimidazole (**14**) from C isomer (Scheme 1).



Scheme 1

The nitration of synthesized benzimidazole (**14**) gave Mono - and Di - nitro compounds (**15a-c**). Isolated target 4-Nitro-5-hydroxy-2-(1-adamantyl)benzimidazole (**15b**) underwent reduction and subsequent cyclisation reaction with some aromatic aldehydes to give 7-(adamantan-1-yl)-2-(aryl)-8H-imidazo[4,5-e]benzoxazoles (**16-17**) (Scheme 2).



Scheme 2

Thus, there were synthesized 5-hydroxy-2-(1-adamanty)benzimidazole and N-[alkyl(aryl)-benzoxazol-6-yl]adamantane-1-carboxamide by four steps and 7-(adamantan-1-yl)-2-(aryl)-8H-imidazo[4,5-e]benzoxazole derivatives by seven steps starting from 3-aminophenole. All obtained compounds were characterized by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, DEPT, Mass spectroscopy and Elementary Analysis.

The synthesized compounds were tested on their antiviral activity. SAR of the synthesized compounds was estimated on the basis of a PASS prediction results.

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## SYNTHESIS OF NITROSO GROUP CONTAINING N-GLYCOSIDES

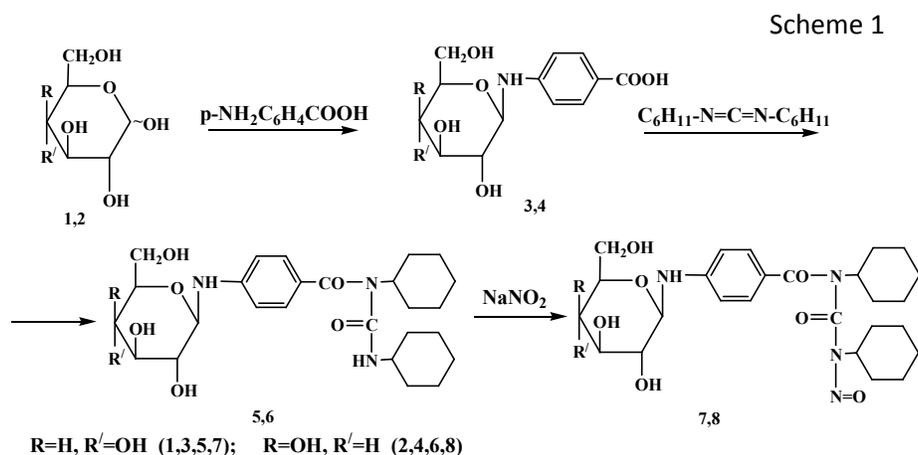
**N. Sidamonidze\*, R. Vardiashvili, M. Nutsbidze**

Ivane Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciences  
Department of Chemistry; 3, I. Chavchavadze Ave., 0179, Tbilisi, Georgia  
\*sidamonidzeneli@yahoo.com

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

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

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



The goal of present investigation consists in synthesis of N-glycosides containing in a molecule nitrosogroup (N=O). As an initial substance in the given work has been used the products of condensation of glucose (1), galactose (2) and *p*-aminobenzoic acids — N-*p*-carboxyphenyl-β-D-glucosyl(galactosyl)amine (3,4). By interaction of the last agent in usual peptide synthesis conditions with N,N'-Dicyclohexylcarbodiimide had been received N-urea (5,6). By interaction of compounds (5, 6) with sodium nitrite corresponding nitrosoderivatives

(7,8) has been received. Reaction proceeds according to the following scheme 1. The structures of obtained compounds were established by physical-chemical methods of analysis.

**$\beta$ -N-(*p*-carboxyphenylglucopyranosyl)-acylurea (5).** Yield 0.59 (59.4%), mp. 146-147<sup>0</sup>C, R<sub>f</sub> 0.72 (system a),  $[\alpha]_D^{17}$  - 34.6<sup>0</sup> (c 0.41, C<sub>2</sub>H<sub>5</sub>OH). Found, %: C 61.9; H 7.82; N 8.04. C<sub>26</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>. Calculated, %: C 62.02; H 7.35; N 8.35.

<sup>13</sup>C NMR spectrum ( $\delta$ , ppm), CDCl<sub>3</sub>: 85.76 (C-1), 74.02 (C-2), 78.51 (C-3), 72.1 (C-4), 76.44 (C-5), 59.72 (C-6), 167.5-170.0 (C=O), 12.5-23.0 (CH<sub>2</sub>-cyclohexyl). Aromatic group: 150.58 (C-1), 113.40 (C-2), 130.22 (C-3), 117.70 (C-4), 131.20 (C-5), 111.35 (C-6).

**$\beta$ -N-(*p*-carboxyphenylgalactopyranosyl)-acylurea (6)** was prepared analogously.

Yield 0.52 (52.8%), mp. 162-163.5<sup>0</sup>C, R<sub>f</sub> 0.49 (system c),  $[\alpha]_D^{17}$  - 27.3<sup>0</sup> (c 0.39, C<sub>2</sub>H<sub>5</sub>OH). Found, %: N 7.93. C<sub>26</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>. Calculated, %: N 8.35.

<sup>13</sup>C NMR spectrum ( $\delta$ , ppm), CDCl<sub>3</sub>: 92.7 (C-1), 79.3 (C-2), 77.54 (C-3), 77.0 (C-4), 76.6 (C-5), 62.5 (C-6), 166-168.5 (C=O), 12.0-22.8 (CH<sub>2</sub>-cyclohexyl). Aromatic group: 150.40 (C-1), 112.5 (C-2), 130.0 (C-3), 116.80 (C-4), 132.10 (C-5), 112.5 (C-6).

**$\beta$ -N-(*p*-carboxyphenylglucopyranosyl)-nitrosoarea (7).** Yield 0.13 (62.4%), mp. 132-134<sup>0</sup>C, R<sub>f</sub> 0.62 (system b),  $[\alpha]_D^{18}$  - 27.3<sup>0</sup> (c 0.59, C<sub>2</sub>H<sub>5</sub>OH).

Found, %: C 58.02; H 7.08; N 10.81. C<sub>26</sub>H<sub>36</sub>N<sub>4</sub>O<sub>8</sub>. Calculated, %: C 58.64; H 6.76; N 10.53.

PMR spectrum ( $\delta$ , ppm, J/Hz), TMS: 5.42 (1H, d, J<sub>1,2</sub> = 8.0, H-1), 5.30 (1H, dd, J<sub>2,1</sub> = 8.0, J<sub>2,3</sub> = 9.5, H-2), 5.05 (1H, dd, J<sub>3,2</sub> = 9.5, J<sub>3,4</sub> = 3.0, H-3), 5.20 (1H, dd, J<sub>4,3</sub> = 3.0, J<sub>4,5</sub> = 9.5, H-4), 3.80 (1H, ddd, J<sub>5,4</sub> = 9.5, J<sub>5,6'</sub> = 5.0, J<sub>5,6''</sub> = 2.5, H-5), 4.0 (1H, H-6', dd, J<sub>6',6''</sub> = 12, J<sub>6',5</sub> = 2.5, ), 4.16 (1H, H-6'', dd, J<sub>6'',6'</sub> = 12, J<sub>6'',5</sub> = 5.0, ), 1.8-1.0 (20 H, m, 10CH<sub>2</sub> cyclohexyl), 7.1-7.5 (4H, m, aromatic group), 3.25 and 4.1 (2H, s, CH=NH).

**$\beta$ -N-(*p*-carboxyphenylgalactopyranosyl)-nitrosoarea (8)** was prepared analogously. Yield 0.11 (52.3%), mp. 154-155<sup>0</sup>C, R<sub>f</sub> 0.59 (system d),  $[\alpha]_D^{17}$  - 41.9<sup>0</sup> (c 0.44, C<sub>2</sub>H<sub>5</sub>OH). Found, %: N 9.98; C<sub>26</sub>H<sub>36</sub>N<sub>5</sub>O<sub>8</sub>. Calculated, %: C N 10.53.

PMR spectrum ( $\delta$ , ppm, J/Hz), TMS: 5.64 (1H, d, J<sub>1,2</sub> = 8.0, H-1), 5.08 (1H, dd, J<sub>2,1</sub> = 8.0, J<sub>2,3</sub> = 9.5, H-2), 5.21 (1H, dd, J<sub>3,2</sub> = 9.5, J<sub>3,4</sub> = 3.0, H-3), 5.32 (1H, dd, J<sub>4,3</sub> = 3.0, J<sub>4,5</sub> = 9.5, H-4), 4.14 (1H, ddd, J<sub>5,4</sub> = 9.5, J<sub>5,6'</sub> = 5.0, J<sub>5,6''</sub> = 2.5, H-5), 3.86 (1H, H-6', dd, J<sub>6',6''</sub> = 12, J<sub>6',5</sub> = 2.5), 3.72 (1H, H-6'', dd, J<sub>6'',6'</sub> = 12, J<sub>6'',5</sub> = 5.0, ), 1.8-1.0 (20 H, m, 10CH<sub>2</sub> cyclohexyl), 7.4-7.7 (4H, m, aromatic group), 2.8 and 4.2 (2H, s, CH=NH).

## USE OF DIHYDROTESTOSTERONE, IT'S ANALOGUES AND OTHER 5 $\alpha$ -REDUCED ANDROGENS IN CLINICAL PRACTICE, ATHLETICS, RESEARCH AND ITS ASPECTS

M. Nanikashvili

New School - International School of Georgia.  
mikananikashvili.work@gmail.com

Since the discovery of the first-ever to be discovered androgen - a male sex hormone, coined Androsterone (5 $\alpha$ -androstan-3 $\alpha$ -ol-17-one) in 1931 by Adolf Butenandt [1], various other androgens have been discovered. One such hormone is 5alpha-Dihydrotestosterone, considered

to be the most potent endogenous androgen in humans based on its androgenic effects and binding affinity to the androgen receptor (AR), a nuclear receptor which when activated by a ligand is believed to mediate the majority of effects produced by androgens [2,3,4,5].

5- $\alpha$ -Dihydrotestosterone has been extensively studied for nearly 6 decades for its role in various physiological and pathological phenomenon's like development and maintenance of primary and secondary sexual characteristics, androgenic alopecia (commonly referred to as male-pattern baldness), benign prostatic hyperplasia (BPH) and various cancers mainly prostate and breast cancers [6]. To this day there is no clear consensus on the exact role of DHT in these [7].

Due to dihydrotestosterone potent androgenic and anabolic effects it has caught the attention of clinicians and researchers for its potential uses in clinical practice. A distinct advantage of dihydrotestosterone over testosterone in estrogen sensitive conditions is that it doesn't undergo aromatisation to estrogens. It has been used with promising results in conditions such as:

- Renal atrophy [8, 9]
- Micropenis [10,11]
- Gynecomastia [12, 13]

However clinical use of dihydrotestosterone comes with limitations and issues such as unwanted virilization, low oral bioavailability, weak anabolic effects in terms of stimulating skeletal muscle growth and unwanted suppression of testosterone secretion in high doses. Pharmaceutical companies have attempted to develop analogues of dihydrotestosterone, slightly differing in molecular structure with the goal of addressing this issues. Numerous analogues of dihydrotestosterone have been developed, including but not limited to:

- Mesterolone (1 $\alpha$ -Methyl-4,5 $\alpha$ -dihydrotestosterone)
- Drostanolone (2 $\alpha$ -Methyl-4,5 $\alpha$ -dihydrotestosterone)
- Oxandrolone (17 $\alpha$ -Methyl-2-oxa-4,5 $\alpha$ -dihydrotestosterone)
- Stanozolol (17-Methyl-5alpha-androstano(3,2-c)pyrazol-17beta-ol)
- Oxymetholone (2-Hydroxymethylene-17 $\alpha$ -methyl-4,5 $\alpha$ -dihydrotestosterone)
- Metenolone (1-Methyl- $\delta^1$ -4,5 $\alpha$ -dihydrotestosterone)

The above mentioned pharmaceuticals have been used with various results and offer distinct advantages/disadvantages in clinical practice and to this day only a few are still frequently used or available on the market. However dihydrotestosterone and it's analogues have become drugs of abuse in athletics, particularly in swimming, weightlifting, sprinting, combat sports and bodybuilding [14, 15]. Due to anti-catabolic, body fat loss stimulating, strength and mood enhancing effects while not very anabolic, dihydrotestosterone and it's analogues have been used by athletes seeking the positive effects on performance while not going up in weight class.

Mesterolone, a 2 $\alpha$ -methyl derivative of DHT has shown interesting psychotropic effects that might be relevant in conditions such as depression, anxiety and narcolepsy [16-18].

Other 5 $\alpha$ -reduced androgens, particularly Androsterone and Androstanediol have interesting pharmacological effects that might be relevant in conditions such as epilepsy and acute seizure management [19, 20], possessing positive allosteric modulatory effects on the GABA $\alpha$  receptor [21].

Risks associated with use of dihydrotestosterone and its derivatives are not clear. Long-term data is limited but based on short-term data, chronic use of dihydrotestosterone producing hyper physiological levels appears to be relatively safe [22-24].

To this day many questions regarding dihydrotestosterone and other 5 $\alpha$ -reduced androgens are left unanswered and warrant further investigation.

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## GANB-MATRICES AND COORDINATION COMPOUNDS

### M. Gverdtsiteli, M Rusia

Ivane Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciences  
3, I. Chavchavadze Ave., 0179, Tbilisi, Georgia

ANB-matrix is modified contiguity matrix of molecular graph. Its diagonal elements are the atomic numbers of the chemical elements, nondiagonal elements the multiplicities of the chemical bonds.

For  $[ML_n]$  type coordination compounds, where  $n$  is coordination number of M-metal, L-monodentate ligands GANB-Matrice (group ANB-matrix) was elaborated. The range of GANB is 2. The first diagonal element is  $Z_M$ , the second -  $nZ_L$ ; the nondiagonal elements is  $n$  (pseudomultiplicity of  $(nL)$  pseudoligand). It has the form

$$\begin{vmatrix} Z_M & n \\ n & nZ_L \end{vmatrix}$$

For example, for  $ML_4$  GANB- has the form:

$$\begin{vmatrix} Z_M & 4 \\ 4 & 4Z_L \end{vmatrix}$$

This method can be used as for simple ligands (F, Cl, etc) as for complex ligands ( $NH_3$ ,  $H_2O$  etc).

Calculations show that the decimal logarithm of determinant of the GANB-matrix is effective topologic index for deriving and investigating the correlation equation “structure-property” type.

6 different types of the coordination compounds were investigated and correlation equations constructed. All correlations, according Jape’s criterion, are satisfactory (the value of  $r$  correlation coefficient changes in the range 0,975 ~ 0,980).

## GANB-MATRICES AND AB<sub>N</sub> TYPE MOLECULES

**M. Gverdtsiteli, T. Lobzhanidze**

Ivane Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciences  
3, I. Chavchavadze Ave., 0179 Tbilisi, Georgia

Contiguity matrix and its various modifications are efficiently used in mathematical chemistry for constructing different topologic indexes. For example, the diagonal elements of ANB-n matrix are atomic numbers of chemical elements, nondiagonal ones- the multiplicities of the chemical bonds.

GANB-matrix was elaborated for AB type molecules, where the valency of A is n, the valency of B is 1. The range of GANB of A is two. The first diagonal element is Z<sub>A</sub>, second - n·Z<sub>B</sub>; nondiagonal elements are n (pseudomultiplicity of the bond between A and pseudo - (b) atom (nB)).

$$\begin{vmatrix} Z_A & n \\ n & n \cdot Z_B \end{vmatrix}$$

For example, for AB<sub>3</sub> type molecules GANB- matrix has the form:

$$\begin{vmatrix} Z_A & 3 \\ 3 & 3Z_B \end{vmatrix}$$

Calculations show that the decimal logarithm of the determinant of GANB-matrix  $-\lg(\Delta_{GANB})$  is effective topologic index for the construction and investigation of the correlation equations “structure-properties type. About 10 chemical systems were investigated and corresponding correlation equations were derived. All correlations, according Jape’s criterion, are satisfactory ( $r$  changes in the range 0,977 ~ 0,984).

## OBTAINING GRAPE-SEED OIL THROUGH THE SUPER CRITICAL EXTRACTION

**M. Gabidzashvili<sup>1</sup>, M. Vanidze<sup>2</sup>, A. Kalandia<sup>2</sup>, I. Japaridze<sup>2</sup>,  
N. Guleishvili<sup>1</sup>, I. Bochoidze<sup>1</sup>**

<sup>1</sup>Kutaisi Akaki Tsereteli State University, 59, Tamar Mefe Ave., Kutaisi, Georgia

<sup>2</sup>Batumi Shota Rustaveli State University, 35/32 Ninoshvili/Rustaveli str., Batumi 6010

There are several methods of producing grape-seed oil: oil is obtained from grape seed by pressing at low temperatures, the method does not allow for obtaining a large amount of oils,

which explains to produce their relatively high prices; pressing at high temperatures is carried out with mass heating up to a temperature of 200 °C, so the obtained oil is refined then, as a result of which it loses in a number of biologically active substances; chemical extraction, which is carried out using organic solvents, thereafter needs to remove solvent, which is associated with additional work and costs.

Supercritical fluid CO<sub>2</sub> is a good solvent for nonpolar and semi-polar substances, and can be extracted with high selectivity. In supercritical conditions, the SO<sub>2</sub> extraction allows for avoiding the undesirable effects of air oxygen and organic solvents to remove ballast substances. At the same time, the technological process is environmentally friendly, carbon dioxide is not a toxic substance, it is almost completely forced out of the extract at the final stage of the technological cycle, without any additional process.

For the extraction, there was used a Water Corporation's supercritical fluid extractor SFE - 100-2-C10, which was used for producing fat from the grape-seed of Mujuretuli, Tola's Saperavi, Kabistoni, and Dzelshavi red varieties.

To obtain fatty substances from the grape-seed, we have crushed the freeze-dehydrated seed into particles of 0.1-0.225 mm in size, and placed them in the extractor. For the extraction, there have been selected the following parameters: pressure - 300 bar, temperature - 40°C, CO<sub>2</sub> delivery rate - 1,2 kg/h, extraction duration was – 3 hours.

The yield of fat obtained by super fluid extraction varies from 18 to 27.36%. The refraction index in the obtained fat was determined with a refractometer, which is due to the fat structure, and is one of the characteristic parameters of fat. The refraction index was determined using a digital refractometer.

Studies of the obtained oil were carried out with an air-liquid chromatograph.

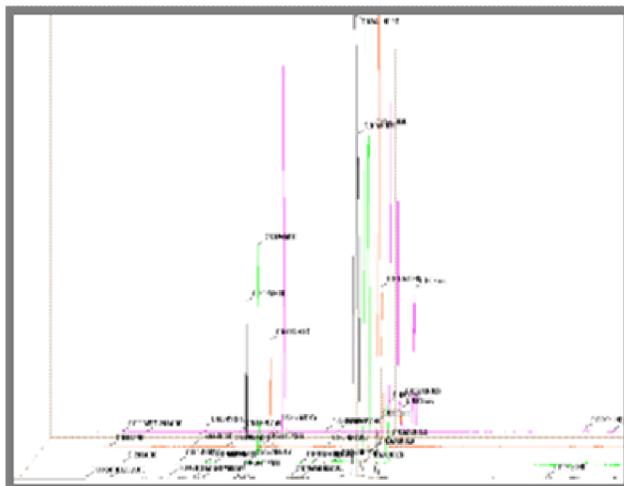
The overall time of chromatography was 42-43 minutes. Detection of fatty acids divided by chromatography, was carried out with a flame ionisation detector.

For the analysis of fat, we used both raw and fermented seeds of Mujuretuli, Tola's Saperavi, Kabistoni and Dzelshavi grape varieties. Before chromatography, there was carried out etherification (with ethanol) of sample (fat).

Table. Grape-seed fat refraction indices

Grape-seed fat of	Yield of fat, %		n <sub>20</sub> - refraction	
	Non-fermented	Fermented	Non-fermented	Fermented
Mujuretuli	20,7	19,2	1,4759	1,4758
Tola's Saperavi	21,46	20,5	1,4758	1,4760
Dzelshavi	21,0	18,85	1,4759	1,4760
Kabistoni	18,87	17,3	1,4782	1,4787

The quantitative content of carbonic acids is determined by the peak ratio of individual compounds (with accuracy of 0.01%), but for identification of compounds, there were used authentic compounds and data from literature. Also the components obtained through the chromatographs were identified by comparing with data of sample with a known composition, and we have determined the specific composition of carbonic acids in grape-seed oil.



Component Name	Raw seed (Area %)	Fermented seed (Area %)
C 10:0 CAPRIC	0.024	0
C 14:0 MYRISTIC	0.053	0.067
C15:1cis10-PENTA	0.095	0.12
C 16:0 PALMITIC	8.213	8.115
C 17:0 HEPTADEC	0.055	0.057
C18:2n6cLINOLEIC	68.334	67.728
C 18:1n9c OLEIC	17.828	18.685
$\alpha$ -C 18:3n3 LINOLENIC	0.358	0.453
C18:0 STEARIC	4.888	4.17

Chromatographic study has shown that the chemical composition and quantitative content of fatty acids remained practically unchanged during the process of fermentation, and they can be mixed before extraction.

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## ANTIOXIDANT ACTIVITY OF THE FLESH OF RED AND BLACK HAWTHORN WILD GROWING IN GEORGIA

**N. Guleishvili<sup>1</sup>, A. Kalandia<sup>2</sup>, M. Vanidze<sup>2</sup>, I. Japaridze<sup>2</sup>, M. Gabidzashvili<sup>1</sup>, I. Bochoidze<sup>1</sup>**

<sup>1</sup>Kutaisi Akaki Tsereteli State University, 59, Tamar Mefe Ave., Kutaisi, Georgia

<sup>2</sup>Batumi Shota Rustaveli State University, 35/32 Ninoshvili/Rustaveli str., Batumi 6010

The advantage of antioxidants of natural origin is considerable in comparison with the synthetic ones. It is known that non-toxic antioxidants contain vegetable oils, extracts and other plant products..

Hawthorn fruit and flowers are plant raw materials. Biologically active substances in them improve blood circulation, affect the cardiovascular system, and participate in the redox processes. Therapeutic preparations obtained from hawthorn are used during various functional disorders in cardiac work, angioneuroses, arterial hypertension, and arrhythmias.

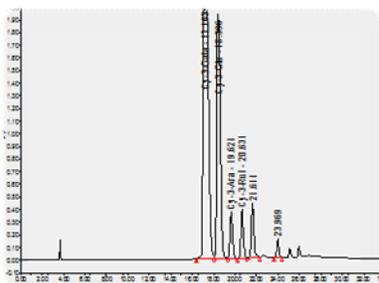
Despite the long history of use, the studies of different species of hawthorn, their chemical compositions and pharmacological properties still are of interest of scientists from many countries (Ukraine, Lithuania, Germany, China, Korea, Slovakia, Serbia, India, USA, Italy, Portugal, Turkey, Russia, etc.).

Red and black hawthorn fruits are rich in phenolic compounds. Using the methods of spectral analysis, the overall content of phenols was determined by the use of total flavonoids, flavan-3-oles, leucoanthocyanins, anthocyanins and method of free radical oxidation - DPPH method, there has been determined the 50%-inhibition value of extracts.

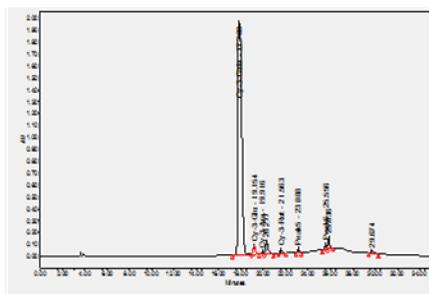
Table 1. The concentrations of flavonoids, flavan-3-oles and leuco-anthocyanins in the flesh of red and black hawthorn

Sample – the flesh of the ripe fruit	Flavonoids mg/100 g		Flavan-3-oles mg/100 g		Leuco-anthocyanins mg/100 g	
	On a raw weight basis	On a dry weight basis	On a raw weight basis	On a dry weight basis	On a raw weight basis	On a dry weight basis
Red hawthorn	268,8	987,66	208,47	765,87	33,48	122,99
Black hawthorn	313,9	1043,9	269,3	895,5	40.62	135,08

The total concentration of phenols in the flesh of red and black hawthorn was determined by Folin-Ciocalteu method, and the anthocyanins content – by differential pH method. There was also determined antioxidant activity.



	Name	Retention Time	Area	% Area	Amount	Units
1	Cy-3-Gala	17.799	48146335	89.54	1.81	mg/g
2	Cy-3-Glu	19.154	1047588	1.95	0.04	mg/g
3	Cy-3-Ara	19.916	248587	0.46	0.01	mg/g
4	Cy-3-Rut	21.563	392589	0.73	0.014	mg/g
5	Total anthocyanins				2,025	mg/g



	Name	Retention Time	Area	% Area	Amount	Units
1	Cy-3-Gala	17.163	73172811	52.22	5,77	mg/g
2	Cy-3-Glu	19.621	6031298	32,41	3.58	mg/g
3	Cy-3-Ara	20.631	6037504	4.31	0.476	mg/g
4	Cy-3-Rut	21.611	7262084	5.18	0.57	mg/g
	Total anthocyanins				11,05	mg/g

Table 2. Total amount of anthocyanins and phenols, and antioxidant activity in the flesh of red and black hawthorn

Sample – the flesh of the ripe fruit	Total phenols mg/100 g		Anthocyanins mg/100 g		Antioxidant activity	
	On a raw weight basis	On a dry weight basis	On a raw weight basis	On a dry weight basis	Extract dissolution factor - F	AA, %
Black hawthorn	396,32	1318,0	332,83	1105,0	10	46.9
Red hawthorn	352,06	1293,4	49,38	202,5	5	45.4

The concentration of total phenols in the flesh of black hawthorn - 1318,0 mg/100g is higher than in the flesh of red hawthorn - 1293,4 mg/100g, the content of anthocyanins approximately 5 times higher than in red hawthorn. Thus, antioxidant activity of black hawthorn is double the antioxidant activity of red hawthorn.

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## **PRELIMINARY TESTS ON EXTRACTION SUBSTANCES IN WALNUT FRUITS OF THE CHANDLER BREED COMMON IN WESTERN GEORGIA**

**M. Neparidze, N. Gelovani, I. Gvelesiani, I. Metreveli**

Georgian Technical University  
77, Merab Kostava St., 0175, Tbilisi, Georgia

Walnut (Latin *Juglans regia*) is a family of walnut leaves, It is widespread in almost all regions in Georgia. There are many different, prolific species and varieties of walnuts. As for Chandler's nuts, he gives a good harvest, Resistant to diseases and During the planting distance between trees is insignificant. It is known that the varieties of walnut should be planted at a distance of 10x10 m, rarely 8x10 m, 8x8 m, and the Chandler's nuts seedlings are 6x6 m and 6x5 m.

The size of the core varies in qualitative parameters. For example the larger the core, the higher its quality. The average size of the walnut is about 35 mm.

The composition of walnut fruits includes many organic and mineral substances. From organic substances in fruits are presented: fats (fatty nut oil), proteins, carbohydrates, tanning, coloring, aromatic substances (essential oils), vitamins, etc.

We made preliminary attempts to determine extractives in ripe Chandler fruit. Product was dried to constant weight. The cheese brought to a constant weight contains only the hygroscopic water. Because the results of the analysis are expressed in percentages, by calculating the absolutely dry substances, so, before you the analyte, we determined humidity. We dried the walnut fruit at a temperature of 60 ° C.

The process of drying the fruit of the Greek arech is considered complete, when the samples are destroyed during crushing.

Initially, we isolated an oil extract from walnut fruit - pressing. The nutritional value of vegetable oil depends on the method of isolation. Walnut oil obtained by cold pressing is more aromatic than refined walnut oil.

Destroyed the integrity of dried walnut fruit, Place it under special press Without thermal treatment. Cold or first spin differs from hot pressing because the raw material not only does not heat up, but even special measures for cooling are taken. With cold pressing, the crushed mustards are simply squeezed out on a special press with the cooling of its head so that the temperature caused by the pressure at the moment of pressing does not exceed 55 ° C.

This oil is slightly lighter than when hot pressed, less viscous, almost tasteless, but possesses A delicate aroma, reminiscent of the smell of raw seeds. After spinning, the oil was filtered off, allowed to stand and the precipitate was separated in a centrifuge.

The oil is yellowish - transparent, pleasant odor and flavorful liquid. It has high concentration of Omega-3, Omega-6.

Determination of extract substances in our case is required, as the normative-technical documentation does not indicate the method of quantification of the active substances. We made preliminary attempts to determine the qualities of biologically active substances in ripe walnut fruit, The results are proved to be in the ripe fruit of the nutrient varieties of chandelier: fibers,

vitamins B1, B5, B6, B9, E, K, elements (potassium, calcium, magnesium, phosphorus, iron, manganese, Copper, zinc) existence.

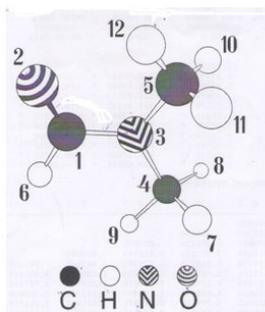
## SYNTHESIS AND IR SPECTRA OF COORDINATION COMPOUNDS OF 3D-METALS WITH N,N-DIMETHYLFORMAMIDE

**N. Gegeshidze<sup>1,2</sup>, M. Tsintsadze, L. Skhirtladze<sup>2</sup>, A. Mamulashvili<sup>1</sup>, T. Edilashvili<sup>1</sup>**

<sup>1</sup>Georgian Technical University, 77, M. Kostava St., 0175, Tbilisi, Georgia

<sup>2</sup>R. Agladze Institute of Inorganic Chemistry and Electrochemistry  
11, Mindeli Str., 0186, Tbilisi, Georgia; \*nana.ge18@yahoo.com

The goal of our research was the study of properties of complex formation of N,N-dimethylformamide in different solutions, manifestation of his donor properties and synthesis of new coordination compounds on the basis of obtained results, and also study of physical-chemical properties of synthesized compounds.



Molecule of N,N-dimethylformamide

With the quantum-chemical method AM1 are calculated the power, geometrical and structural features of N,N-dimethylformamide. According to electronic structure, solvent effect on complex formation ability N,N-dimethylformamide with metals is established.

Analysis of the values of electron densities and effective charges shows that the high values of the electron density is characterized by an oxygen atom O (4).

This circumstance determines the basic properties of the oxygen atom O (4), i.e. its properties with the metal donor-acceptor bond.

Coordination compounds of copper(II), cobalt(II) and nickel(II) with N,N-dimethylformamide. Copper(II), cobalt(II) and nickel(II) chlorides have been taken as initial salts. Synthesis has been carried out in ethanol solutions.

Synthesized coordination compounds are separated in solid form. Composition, individuality, solubility of obtained compounds in different solvents is established.

The complex of N,N-dimethylformamide is determined by the coordination of coordination with the manufacturer (synthesized compounds).

As analysis of the spectrums shows, the vibration frequencies of N,N-dimethylformamide are observed in the spectrum of synthesized complexes. The vibrational frequency of the N,N-dimethylformamide  $\nu(\text{CO})$  molecule is found in the region  $1619.99 - 1635.7\text{cm}^{-1}$ , and the molecular spectrum of the uncoordinated N,N-dimethylformamide molecule in  $\nu(\text{CO})$  is  $1661.28\text{cm}^{-1}$ , i.e. is reduced to  $\sim 25\text{cm}^{-1}$ . This indicates that in the synthesized complexes the coordination of the N,N-dimethylformamide molecule is carried out by the oxygen atom.

Table. Final heat of formation, net atomic chages and dipole contributions, atomic orbital electron populations in the molcul of N,N-dimethylformamide

№	Solvent, $\epsilon$	$\Delta H$ , KJ	$\mu$ , Д	Atom	Charge, q	Electron density	Atomic orbital electron populations			
							2S	2P <sub>x</sub>	2P <sub>y</sub>	2P <sub>z</sub>
1	Gas	-154.60	3.55	O(2)	-0.365	0.365	1.915	1.110	1.873	1.466
				N(3)	-0.353	5.353	1.417	1.063	1.073	1.746
2	Water, 78.5	-208.52	5.85	O(2)	-0.365	0.365	1.914	1.156	1.907	1.610
				N(3)	-0.353	5.353	1.472	1.086	1.073	1.681
3	DMSO, 49.0	-204.72	5.88	O(2)	-0.580	6.580	1.914	1.156	1.907	1.610
				N(3)	-0.314	5.314	1.472	1.086	1.073	1.681
4	Methanol, 32.6	-203.01	5.81	O(2)	-0.575	6.575	1.914	1.156	1.908	1.597
				N(3)	-0.315	5.315	1.474	1.082	1.073	1.686
5	Ethanol, 24.3	-205.02	5.69	O(2)	-0.574	6.574	1.914	1.154	1.905	1.601
				N(3)	-0.316	5.316	1.472	1.084	1.073	1.687
6	Acetone, 20.7	-204.23	5.67	O(2)	-0.571	6.571	1.915	1.153	1.905	1.599
				N(3)	-0.316	5.316	1.471	1.084	1.073	1.688
7	Chloroform, 4.7	-188.93	4.97	O(2)	-0.507	6.507	1.915	1.140	1.896	1.558
				N(3)	-0.331	5.332	1.417	1.077	1.073	1.710
8	Hexane,1.9	-170.37	4.17	O(2)	-0.430	6.430	1.915	1.124	1.884	1.507
				N(3)	-0.345	5.345	1.471	1.070	1.073	1.732

## MIXED LIGAND (HYDRAZONE, AMINOPYRIDINE) COORDINATION COMPOUND OF CADMIUM AND ZINC

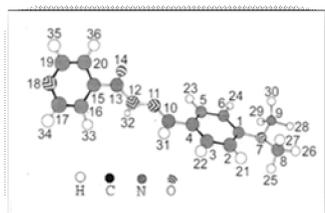
**N. Kilasonia<sup>1,2\*</sup>, M. Tsintsade<sup>1</sup>, M. Mamiseishvili<sup>1</sup>, N. Tabuashvili<sup>1</sup>**

<sup>1</sup>Georgian Technichal University, 77, M. Kostava St., 0175, Tbilisi, Georgia

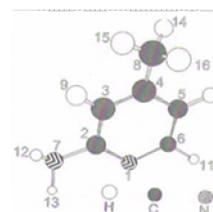
<sup>2</sup>R. Agladze Institute of Inorganic Chemistry and Electrochemistry

11, Mindeli Str., 0186, Tbilisi, Georgia; \*nino-kilas@mail.ru

The literature lacks information about mixed coordination compounds, so we aimed to get the coordinates of cadmium and zinc molecular compounds on the basis of two organic molecules. These ligands are para-diethylaminobanzaldehyde, isonocytinyldiazon and ortho-amino-4-methylpyridine. We have selected zinc chloride and cadmium tycoonate.



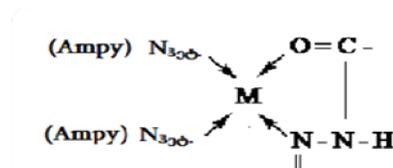
**para-diethylaminobanzaldehyde isonocytinyldiazon**



**ortho-amino-4-methylpyridine**

For the purpose of determining the structure of synthesized coordination compounds, we studied their infrared spectra. The frequency of vibration of different functional groups in the

molecules of synthesized compounds compared to the free ligands, indicates the complexity of the metallic. Basically, the changes are noticeable in the range of the spectrum, which, according to the theoretical calculations, corresponds to atoms with the ability to connect with the metal-complex.



According to the spectrum analysis, hydrazide molecules coordinate with metallic formation of carbonyl group oxygen atom and hydrazide group nitrogen atom. At this time five-member metalocycles are formed. As for the aminopyridine molecule, it is coordinated with the metallic compound heterocyclic nitrogen atom. The spectrum also contains water molecules that are in the field of spectrum. Based on the above mentioned, the structure of cadmium and zinc complexes can be considered (M - complex producing metal).

## SOLVENT EFFECT ON COMPLEX FORMATION OF BENZALDEHYDE FORMYLHYDRAZONE

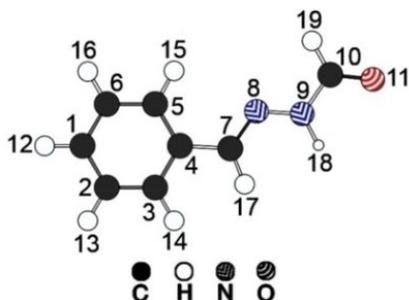
**T. Giorgadze<sup>1\*</sup>, M. Tsintsadze<sup>1,2</sup>, D. Lochoshvili<sup>2</sup>, M. Kereselidze<sup>2</sup>**

<sup>1</sup>Georgian Technical University, 77 Merab Kostava St., Tbilisi, Georgia, 0175

<sup>2</sup>R.Agladze Institute of Inorganic Chemistry and Electrochemistry

1, Mindeli Str., Tbilisi, Georgia, 0186,

\*tamar-giorgadze@mail.ru

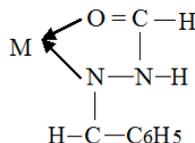


There was calculated energetic, electronic and structural properties of a molecule of benzaldehyde formylhydrazone through semi-empirical quantum-chemical AM1 method in gas condition and in different solutions.

As per the quantum-chemical calculations, the population of S-orbitals(1,914-1,915) on the O (11) oxygen atom molecule of benzaldehyde formylhydrazone practically does not change, on N(8) and N(9) nitrogen atoms the population of p-orbitals change in  $p_x > p_y < p_z$  rows. Bonding length is most important in  $R_{4,7}$ ,  $R_{7,8}$  and  $R_{9,10}$  (1.308 - 1.467Å boundaries). N(8), N(9) nitrogen and O(11) oxygen atoms are characterized with relatively higher electronic density.

$N_8-N_9-C_{10}$  and  $N_8-N_9-H_{18}$  bond angles correspond to 120.26°-121.33°, i.e. nitrogen N(9) atom  $sp^2$ -is in hybridized. The atom (angle  $C_7-N_8-N_9 \approx 120^\circ$ ) of azomethin ( $>C=N-$ ) nitrogen N(8) is also in  $sp^2$ -hybridized condition.

Relatively higher values of effective nuclear charges are notable on oxygen atom (0.342— -0.549), nitrogen N(9) ((-0.308 — -0.311) and relatively smaller on azomethine N(8) atoms (-0.035— -0.103).



Based on the analyze of orbital occupation nitrogen N(9) atom's pair of electrons are concentrated on  $p_z$ -orbitals. Since in such cases  $\pi$ -orbitals correspond to them, and then the area of overlapping of atomic orbitals between a donor and an acceptor has a zero value. So, irrespective to the value of high negative charge nitrogen N(9) atom is unable to provide such pair electrons that would be able to produce  $\sigma$ -donor-acceptor bonding. The different picture has been noted on azomethine nitrogen and oxygen atoms.

## SUBSTANCES FROM THE HARVESTING OF CHERRY, QUINCE AND SAMBÚCUS NÍGRA FRUIT

**L. Targamadze, N. Gelovani, I. Gvelesiani, I. Tsomaia**

Georgian Technichal University  
77, M. Kostava St., 0175, Tbilisi, Georgia

Useful properties of medicinal plants are due to the existence of various biologically active substances, such as alkaloids, glycosides, saponins, essential oils, gumpies, gums, mucus, vitamins, phytochemicals, and others that have some effect on the physiological processes in human and animal organisms.

In the arsenal of medicines there is an important place for medicinal herbs or biologically active food additives, the magnitude of their use (especially in recent years) is growing rapidly around the world.

The objects of research were cultures spread across different regions of Georgia: 1. Elderberry: *SambucusEbulus* and *SambucusNigra*, 2. Cherry - *Prunus Cerasus*, 3. Quince – *Cydonia* and 4. *SilybumMarianum*.

Modern research proves that fruits have a positive effect on health. We have prepared non-fermented natural fruit juices from selected raw materials from full maturity - Extraction of juice from selected products was carried out by cold pressing. The chemical composition of the juice obtained from the pressure practically does not change during its preparation and storage.

The resulting juices were concentrated in a vacuum evaporator at low temperatures, finally, we get the powder from the concentrate. The majority of dry extracts serve different forms of dosage and combined preparations. Dry extracts were packaged in sealed containers, many of them are gyroscopic.

After the removal of the juices we removed the mass of a special drying apparatus, and nowadays the use of fruit dryer machines. The dried raw material was added to each other in the ratio 1:1:1:0.1 and determine the extractive substances in it.

As it turned out, peptic substances, antarctic agents, tissue substances and a complex of vitamins remain in the selected raw materials.

In this process, the importance of raw dispersion was revealed. As it turned out, the degree of shredding determines not only technological parameters, such as: loose, uniformity, dosage accuracy, bulk mass; but can also significantly change the speed and completeness of suction by the plant's organism.

The degree of shredding is individual in each particular case. The raw material is influenced by insufficient dispersion as well as the particle micronization. Therefore, the ingredients in the drugs should have the optimum quality of the shredding.

## SYNTHESIS OF 2-, 5(6)-DIADAMANTANE CONTAINING BENZIMIDAZOLES

**M. Lomidze\*, D. Zurabishvili, I. Gogolashvili, M. Trapaidze, Sh. Samsonya**

Institute of Organic Chemistry, Faculty of Exact and Natural Sciences  
Iv. Javakhishvili Tbilisi State University, 3, I.Chavchavadze Ave., 0179, Tbilisi, Georgia

\*Lomidze\_medea@yahoo.com

Adamantane derivatives are characterized by antiviral, antimicrobial, anticancer, antiparkinsonian and other activities. The preparations made on their base are widely used in medicine. It is proved experimentally that including of a fragment of adamantane in a medication can fully change, or partially enhance its biological activity, often decreases toxicity, which can be explained by change of the spatial organization of the preparation, hydrophobicity, lipophilicity and creating favorable conditions for transportation through the biological membranes, also effect on prolonged action of the preparation, etc [1-6].

The present work is dedicated to the synthesis of new derivatives of adamantane benzimidazoles, namely, 2-,5(6)-diadamantane containing benzimidazoles.

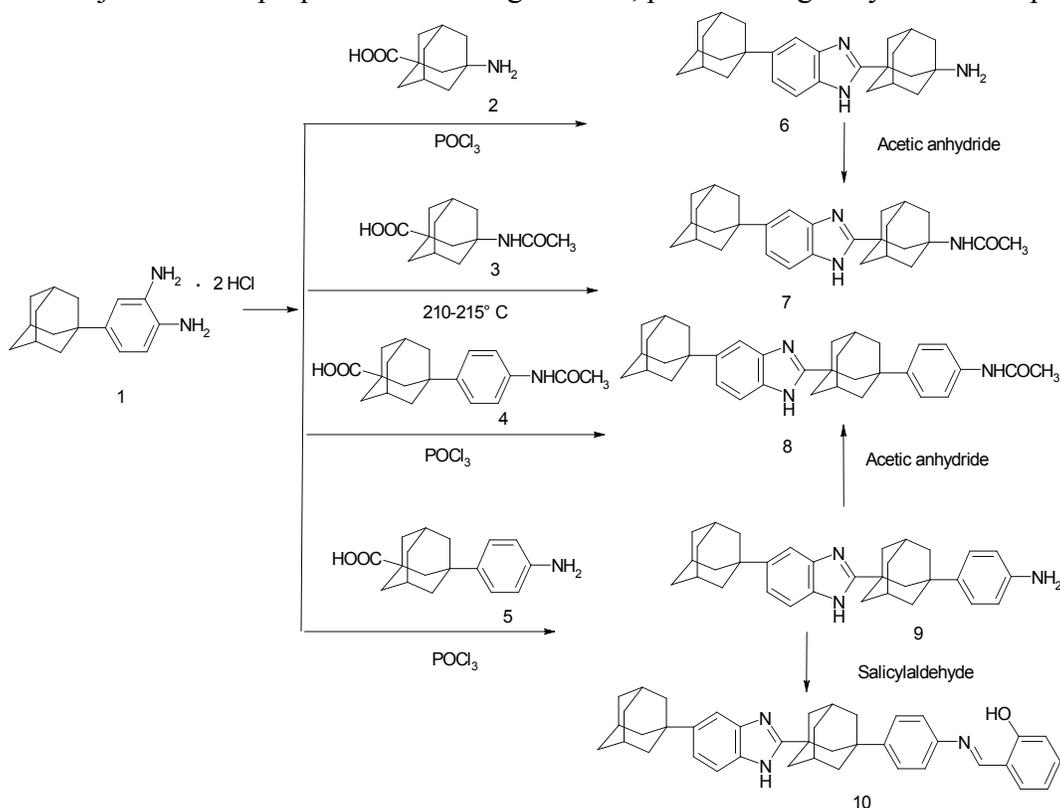
The condensation reaction of 3-acetylaminoadamantane-1-carboxylic acid (**1**), 3-(*p*-acetylamino-phenyl)adamantane-1-carboxylic acid (**2**), 3-aminoadamantane-1-carboxylic acid (**3**) and 3-(*p*-aminophenyl)adamantane-1-carboxylic acid (**4**) [7] with dihydrochloride 4-(1-adamantyl)-*o*-phenyldiamine (**5**) has been studied [8] and the corresponding benzimidazoles **6-9** were synthesized (Scheme 1).

The reaction is carried out at an equimolar ratio - acid: diamine by reflux in the POCl<sub>3</sub> and heating of components (ratio 2: 3) at 210-215°C.

The condensation of amine **8** with salicylaldehyde was carried out at moderate heating conditions in anhydrous alcohol solution and corresponding Schiff bases **10** was obtained. The interaction of compounds **6** and **8** with acetic anhydride gave white crystals of benzimidazoles **7, 9** as well.

The structure of synthesized compounds is confirmed by the IR, UV,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and mass spectral data.

The virtual screening of synthesized compounds was conducted by Pass program (See link: <http://www.way2drug.com/PASSOnline/>). According to the obtained results, synthesized compounds are expected, in the experiment, of possibly having the following activities (Pa 0.500-0.888): Antiviral (Influenza, Picornavirus, Adenovirus); kidney function stimulant, antiischemic, cerebral, neurodegenerative diseases treatment, antiparkinsonian; renal disease treatment, nootropic, anticancer. For example, compound 6 have high possibility of revealing anti-cancer activity: brain glioma (Pa 0.888), lung carcinoma (Pa 0.748). The synthesized compounds belong to the 4 and 5 class by LD-50 classification (<http://pharmaexpert.ru/GUSAR/acutoxpredict.html>) and are characterized by low toxicity. Synthesized compounds represent perspective objects for the purpose of searching the new, pharmacologically active compounds.



Scheme 1

“This work was supported by Shota Rustaveli National Science Foundation (SRNSF)[ grant # 217996, Project Title: New Derivatives of Adamantane Benzimidazoles and Imidazo[4,5 e] benzoxazoles: Synthesis and Study]”.

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## THEORETICAL EVALUATION OF CONTRIBUTIONS OF FUNCTIONAL GROUPS TO DETERMINING MOLECULAR PROPERTIES

**G. Lekishvili**

Department of Medical Chemistry, Faculty of Pharmacy, Tbilisi State Medical University,  
33, Vazha Pshavela ave., 0186, Tbilisi, Georgia; giorgi@lekishvili.info

Logarithm of the determinant of ANB matrices (see e.g., [1]) has been fruitfully used for QSAR/QSPR modeling. It is straightforward to show that the ANB matrix ( $\Gamma$ ) can be expressed as follows:

$$\Gamma = \mathbf{W} + \mathbf{\Delta} + \mathbf{A} = \mathbf{W} + \mathbf{Q}$$

Where  $\mathbf{\Delta}$  is the diagonal matrix of vertex degrees,  $\delta_i = \sum_{j=1}^n A_{ij}$ ,  $\mathbf{A}$  is the adjacency matrix,  $\mathbf{Q}$  is the signless Laplacian matrix and  $\mathbf{W}$  is a matrix given with the following equations:  $w_{ii} = Z_i - v_i$ ,  $w_{ij} = \pi_{ij}$  (here,  $v_i$  is the valence of the  $i^{\text{th}}$  atom and  $\pi_{ij}$  is the number of  $\pi$ -bonds between the  $i^{\text{th}}$  and  $j^{\text{th}}$  atoms). Obviously,  $\mathbf{W} = 2\mathbf{I}_n$  and  $\Gamma = 2\mathbf{I}_n + \mathbf{Q}$  if one models hydrocarbons. Once the signless Laplacian is positive semi-definite, all eigenvalues of  $\Gamma$  are positive here, therefore the logarithm of its determinant equals the trace of the matrix logarithm. Matrix functions can be expanded into Taylor-Maclaurin series; using a helper matrix ( $\mathbf{M} = 0.1 \times \Gamma$ ) with a suitable spectral radius and taking into account that  $\text{tr}((\mathbf{M} - \mathbf{I}_n)^k)$  yields the  $k^{\text{th}}$  spectral moment that allows for calculations of embedding frequencies of sub-graphs [2, 3], and, also,  $\lg(\cdot) = \ln(\cdot) / \ln 10$ , we have:

$$GG \approx 0.0000008\kappa_5 - 0.000017\kappa_4 + 0.0002\kappa_3 - 0.0142\kappa_2 + 0.1460\kappa_1 + 0.3663n$$

Here,  $\kappa_j$  is the  $j^{\text{th}}$  spectral moment of the signless Laplacian. Their dependence on embedding frequencies of sub-graphs was reported earlier [4]. It is noteworthy that, in principle,  $GG$  can be approximated at an arbitrary precision once the corresponding spectral moments are calculated and here the summation is truncated only for practical considerations. Obviously, for smaller molecules, first four moments are tried, whereas for nanotubes or zeolites one uses also higher moments. For the former, we demonstrate a simplified equation:

$$GG \approx 0.3663n + 0.2366m - 0.0267 |K_{1,2}| + 0.0005 |K_{1,3}| - 0.000036 |D_{1,1}| - 0.001 |C_3|$$

Here, sub-graphs are given in the common notation.

As we see, the success of Logarithm of the determinant of ANB matrices is not resulted in by randomness; rather, it reflects contributions of functional groups (modeled with sub-graphs) to molecular properties.

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## SYNTHESIS AND CHARACTERIZATION OF MIXED-LIGAND COMPLEXES OF ARSENIC-ORGANIC COMPOUNDS

**T. Lobzhanidze<sup>1\*</sup>, I. Metskhvarishvili<sup>2</sup>, K. Giorgadze<sup>1</sup>**

<sup>1</sup>Department of Chemistry, Faculty of Exact and Natural Sciences  
Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

<sup>2</sup>Laboratory of Cryogenic Techniques and Technologies,  
Ilia Vekua Sukhumi Institute of Physics and Technology, Tbilisi, Georgia

\*[tea.lobzhanidze@tsu.ge](mailto:tea.lobzhanidze@tsu.ge)

Unlike the other coordination compounds, one of the most important features of the tetrasubstituted arsonium salts is their tendency to produce cationic and anionic complexes in alcohol-water solution. The mixed-ligand complexes have great prospects of application. Most likely, these compounds have high and specific biological activity. The arsonium salt and cadmium bromate are used as initial materials of reaction in the molar ratio of 1:1. The reaction is carried out at room temperature in alcohol-water solution. The structure and composition of synthesized mixed-ligand complexes of arsenic organic compounds were established by TGA, electroconductivity, element analysis and IR spectroscopy methods.

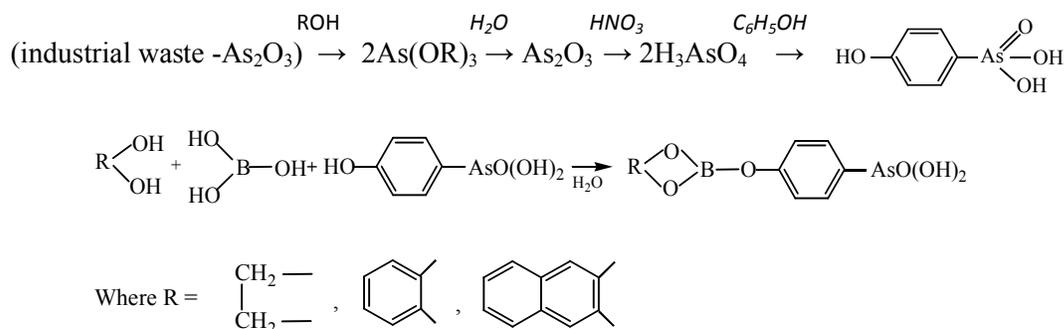
## BORORGANIC BIOACTIVE COMPOUNDS: SYNTHESIS AND STUDY

**L. Turiashvili, B. Jioshvili**

Iv. Javakhishvili Tbilisi State University, Faculty E&NS, Department of Chemistry  
3, I. Chavchavadze Ave., 0179, Tbilisi, Georgia

The synthesis of biologically active compounds is one of the considerable problems of modern arsenic organic chemistry. Polyelemental composition of the compound increases the ability of their practical use. Biologically active elements (sulfur, phosphorus, arsenic, boron, some transition metals) give to the compound many important properties.

Arsenic-containing borates with mixed organic radicals have been synthesized based on arsenic compounds obtained by transformation of arsenic industrial waste (Scheme).



For evaluation of biological activity of obtained compounds the virtual bioscreening method was used [the scope of the program of internet system (PASS C&T)], which, with high accuracy, can make prognosis about biological and pharmacological activity. The estimation of probable bioactivity of chosen compounds was carried out via parameters Pa (active) and Pi (inactive); when  $P_a > 0.7$ , the compound also could be shown bioactivity experimentally [114-120]. Following from above mentioned virtual bioscreening, based on analysis of obtained results, the synthesized compounds (I-IV) with experimentally high probability (Table 7.3) ( $P_a = 0.70-0.98$ ) possibly will show the following bioactivity: *Antibacterial (Antispirochetal, Antitreponemal, Subtilisin inhibitor, Salmonella)*, *Antiparasitic (Antiprotozoal - Amoeba, Histomonas, Trypanosoma, Trichomonas)*, *Growth stimulant and etc.*

The structure of synthesized compounds was established by element analysis, NMR, IR and mass-spectroscopy methods.

## EXTRACTION OF BORON AND ARSENIC(III) OXIDE FORMS

**Rus. Gigauri<sup>1\*</sup>, N. Mchedlishvili<sup>2</sup>, I. Barbakadze<sup>2</sup>**

Rafiel Agladze Institute of Inorganic Chemistry and Electrochemistry,  
Ivane Javakhishvili Tbilisi State University, 11, Mindeli Str., 0186, Tbilisi, Georgia  
Georgian Technical University, 77, M. Kostava St., 0175, Tbilisi, Georgia  
\*gigaurirusudan@gmail.com

In order to avoid the global warming owing to the climate changes, UNO and other international organizations take decisions that oblige countries to develop technologies with minimum discharge of carbon dioxide in the atmosphere. Novel or existing technologies require alternative sources of renewable energy – energy resources, which ensure strict control and limitation of the amount of carbon dioxide discharged as a result of the burning of solid, liquid and gaseous carbohydrates. Mankind is looking for other alternative sources of energy and uses in a number of cases comparatively environmentally safe energy sources. Geothermal waters have been considered exactly as one of such sources.

Thermal waters prevail in the Caucasus region: Karachai-Cherkess, Kizlar and Makhachkala (Dagestan), Chechnya, Ingushetia, North Ossetia; Tbilisi, Zugdidi, Gali, Khobi, Samtredia, Tskaltubo Menji, Tsaisi, etc. (Georgia); Daridagh (Azerbaijan). Thermal waters contain physiologically active substances (boron, arsenic, antimony, zinc, lead, potassium) also organic compounds (ammonia, phenol). The drain of these waters into a natural water system existing on the surface is not reasonable.

Our research was carried out on the Daridagh (Azerbaijan) carbonic acid-arsenous thermal waters, which contain boron and arsenic oxide forms. The purpose was the extraction of these two elements or the establishment of optimum conditions of their complete separation. Below the geometrical structures of boron and arsenic oxides are given.

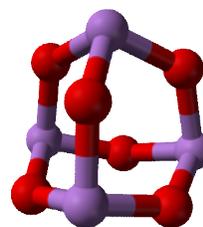
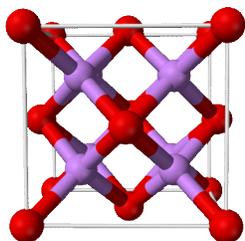


Fig. 1. Geometric structure of boron oxide

Fig. 2. Geometric structure of arsenic(III) oxide

The amount of admixtures is known to affect the physical-chemical properties of the target product, based on which the sphere of application is also restricted. Nuclear engineering, fiber optics, electrical engineering, nanotechnology require the production of ultrapure chemical compounds with the precision of one part in a million and over. The matter is also complicated by the fact that high-tech processes of the separation of substances have not been studied and analyzed yet.

Boron and arsenic do not belong to the conjugate elements, although are met together rather frequently in nature. The daily discharge of the Daridagh thermal water source makes up to 7 kg

arsenic and 27 kg boron, which endangers the region's environment and affects its flora and fauna.

As a result of our research, it has been established that the boron and arsenic (III) oxide forms are easily esterified by the action of aliphatic alcohols and correspondingly alkylboranes and alkyl arsenites are received, where  $R = C_nH_{2n+1}OH$ , while  $n > 4$ . The initial terms of the homological group are found not to esterify with the arsenic oxide forms. This fact was successfully used for separating the initial mixture. The boron oxide or boron acid was found to esterify quantitatively with the lower alcohols, e.g., propyl alcohol.

The subject matter of the method consists in the fact that in the trial mixture placed in the reactor, which contained the boron and arsenic oxides, the boron oxide is esterified by the propyl alcohol together with the azeotrope (benzene), by the azeotropic dehydration method, while the arsenic oxide stays on the bottom of the reactor in the pure form, with 99% yield. The propyl alcohol selectively acts upon the boron oxide only, with the production of alkylborane. It is hydrolyzed by water and its yield varies within 95-97%. The optimum azeotrope-alcohol ratio (3:5) has been established.

The technological process advantage is also that the extracting agent is not lost. 92-93% of the alcohol and the azeotrope mixture are regenerated and returned to the technological process.

The obtained post-extraction products are noted for high purity, belong to the ultrapure compounds and can be applied in nanotechnologies. The geometric tubes of their particles have been studied. The bot mixtures are rather active physiologically. The advantage of the nanotube boron-based nanotechnology is the possibility of controlling mismatch of the component nanoparticles, which determines the physical properties of the nanotube material.

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**DEVELOPMENT OF FORMULATION AND PRODUCTION  
TECHNOLOGY OF CONTAINING BIOLOGICALLY ACTIVE  
SUBSTANCES OF BOTTOM MUD OF LAKE KUMISI  
AND GEORGIAN PLANT MATERIALS**

**Kh. Mishelashvili\*, T. Tsintsadze, K. Batsikadze, Kh. Tsikarishvili, M. Nishnianidze**

Georgian Technical University  
77, M. Kostava St., 0175, Tbilisi, Georgia  
\*kh.mishelashvili@gtu.ge

In the presented study, grounded on the chemical-analytical, technological and biopharmaceutical studies firstly is developed the recipes and production technology of containing biologically active substances of Kumisi lake silt therapeutic mud and Georgia flora beauty aids. Firstly, is proposed new compositions of cosmetic lotions, cosmetic milk, combined scrub - peeling, cosmetic masks. Firstly, is proposed concept to create the recipes of cosmetic milk (liquid ointments).

By chemical-analytical study of Kumisi lake mud are obtained the following results:

Due the qualitative analysis methods are determined the existence of iron, calcium, potassium, magnesium, aluminum, silicon, sodium, iodine ions. By complexometric titration and weight analysis methods are determined the quantitative content of iron (less than 5%), calcium (less than 6.1%), magnesium (less than 2.2%), aluminum (not less than 9%), silicon (less than 37%), calculated on oxides. The study of validated characteristics shows sufficient accuracy and reproducibility of the applied methods. The analysis of the organic phase by qualitative reactions, TLC and spectrometry are revealed the existence of carotenoids, chlorophylls, lipids.

At development of scrub-peelings recipe and production technology is stipulated that existence in their composition of the alphahydroxylacids or betahydroxyacids with scrub particles, more intense promotes to skin cells regeneration, removal of small wrinkles, acnes, pigmentation. Due this was studied the compatibility of containing emollient and hydrating substances developed ointment with the wine, lemon, apple, salicylic acid (individually as well as in combination) and scrub particles. As scrub additives are used the Kumisi mud up to 6%, and a finely crushed nut shells (size 0,2-0,4mm) up to 4%. The addition of 2% of bentonites or green clay, for adsorption effect in case of oily and problematic skin, as well as addition of 0.5% of medical sulfur, 1% of metronidazole and 0.5% of resorcinol does not affect on the external appearance of production and expiry date. There are developed the scrub-peeling recipes for normal, dry, oily and problematic skin.

At development of recipes and production technology of medical masks the quality, with the therapeutic effect, will be defined by a series of rheological parameters that determine convenience for coating on skin and the possibility of keeping on skin - shear resistance (sr) and viscosity ( $\nu$ ) values. At application as plasticizers are studied several vegetable oils (totally 12), perfume oil and glycerin. For skin nourishing by mineral ingredients are used Kumisi lake mud that also contains a lipid fraction. Due taking into account the properties of plasticizers and the therapeutic effect as plasticizer-additives is selected sea-buckthorn oil. Are developed masks for

normal, oily and problematic skin, with addition in its composition of bentonite or blue clay and keratolytics.

At creation of recipe of cosmetic milk (liquid cream) in the selected combinations is provided stable hydrophilic-lipophilic balance that also contributes to the stability of emulsion. For acne treatment in the composition is added up to 1% salicylic acid and 0.5% resorcinol.

At development of the lotions recipe as main objective is presented the correct selection of components, medicinal properties, compatibility and solubility, concentration of alcohol, types of fatty and mineral supplements, vegetable, mineral and synthetic biologically active additives accordingly of the prescription. In the presented work is applied the extract of hawthorn berries and mint leaf, aloe. All of the above-mentioned plants in sufficient quantities are presented on the area of Georgia. The application of released from Kumisi therapeutic mud the salt extract, gives the possibility due the saturation of the skin with these mineral components, not only to achieve the additional effect to improve of skin appearance, but also to stabilize the storage of lotions, which cannot be reached by including in the lotion of only distilled water.

## **KVEVRI (WINE-VESSEL) AS A MULTI-PURPOSE VESSEL**

**Kh. Tsikarishvili\*, M. Tsintsadze, D. Gugunishvili**

Georgian Technichal University  
77, M. Kostava St., 0175, Tbilisi, Georgia  
\*kh.tsikarishvili@gtu.ge

The kvevri is made from clay vessel for wine making and storage that has an ancient history. However, it is noteworthy that the application of large sized clay vessels is not limited to this.

The kvevri were used to store different products. It often represents the best storage of grain. According to the archaeological data, at excavation of Urbnisi settlement were found arranged in two groups kvevri in one of the VI century wine cellars. The dig in the soil kvevri were intended for wine, and discovery of the grain in the half-dig in the soil and for ventilation perforated bottom kvevri the was unequally determine their purpose.

In the kvevri, besides the grain, other products were stored. As shown in the 14th century document, the kvevri represent a honey and oil storage vessel.

According to ethnography L. Pruidze, in comparison with the latter period, there were in Racha Marani (wine cellar) kvevri for cheese, pickles, vodka, crust, squash and fruit. The kvevri were applied also for vodka and fruit distillation device. Especially near the hearth were arranged the kvevri for vinegar.

How efficiently were performed the function of product storage by kvevri is clearly indicated by ethnographer N. Topuria data, according to which the cheese would be during the year stored in kvevri in Mtiuleti. Ine Khevsureti also have kvevri for meat and cottage cheese, while the Megrelians store sulguni cheese in the kvevri.

The oldest tradition of pear storage in kvevri was revealing in the fact that one of the winter pear breed stored in kvevri, obtain the name associated with the kvevri – “Khechecuri” (Churi is called to kvevri in Western Georgia).

In case of necessity, in the fortress, the kvevri were also used for bakery. However, the main purpose of the kvevri function was water storage vessel in such places.

Due to the large volume of the kvevri, they were successfully applied to dyeworks for paint solutions preparation and tissue painting. Many of the XVIII centuries documents indicates that kvevri were represented as the main vessel in the dyeworks.

The kvevri was also used by leather masters. Due a trim solvent, it was scrubbing the inflamed leather. The specific case of the kvevri application is to use them to strengthen the volume of the sounds in the churches. In Racha-Lechkhumi region is distinguished by the fact that it is rare for the old cathedral not to have "sound kvevri".

The mentioned diversity of the kvevri application once more times indicates to the fact that this vessel played a big role in Georgian life.

## **DENTAL TREATMENT AND PROPHYLACTIC MEANS USING MINERAL RESOURCES OF GEORGIA**

**M. Nishnianidze\*, N. Shashiashvili, I. Gvelesiani, Kh. Mishelashvili**

Georgian Technichal University  
77, M. Kostava St., 0175, Tbilisi, Georgia  
\*nishnianidze.maka@gmail.com

Important resources of vegetable as well as mineral raw materials are available in Georgia. However, portion of its perfumes and cosmetics on the market are small. Lugela is the only factory-produced toothpaste. This article presents the data of developed recipe of a new toothpaste, containing some of the natural resources, available in Georgia.

The basic requirements to toothpastes may be formed as follows: high-quality cleaning features, pleasant taste, deodorizing and refreshing action, absence of local irritant, allergy causing, and toxic agents, As well as stability during storage. The pastes contain: natural and synthetic, anti-microbial, anti-stomatitis action as well as various therapeutic agents. In the present study qualitative and quantitative composition of the toothpaste is selected so that the toothpaste had an effective preventive and curative action. The effective cleaner - chemically precipitated chalk with the particle sizes within the range of 2 - 20 microns and with a specific antiseptic activity is used as an abrasive agent.

Sodium carboxymethylcellulose is used to stabilize the toothpaste suspension. Foaming agent - sodium lauryl sulfate or sodium laurite sulfate, also having small emulsifying, superficial - cleaning and antibacterial action. Glycerin is used for obtaining a homogenous plastic mass. The characteristic feature of the designed composition is that the composition contains as the antimicrobial agents the complex of biologically active components, extracted from the plants which are found in Georgia – tannin containing extracts (Smoke-tree leaves, hazelnut leaves, oak bark), eucalyptus and rose hip oils, propolis extract.

Mineral waters Chargali and Utsera are used for mineralization of the teeth enamel and improvement of the antiseptic activity. For example, a variety of Utsera wells have about 6.5 - 11 g / l mineralization, containing carbonic acid of pH 6,4 - 6,8 in the form of main components: HCO<sub>3</sub> - 4,2 - 7,9 g / l; Na + - 1,2 - 2,4 g / l; divalent iron content of 2 - 10 mg / l; K + 4,9 - 7,9

mg / l; also containing lithium, strontium, and others. Chargali mineral water has a similar mineralization. The obtained samples of the toothpaste are stable in storage, using of citrus oils as odorants gives them a pleasant smell and taste, as well as improved antiseptic qualities. Here are provided some of the indicators. Calcium carbonate mass share no more than 38,0%. Appearance and consistency - a homogeneous mass without grains. The color, smell, taste, microbiological purity - meets with the requirements of the state standards. Mass share of heavy metals no more than 0.002%, total content of the tannins (tannic substances) is 3.2 - 3.4 g/l. Qualitative tests for zineol, the carotinoids, metal ions, and potassium ions is positive, foam quantity (in sm) of not less than 6.0.

Teeth elixirs or rinsing means are additional means for hygiene of a mouth cavity. Teeth elixirs may be released in the form of liquids, liquid concentrates or dry substances which need to be diluted. They are composed of substances which have anti-inflammatory, antifungal, plasticostimulating, sensibilizing and other properties. Considering the quite rich flora of Georgia, quite high antibacterial and antiseptic activity of herbal extracts, existence of getting used to them while their application, leaves of smoke-tree, leaves of eucalyptus, blooms and fruit of hawthorn, leaves of virgate John's-wort, extracts of salvia, eucalyptus and brier oils were used when working out medicinal-prophylactic elixirs containing herbal phyto-complexes.

In connection with the creation of new formulations of tooth powder, toothpaste and the elixir were necessary to develop appropriate quantitative analytical techniques determining of a number of biologically active components. Methods for determination of calcium carbonate in the paste, tooth powder, the tannin amount in tooth powder and elixirs, as well as sodium bicarbonate in the tooth powder. The accuracy and reproducibility of methods confirmed the results validation results of the analysis.

Is elaborated  $\text{CaCO}_3$  granulation technology for tooth powders. The high flowability of the pellets gives an opportunity to change the traditional system of packaging and to avoid the possibility of microbial contamination during use.

## **DEVELOPING OF SUNSCREEN FORMULATION WITH APPLICATION OF NATURAL PLANT EXTRACTS COMMON IN GEORGIA**

**S. Gvindjilia\*, T. Tsintsadze, M. Gabelaia, P. Yavich**

Georgian Technical University  
77, M. Kostava St., 0175, Tbilisi, Georgia  
\*salomegvinjilia90@gmail.com

UV radiation represents a constantly acting factor of environment that has a powerful effect on many physiological processes taking place in the human body, both positive and negative. The spectrum of ultraviolet rays of the Sun reaching the earth's surface is in the range of 400 – 280 nm. The ultraviolet A (UVA) long-wave range of 400 – 315 nm, ultraviolet B (UVB) – midrange of 315 – 280 nm.

Functional skin damage caused by UVB radiation would be characterized as sharp, caused by a large dose of radiation in a short period of time (sunburn, photodermatoses). The delayed damage is stipulated due to prolonged moderate UVA radiation. They are most dangerous for

human health, because deeper layers of the skin are exposed to the action, and would cause degenerative changes in cells of skin, fibrous tissue and blood vessels that leads to photodermatosis, keratosis and, as a result, premature aging of the skin. The UV radiation may have a terminal effect with an expected effect on the DNA structure of the molecule, causing the formation of melanoma, skin cancer.

There are two types of sunscreens containing a physical or chemical filter. The first reflects ultraviolet radiation, and the second absorbs UVB rays. SPF (Sun Protection Factor) is a sunscreen factor. It designates the ability of cosmetic means to protect the skin from harmful UVB rays and prolong the time of safe sun exposure. As chemical filters are most often used mexoril, avobenzene, oxybenzone, benzophenone, etc. However, these substances can provoke allergic reactions and activate the process of the appearance of free radicals in the epidermis at UV radiation.

It is more advisable to apply vegetable extracts as chemical filters. In this work are applied glycerin extracts from the leaves of green tea, peel and seeds of grapes, calendula flowers, chamomile medicinal, and corms of autumn crocus. All plants are common on the territory of Georgia.

Preliminary studies by UV spectroscopy of 0.06% glycerin extracts from the above-mentioned plants on the device, CECIL CE9500 Aquarius'' shows that almost all samples absorb UV radiation in both UVB and UVA cases. Based on the obtained data, several variants of the formulation of sunscreen creams were developed.

In the composition of creams, separate extracts and their various combinations were introduced in a ratio of up to 5% of the total mass. The study of the absorptive capacity of creams was carried out on a spectrophotometer, AVASPEC-2048 FIBER OPTIC SPECTROMETER'' in the wavelength range of 200-400 nm.

It was determined that all samples absorb UV radiation in this range, with the absorption peak being at a wavelength of 250-300 nm, and creams containing green tea extract and extract of ossicles and grape rind have the most absorbing ability. SPF of samples are about 25-30.

The obtained data gives the possibility to consider the application of glycerin extracts of the above-mentioned plants as protective agents against UV radiation in cosmetic creams.

## **SYNTHESIS OF CHIRAL SULFOXIDES AND STUDY OF THEIR ENANTIOSEPARATION BY HPLC METHOD**

R. Kakava<sup>1</sup>, M.L. Konjaria<sup>1</sup>, N. Shashviashvili<sup>1</sup>, A. Volonterio<sup>2</sup>, B. Chankvetadze<sup>1</sup>.

<sup>1</sup> Institute of Physical and Analytical Chemistry, Faculty of Exact and Natural Sciences, Ivane Javakhishvili Tbilisi State University, 3, Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia

<sup>2</sup> Dipartimento di Chimica, Materiali ed Ingegneria Chimica "Giulio Natta", Politecnico di Milano, Italy

### **Introduction:**

Enantiomeric separation of chiral compounds is extremely important because most of the bioorganic molecules, synthetic drugs and agrochemicals are chiral compounds. Enantiomers in racemic drug compounds are characterized with different biological activities, including

pharmacodynamics, pharmacokinetics and toxicology. That is why, enantiomerically pure drug forms are more safe and efficient (1-4).

The main goal of the present study was to determine relationships between chemical structure of chiral compound and enantioselectivity in high-performance liquid chromatography.

#### **Materials and Methods:**

In order to understand the relationships between chemical structure and enantioselectivity, about 50 new chiral sulfoxides were synthesized and their chiral separations were performed with polar organic and normal-phase mobile phases using variety of cellulose based chiral selectors. Majority of these chiral selectors were not described in literature before.

#### **Results:**

The main factors contributing in molecular recognition of macromolecules were revealed. Correlation between chemical structure and enantioselectivity was established.

**Conclusions:** Distribution of electron density and geometry of analyte molecules seem to be the major factors affecting enantioselectivity and molecular recognition ability of chiral molecules.

#### **Acknowledgements**

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## **USE OF ALCALOID FROM COLCHICUM IN MEDICINE**

**N. Popkhadze**

Scholarly Information Center at Phassis Academy in Tbilisi, Georgia  
Aiakolkhetikardugeorgia@gmail.com

Medicinal and pharmaceutical drugs have a significant role in the economy of many countries. Our republic has a potential to enhance economic growth by applying novel methods of producing and/or improving methods for improving health of the population. This presentation concerns modern trends in the use of the alkaloids and other substances derived from the plant known for millennia mostly by the name Colchicum. The name is derived from the name of the area called Colkheti/ Kolkheti. Kolkheti is mentioned on at least four available, archaeologically recovered clay tablets posed in the library of king Zimri Lim in the palace built almost 4000 years ago in the basin of the river called Idigana in those days and renamed into Tigris later. Zimri Lim was King Hammurabi's neighbor in area. They were friends. Later they became enemies and Hammurabi annexed his kingdom. Hammurabi's law stressed that if a

doctor harmed a patient, the doctor would receive same damage that he inflicted on a patient. The area called Kolkheti//Kolkheti was well known to these rulers as both tried to have Kolkheti's ruler on his side and feared that Kolkheti would take opposite side. Zimri Lim sent a group of spies to one of the areas of Kolkheti. Scholars have supposed that the name of the land called Kolkheti has been the basis for the name of the plant Colchicum. This flower is spread nowadays on a vast territory and has a commercial use in several modern republics. Its biological, chemical and pharmaceutical properties have been investigated for a long time in ancient Kolkheti//Colcheta//Colchis.

The Pharmaceutical Factory in Tbilisi had a commercial output of the medicine produced from this plant. It was an unguentum in beautiful tubes and had the inscription in the Kolkheti language called nowadays Kartuli//Georgian, and in the Latin language: Colchicine. This ointment was used against gout. The Internet search engines provide ample published materials on the uses of the substances made from this famous plant. Our ancestors wrote on clay tablets the lists of trees, flowers, objects made from clay, from metal, from wool, from milk etc. These lists have survived to this day and are used in scholarly publications. The medicinal plant resembling Colchicum is mentioned in the ancient Egyptian Ebers papyrus- according to a publication in the USA in 1953. A dissertation thesis in Berlin in 1878 was totally dedicated to the use of Colchicum plant in medicine, pharmacy and chemistry as known from ancient Hellenic and Latin writings. Based on historical sciences, chemical knowledge originated thousands of years ago in old Georgia, and the name "chemistry" derives from Colchian language {Gakhokidze Ramaz. The Prephilosophical Thinking of Georgian Ancestors- the Basis of Metallurgy and Gold Production, - In: Philosophical Investigations. Tbilisi, Publ. "Universal", v. 19, pp. 198-284. 2015}.

I wish to attract the attention of the participants of this scholarly event to 22 acting USA Patents and 10 pending applications for USA patents concerning Colchicum and Colchicines – the product of Colchicum. I suppose it is worth mentioning that the information is available about electrochemical behavior of colchicines using graphite-based screen-printed electrodes, authored by five scholars from Romania and Italy. The proposed electrochemical method provides simple, sensitive, accurate and fairly reproducible quantitative analysis of colchicine in tablets. It passed all necessary statistical pulse voltammetric methods and the results were correlated. Their method was applied for determination of colchicine in tablets without any separation, or complex sample preparation, since there was no significant interference from the experiments. Using cost effective, disposable screen-printed electrodes the developed method could be applied for quality control dissolution tests regulated by Pharmacopoeias and in vitro dissolution profile testing since cross-contamination can be easily avoided.

Our republic imports colchicines from Romania nowadays. The Romanian authors published that analytical grade colchicines for biochemistry was purchased from Merck, Germany. In a book of Akaki Gakhokidze published in Tbilisi in 1961 the history of Pharmacy and Chemistry is overviewed and stressed that in ancient kingdoms Pharmacy and Chemistry were inseparable: a pharmacist was a chemist and a chemist was a pharmacist. This important book containing a chapter on sugar production, on naphtha and other important topics, is unavailable now and it is advisable to reprint it with new comments of the editor. Medeia – the famous ruler of the kingdom called Media – the daughter of king Aiaeti of Aiakolkheti//Kolkheti was called Pharmaca for being an expert pharmacist//chemist. In my opinion, her statue in Batumi is a

statue to local national science including chemistry and pharmacy. Our ethnic science originated in remote times and this fact ought to be adequately represented at the scholarly international meetings and more attention ought to be attracted in our republic to the use of the plant called Colchicum. The author of this presentation will attract the attention of the participants of this scholarly event to good results obtained by Prof. Pamaz A. Gakhokidze by application to various crops Biorag – a compound created, invented by him and named by him by initial letters of his first and last names: Bio = R(amaz)+G(akhokidze). Groups of population of our republic have used this additive to improve crops and are satisfied with results. Prof. Gakhokidze has invented a compound to be used against an insect called here Asian Parosana - with good results. Parosana destroys harvest in great amount.

Global drug major Takeda Pharmaceuticals has brought two Indian drug firms — Granules India and Hetero Drugs — to court over charges of patent infringement of its drug to treat Gout and Familial Mediterranean Fever. Granules India and Hetero Drugs, both headquartered in Hyderabad, have recently filed ANDAs (Abbreviated New Drug Application) with the US Food and Drug Administration seeking approval to sell the generic version of the drug Colcrlys (Colchicine USP). The drug is used for treating and preventing gout flares and Mediterranean fever. Takeda Pharmaceuticals, the Japanese giant, has filed a patent infringement case in the US District Court for the District of Delaware to prevent the two firms from selling the drug in the US market. Colchicine has been around as a medication in the US, mostly used to treat gout. Originally extracted from plants, it is a toxic natural product and secondary metabolite.

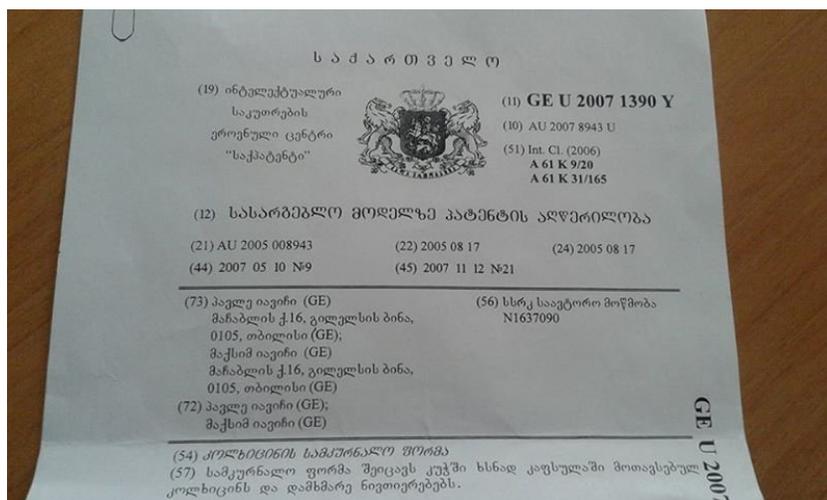
Takeda Pharma holds the NDA (New Drug Approval) for Colcrlys to treat gout, which the USFDA granted approval in 2009 for commercial manufacture and sale exclusively for a defined period. The estimated market for the drug is \$450 million. Interestingly, Takeda already has a case pending against Mylan over the drug patent. Colcrlys and Takeda's authorised generic of Colcrlys are the only oral single active ingredient Colchicine products approved by the FDA for treatment of gout. Granules India in its Para IV notice in July claimed that it is entitled to bring its product to the market prior to the expiration of Takeda's patents because "they are invalid, unenforceable and would not be infringed".

The company has produced a 0.6 mg Colchicine dosage version and sought the FDA approval to sell its generic version to treat Mediterranean fever. Incidentally, in May 2016, Takeda Pharma suffered a setback when it lost a patent infringement case to Hikma Pharmaceuticals, UK. The Delaware Court backed Hikma's rights to sell a drug Mitigare with the same active ingredient as Takeda's Colcrlys, because it was not indicated for uses covered by the patent in question. Gout is a form of severe arthritis due to build up of uric acid in the body. Familial Mediterranean fever is a hereditary inflammatory disorder, which occurs usually in people from that region.

Dr. G.P. Singh published on 11<sup>th</sup> July, 2017, that Colchicum has several uses in Hemeopathy



In Tbilisi work is going on investigations using Colchicum. Sakartvelo/Georgia's Patents Office has issued a document presented below – to Yavich Pavel A. and Yavich Maksim, both at Machabeli street, No 16 in Tbilisi. Document is GE U 2007 1390 Y on the improvement of the prototype of Patent USSR No.1637090 of these authors on the use of Colchicine in medicine. Prof. Pavel A. Yavich is Head of the Department at the Pharmacochemical Institute in Tbilisi. He has many publications in several languages both in Sakartvelo//Georgia and abroad.



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## ANTIVIRAL ACTIVITY OF BENZOPYRROLOINDOLE AND INDOLOINDOLE DERIVATIVES, SYNTHESIS OF NEW BASIS COMPOUNDS

**M. Trapaidze\*, N. Esakia, N. Nikoleishvili, S. Kvinikadze and Sh. Samsoniya**

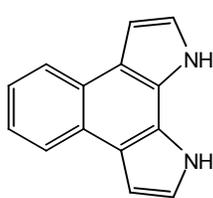
Ivane Javakhishvili Tbilisi State University, Faculty of E&NS, Department of Chrmistry,  
3, Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia

\*marina.trapaidze@tsu.ge

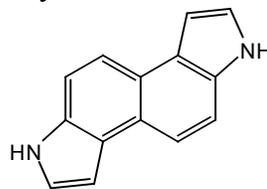
Antimicrobial activity of synthesized compounds based on benzopyrrololindoles and indoloindoles have been studied in various test-strains in vitro. Benzopyrrololindole formyl-,

diazo- and diethylalomanoderivatives have demonstrated high activity against *Staphylococcus aureus* da *Bacillus subtilis* bacteria and high activity towards mycobacterium and fungi [1, 2].

In this paper we present the results of biological activity of benzopyrroloindole and indoloindole derivatives on a wide range of antiviral activity.



1H,10H-benzo [e]pyrrolo[3,2-g]indole



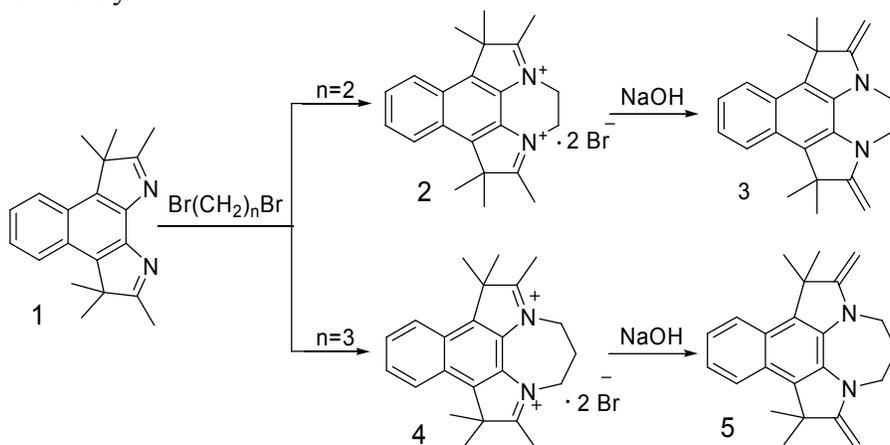
3H,8H-indolo[5,4-e]indole

Compounds were experienced with 20  $\mu$ M (micromolysis) concentrations against various family viruses: The different viral strains used for the study include the recombinant Zaire Ebola virus (EBOV) engineered to express the enhanced GFP (EBOV-eGFP), Marburg Ci67 (MARV) Venezuelan equine encephalitis virus (VEE), Eastern equine encephalitis virus (EEE) FL91, Rift Valley fever virus (RVFV) ZH501 and Crimean-Congo hemorrhagic fever (CCHF).

The results of bioscreening are as follows: 3H,8H-indolo[5,4-e]indole is active in VEE, EEE, and RVFV viruses, causing them to be inhibited by 73%, 92% and 94%; 1,6-diformyl-3H,8H-indolo[5,4 e]indole show the inhibition of VEE and EEE viruses by 74% and 71%.

3-formyl-1H,10H-benzo [e]pyrrolo[3,2-g]indole is injected into Ebola, VEE, EEE, RVFV viruses by 8%, 96%, 96% and 98% respectively; 2',3'-Dimethoxycarbonyl-5',6',6',11'.11',12'-hexamethyl-11'-hydrospirofluorene-9,4'-(1'-aza-2'-cyclopentene))[1',5'-a]benzo[e]pyrrolo[3,2-g]indoline introduce Ebola, Marburg and EEE viruses in accordance with 98%, 85% and 27%; 2,9-Di(carbohydrazide)-1H,10H-benzo[e]pyrrolo[3,2-g]indole is inhibited by Ebola and Marburg viruses in 38% and 31% respectively.

On the basis of hexamethyldihydrobenzo[e]pyrrolo[3,2-g]indole, were synthesized new key compounds - the bis-analogs of Fischer's bases (compounds 3,5). They are reactionary compounds, their molecules contain biologically interesting quinoxaline and diazepine rings, with the subsequent changes in the synthesis of new products to persist in search of compounds with biological activity.



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## SECONDARY RESOURCES OF GEORGIA FOR CREATION OF ANTIMICROBIAL COMPOUNDS AND COMPOSITES

**N. Lekishvili<sup>1a</sup>, Rus. Gigauri<sup>1a</sup>, Kh. Barbakadze<sup>1a,2</sup>,  
D. Nikolaishvili<sup>1b</sup>, V. Trapaidze<sup>1b</sup>**

<sup>1</sup>Tbilisi State University, Faculty of Exact and Natural Sciences, 3 Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia: <sup>a</sup>Department of Chemistry, Institute of Inorganic-organic Hybrid Compounds and Non-traditional Materials; <sup>b</sup>Department of Geography

<sup>2</sup>Tbilisi State Medical University, 33, Vazha Pshavela Ave., 0186 Tbilisi, Georgia

Sough Caucasus region (Georgia) is rich in significant natural resources such as barite, concretes, zeolites, basalt, petroleum, manganese, copper, mercury, arsenic, gold, medical mineral waters and Black Sea reserves of hydrogen sulfide [1]. Arsenic takes the special place among them [2].

Arsenic mines are located at southern slopes of the Greater Caucasus mountain range. Their origination is linked with neogene-magmatic processes. Arsenic deposits are basically represented in Racha (Lukhuni) and Lower Svaneti (Tsani) (Georgia) in the form of occurrences. They proven exploitation reserves of the deposit are equal to 38.9 thousand tons. Also, Sakaura and Kodisdziri (Georgia) arsenic manifestations are considered as prospective ones.

Realgar (As<sub>4</sub>S<sub>4</sub>)-auripigment (As<sub>4</sub>S<sub>6</sub>) ores of Racha (Georgia) are unique in the world. The content of a dominant in these ores is particularly high and reaches an average of 12%. Besides, it is very important that these ores do not contain the impurity elements, and the best chance is given to produce not only highly pure metal arsenic and As<sub>2</sub>O<sub>3</sub>, but also other conversable products. For extracting arsenic and some of its compounds from the realgar-auripigment ores of Racha, first of all, the concentrate is burned in a special furnace that does not exclude pollution of environment both by sulfur dioxide and by arsenic compounds – 2-3% of aerosol comes on white arsenic [3].

Arsenic is also a natural associate clement almost of all nonferrous and precious metals. After pyrometallurgical processing of the ores of these elements, which is one of the inevitable conditions for their recovery in an individual state, it comes out of the technological scheme in the form of white arsenic and is present in industrial residuals. The content of arsenic in them often varies within 8-60%. At the same time, they contain commercially important quantities of

precious metal. To avoid environment pollution, the residuals are buried in a special burial ground (sepultchre) that is associated with great material and financial expenses.

We used important reserves of Georgia to extract arsenic from secondary resources (arsenic-pyrite and realgar-auripigment processing and pyrometallurgical industry) in various forms in order to produce relatively cheap and important antimicrobial compounds [4, 5] and inorganic-organic antimicrobial multifunctional materials with specific properties on their basis [6]. The laboratory technologies of their preparation have been elaborated.

These achievements serve not only as an additional technical-economical reserve for any developing country but encourage solving a number of ecological problems too.

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## RESEARCH FOR SYNTHESIS PATHS OF ISOMERIC PYRROLOINDOLO [2,3-B]QUINOXALINE

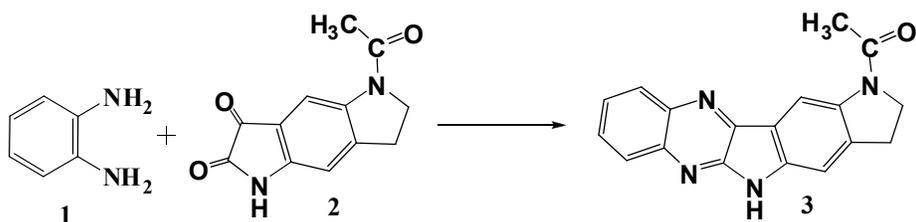
**L. Bobokhidze, D. Kajrishvili, I. Chikvaidze\*, Sh. Samsonya**

Ivane Javakhishvili Tbilisi State University, Faculty of E&NS, Department of Chemistry,  
3, Ilia Chavchavadze Ave., 0179 Tbilisi, Georgia

\*iosebc@yahoo.com

It was successful to integration of indole and quinoxalinenucleis in the tetracyclic indolo-quinoxaline condensed nucleous systems. 6H-Indolo[2,3-b]quinoxaline and its derivatives are powerful intercalatorsof DNA.They are characterized by high antiviral, antifungal, cytotoxic, antimutagenic, anticancerogenic, herpes and other activity. In our opinion, it is interesting to build a new five ring containing condensed heterocyclic system bycondensation with the pyrrole nucleus on the indoloquinoxaline. It is possible to have 12 isomeric pyrroloindoloquinoxaline. The existence of a free pyrrole nucleus in this type of system will further expand the synthesis of

new products and the possibility of finding useful compounds between them. We have studied several ways how to build a five ring containing heterocyclic system of isomeric pyrroloindoloquinoxaline. We tried to make the first representative on the bases of key compounds - 6H-indolo[2,3-b]quinoxaline and its nitrating product, which are synthesized by condensation reaction between isatin and o-phenyldiamine in acetic acid area. 3,6-dihydropyrrolo[3,2:4'5']indolo[2,3-b]quinoxaline (3) - the first representative of this classes we have synthesized by the condensation reaction between 1H,5H-5-acetyl-6,7-dihydropyrrolo[2,3-b]indoline-2,3-dione (2) and o-phenyldiamine (1) in the acetic acid area.



### SPECTROPHOTOMETRIC RESEARCH OF BINARY AND MIXED COMPLEXES OF FE (III) IN THE 3RD COMPONENT

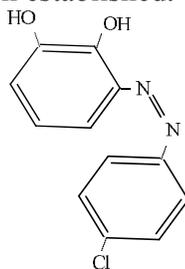
**I. Ugrekhelidze<sup>1</sup>, M. Tsintsadze<sup>1\*</sup>, A. Mahharamov<sup>2</sup>, E. Topuria<sup>1</sup>, N. Imnadze<sup>1</sup>**

<sup>1</sup>Georgian Technichal University

77 Merab Kostava St., Tbilisi, Georgia, 0175; \*m.tsintsadze@gtu.ge

<sup>2</sup>Baku State University, Baku, Azerbaijan

Complexes of iron(III) with 2,3,4-trioxy-4'-chlorobenzyl in the presence of third components of papaverin, dibazol and urotropin were investigated by spectrophotometric method. Optimal conditions of their formation are established. Their spectrophotometric characteristics determined. It is found that binary and mixligand complexes are formed at pH=3, and have maximum absorbance at 412, 437, 434 and 433 nm respectively. Stability constants are calculated by spectrophotometric method complexes compound is 1:2 for monoligand and 1:2:1 for mixligand complexes. Influence of foreign ions complexation is studied. Methods of determination of iron in tea water have been established.



The spectrum of reagent lights was studied at length of 200 - 700 nm wavelength. It has been established that at this precinct of the spectrum it is observed that maximum reaction of the

reagent is maximum two. The effect of pH on the complexity of the complex has been studied in the maximal solution of the complex when  $\text{pH} = 3$ .

Optimal pH - complex formation does not change. Binary and mixed complexes are formed immediately after the mixing of components in the solution. Binary complexes are sustainable for up to three hours, the complexity of mixed complexes is 2 days. The molar coefficients of the lengths of complexes are calculated from the curvature curve, the concentration spacing is established,

## REPORTS OF THE STUDENTS OF SAN DIEGO STATE UNIVERSITY Georgia

### AMERICAN CHEMICAL SOCIETY SDSU-G STUDENT CHAPTER

#### MAKING LIGANDS FOR THE GENERAL CATALYST CONTROL OF THE MONOISOMERIZATION OF 1-ALKENES TO *CIS*-2-ALKENES

D. Grotjahn, E. Paulson, E. Delgado, E. Gojiashvili

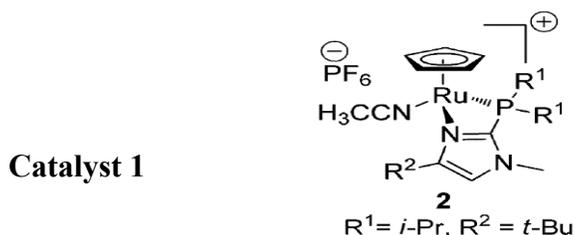
Department of Chemistry, San Diego State University, Dr.Grotjahn's lab.

#### Background

Alkenes are fundamental chemical feedstocks and are used on massive industrial scales. For example: ethene is used as feedstock for polyethylene, styrene, ethanol, acetaldehyde and many others.<sup>1</sup> Furthermore, the alkene functional group is important to many chemical synthesis, including multistep natural product synthesis.<sup>2</sup> Considering this, the ability to control the formation and chemistry of alkenes is very crucial to organic chemistry synthesis.

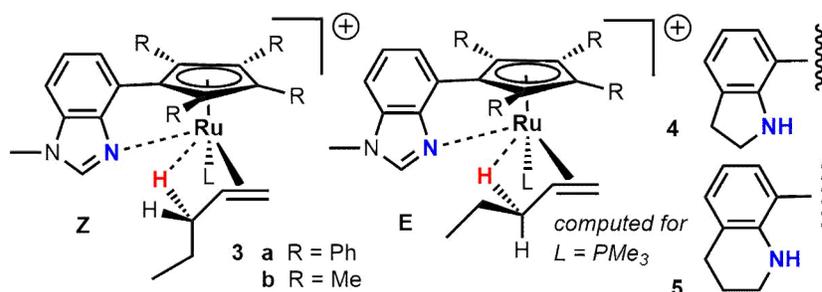
Alkene isomerization is simple, and it may seem that all the synthetic problems in this area should have been solved by now. However, there is one problem still yet to be solved. It is the case to control both regio- and stereochemistry, particularly in the case of converting a 1-alkene to *trans*-2-alkene or *cis*-2-alkene. (*E*)-alkenes are basically more stable than (*Z*)-alkenes. Many desirable synthesis targets feature (*Z*)-alkenes, so do many natural feedstocks, thus alkene isomerization catalysts capable of making or processing (*Z*)-alkenes are of high interest. Our group's goal is to make (*Z*)-selective catalyst.

The team I am working with now, made catalyst (**1**), that has been cited as "being one of the best in terms of catalyst loading, reaction yields, and E-stereoselectivity."<sup>3</sup> For example, with 2 mol% catalyst, 1-pentene is isomerized to 2-(*E*)-pentene in <4 min with 99% yield. Only after leaving the mixture for 24 h does one see 2% of 2-(*Z*)-pentene, and this result is general for linear alkenes.<sup>4</sup> In 2014 same team made adjusted catalyst (**2**) that allows unprecedented catalyst control of both positional and geometric selectivity in making E-alkenes.<sup>5-6</sup> Understanding the origin of selectivity in the CpRu(PN) family of catalysts through computations and new experimental data, is crucial to guide a rational design of (*Z*)-selective catalyst candidates.



### Methods and Preliminary Results

Now, we are working to modify the CpRu(PN) platform to promote (*Z*)-alkene formation. The research I am doing is to place the pendant base on the Cp ring. We have computed a number of *E/Z* pairs such as **3-5** (Scheme 1). For pairs of **3-5E/Z**, relative energies of *Z* species are slightly lower in energy (by up to 1 kcal/mol). In addition to this, for **3a**, the CH---Ru distance for **3aZ** is less (2.05 Å) than for **3aE** (2.32 Å), while the CH---N distances are only 0.02 Å different, all suggesting that **3aZ** barriers for the next reaction (allyl formation) could be less than **3aE**.



**Scheme 1**

Since the computational screening showed promising results, we began the synthesis of the Cp derivatives with pendant bases such as those shown in **3,4** and **5** in Scheme 1. We have already synthesized bases **4** and **5** with decent yields and we are waiting for complexations to determine their effectivity.

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## LIGHT AND PH CONTROLLED DRUG DELIVERY MICRO CONTAINER

G. Petriashvili<sup>1\*</sup>, K. Chubinidze<sup>2</sup>, P. Burnadze<sup>3</sup>

<sup>1\*</sup> Institute of Cybernetics of the Georgian Technical University, Tbilisi, 0175, Georgia

<sup>2</sup> Ivane Javakhishvili Tbilisi State University, 1 Ilia Chavchavadze Ave, Tbilisi 0179, Georgia

<sup>3</sup> San Diego State University / SDSU Georgia, 5 Kostava Str. 3rd Floor Tbilisi 0108, Georgia

E-mail: Paata.burnadze@yahoo.com

The development of a smart microencapsulation system programmed to actively respond to environmental stimuli is gaining increasing importance compared to the traditional forms of drug administration. Delivering drug locally, in the targeted placement and at the controlled portions, is a common way to decrease side effects due to the drug toxicity and, consequently, maximally reduce the undesirable side effects. The drug can either be adsorbed, dissolved, or dispersed throughout the nanoparticle complex or, alternatively, it can be covalently attached to the surface [1]. Assorted types of remotely-triggerable drug delivery systems have been developed, which rely on applying an external stimulus to release the drug load. Ideally, such systems could determine the timing, duration, dosage, and even location of drug release, and could allow remote, noninvasive, repeatable, and reliable switching of therapeutic agent flux. Liquid crystalline materials are promising candidates for the sensing of biomaterials. LC ordering is highly sensitive to molecular-level physical and chemical interactions at the LC interface, which lead to changes in optical appearance [2].

In this study, we introduce two new concepts of the drug delivery system, based on the light and pH sensitive liquid crystal (LC) micro spheres. The proposed system represents an emulsion formed by the immiscibility between the LC micro spheres and a water environment [3]. LC-based sensors are simple, label-free, and allow real-time reporting of various biological events such as the enzymatic hydrolysis of phospholipids, specific phospholipid-protein binding, and DNA hybridization [4].

Light controlled concept describes light activated drug delivery containers, based on spiropyran doped LC micro spheres. Upon exposure to UV/violet light, the spiropyran molecules entrapped inside the LC micro spheres, interconvert from the hydrophobic, oil soluble form, to the hydrophilic, water soluble merocyanine one, which stimulates the translocation of the merocyanine molecules across the nematic liquid crystal-water barrier and results their homogeneous distribution throughout in an aqueous environment.

As regards the second concept, we utilize the same LC/water micro emulsion, but instead of spiropyran molecules inside the LC micro spheres are entrapped pH sensitive fluorescent dye molecule that intelligently responds to the environmental pH change, resulting immediate

translocation across the LC-water barrier and disseminates evenly throughout in an aqueous environment.

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## UTILIZATION OF SECONDARY VEGETABLE OILS AND TRANSFORMATION INTO BIODIESEL

**T. Kupatadze<sup>1</sup> and L. Lobjanidze<sup>2</sup>**

<sup>1</sup>San Diego State University Georgia, Faculty of Chemistry/Biochemistry,

<sup>2</sup>San Diego State University Georgia, Faculty of Computer Science, 5 Kostava Street, 0108 Tbilisi, Georgia

Increasing uncertainty about global energy production and supply, environmental concerns due to the use of fossil fuels, and the high price of petroleum products are the major reasons to search for alternatives to petrodiesel [1]. In last decades, considerable attention has been given towards the production of biodiesel as a diesel substitute. Moreover, biodiesel fuel has become more attractive because of its environmental benefits [2], because plants and vegetable oils and animal fats are renewable biomass sources. Biodiesel represents a largely closed carbon dioxide cycle (approximately 78%), as it is derived from renewable biomass sources. Compared to petroleum diesel, biodiesel has lower emission of pollutants, it is biodegradable and enhances the engine lubricity [3] and contributes to sustainability [3,4]. Biodiesel has a higher cetane number than diesel fuel, no aromatics, no sulfur, and contains 10–11% oxygen by weight [5]. Today the fast food industry is very rapidly developing field of food technology in Georgia. This manufacturing uses a huge quantity of oils, i.e. for preparation of 40 kg potatoes is necessary about 8 liters of oil. Unfortunately, there is no government regulation for recycling used oils until. Therefore, the aim of the current project is to promote waste oil collecting with its following transformation into biodiesel.

Comparison of the optimum conditions of alkaline-catalyzed transesterification process for biodiesel production from pure sunflower cooking oil and waste sunflower cooking oil through transesterification process using alkaline catalysts was studied. To obtain a high-quality biodiesel fuel that complies the specification of standard methods, some important variables such as volumetric ratio, types of reactants and catalytic activities were selected. The highest

approximately 99.5% biodiesel yield acquired under optimum conditions of 1:5 (volumetric) oil-to-methanol ratio at 40°C reaction temperature and 500 rpm stirring speed. The result showed that the biodiesel production from pure sunflower cooking oil and waste sunflower cooking oil exhibited no considerable differences. The research demonstrated that biodiesel obtained under optimum conditions from waste sunflower cooking oil was of good quality and could be used as a diesel fuel which considered as renewable energy and environmental recycling process from waste oil after frying.

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## OBTAINING RESISTANT HYDROXYAPATITE NANOCRYSTALLINE DRUGS FOR DENTISTRY AND BONE TISSUE REGENERATION

**N. Maksarashvili<sup>1</sup>, A. Kvinikadze<sup>2</sup>, R. Gaphrindashvili<sup>3</sup>**

<sup>1</sup>San Diego State University Georgia, Faculty of Chemistry/Biochemistry  
5, Kostava Street, 0108 Tbilisi, Georgia

<sup>2</sup>Ivane Javakhishvili Tbilisi State University, Faculty of Law  
3, I. Chavchavadze Ave., 0128 Tbilisi, Georgia

<sup>3</sup>Georgian Technical University, Department of Chemical and Biological Technology  
69, Merab Kostava Street, 0108 Tbilisi, Georgia

Inorganic-organic composite materials are widely used in orthopedic surgery. The inorganic phase contains calcium phosphates - tricalcium phosphate and nanocrystalline Hydroxyapatite. Hydroxyapatite -  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  – is of high interest for biological research and practical medicine because it is the main inorganic constituent of bone tissue and has great biological compatibility. The size of the bone biomineral particles of Hydroxyapatite (HAP) is 50 x 10 x 5 nm. The use of new implanted composite and nanocomposite materials are especially important for bone tissue regeneration.

It has been reported that ceramics made from Hydroxyapatite and its analogues, which are the main components of bones and teeth, did not cause a negative reaction in the host tissue.

Additionally, they have the ability to actively communicate with the healthy bone tissue without any negative consequences.

Hydroxyapatite is widely used in modern medical techniques and in orthopedic surgery. It is thought that HAP is the future of orthopedy, and hence the importance of this project is indisputable.

However, the synthesis of nanocrystalline Hydroxyapatite is associated with certain difficulties. The goal of this project is to overcome these difficulties and improve the methods of its synthesis.

Basic methods of obtaining Hydroxyapatite are liquid or solid phase synthesis. These methods are most diverse and use different techniques to obtain powders with regulated crystal forms, crystallinity and Ca/P with desired size. The liquid phase method involves precipitation of calcium phosphate, hydrothermal synthesis and hydrolysis.

The microcrystalline powder synthesis method of Hydroxyapatite is based on the classical precipitation method, where Calcium nitrate and Ammonium hydroorthophosphate solution are used as starting reagents.

We are obtaining Hydroxyapatite through the interaction of Calcium nitrate and Ammonium orthophosphate: in the intensive stirring conditions (on the magnetic stirrer ) little by little we added Ammonium Phosphate to certain concentration calcium nitrate. Periodically we checked PH and we remained it within 11-12 adding  $\text{Na}_4\text{OH}$ . Milky suspension was formed.

Next task was to wash suspension of Hydroxyapatite to clean it from Ammonia and separate it from water, in order avoid agglomeration of formed sediments and remain nanosizes of particles.

To get rid of Ammonia two methods are recommended:

1. To wash it with distilled water
2. Heat it up before boiling suspension.

We produced three types of Nanohydroxyapatite:

1. Hydroxyapatite dry powder
2. Hydroxyapatite suspension
3. Hydroxyapatites paste

In order to figure out what were the sizes of particles of received Hydroxyapatite models, we studied them on the rastrul electric microscope.

We checked Hydroxyapatite models in a special apparatus of Malvern “zetasaizer-nano” which confirmed the result on the microscope of x-ray and in addition it gave us the photo of distributed particles. We found out that 20,6% of particles are the size of 4-5 nanometers and 79,4% 50-60 nanometers.



Fig.1. HAP paste powder



Fig.2. HAP suspension



Fig.3. HAP dry

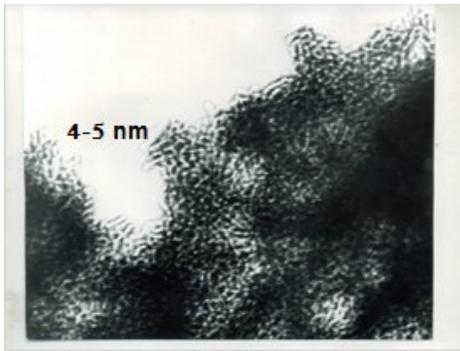


Fig.4. particles of HAP after synthesiz

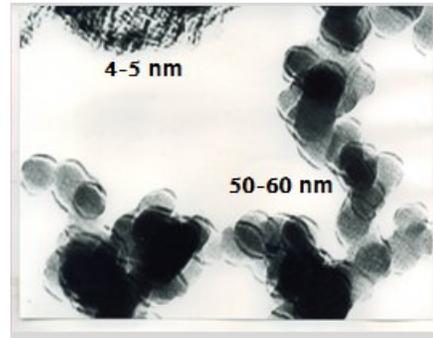


Fig.5. Particles of HAP after synthesiz

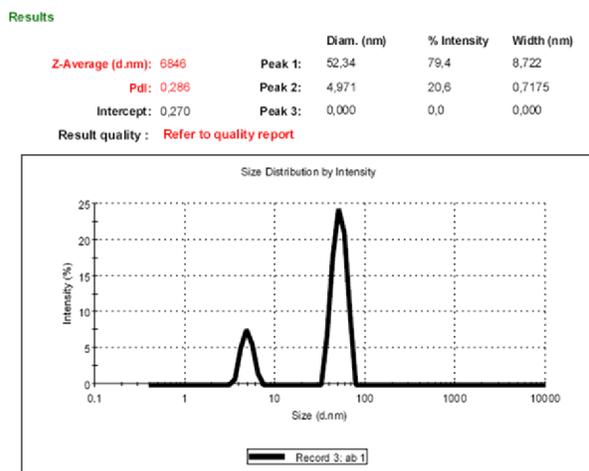


Fig.6. Results of zetasaizer-nano



Fig.7. Zetasaizer-nano

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## INVESTIGATION OF THERMAL PROPERTIES OF NEW SEMICRYSTALLINE POLYMERS

**M. Aptsiauri<sup>1</sup>, N. Kokiashvili<sup>1,2</sup>**

<sup>a</sup>San Diego State University Georgia, Faculty of Chemistry/Biochemistry,  
5 Kostava Street, 0108 Tbilisi, Georgia

<sup>b</sup>Ivane Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciences,  
Department of Chemistry, 3, I. Chavchavadze Ave., 0179 Tbilisi, Georgia

The thermal characteristics of new semicrystalline polymers and phase transitions were investigated by means of Differential Scanning Calorimetry (DSC). Those semicrystalline polymers were synthesized by the group of Professor RamazKatsarava, in Georgia.

We have recrystallized semi crystalline polymers with various organic solvents and next we investigated the effect of recrystallization solvents on the thermal properties of polymers. The thermal characteristics of the crystalline states were found to be strongly influenced by the recrystallization conditions. The influence of different organic solvent in the polymer was determined by the matrix on glass transition ( $T_g$ ), crystallization, and melting ( $T_m$ ) processes of the material.

The ability of a given polymers to a crystallization process substantially affects its final physical and thermal properties. During the crystallization process, most of semicrystalline polymers, the thickness of which is significantly smaller than other dimensions are being generated.

The thickness of lamellar crystals of a given material is a result of its chemical structure and the kinetics of crystallization more importantly affects selected either mechanical or thermal properties of a given polymer.

Experimental data proved a significant mutual interference between the chemical nature of the monomer and the particularities of the organic solvents, which influences the thermal decomposition of the corresponding semi crystalline polymer.

### **PETRE MELIKISHVILI, CHEMIST, FIRST RECTOR OF TBILISI STATE UNIVERSITY**

**D. Lashkhi**

San Diego State University Georgia, Faculty of Chemistry/Biochemistry  
5 Kostava Street, 0108 Tbilisi, Georgia

Establishment of the first national University in the Caucasus was one of the most important events in the history of our country. Georgian University, later known as Tbilisi State University was opened in 1918 laying the foundation for a European-type higher school in Georgia, based on Georgian educational traditions. In 1989 the Tbilisi State University was named after its founder, Ivane Javakhishvili.

Since this whole event is dedicated to the 100<sup>th</sup> anniversary of the foundation of Tbilisi State university and held by Georgian Chemistry Society, it is very important to honor the man because of whom we stand here today, Petre Melikishvili.

Foundation of Tbilisi State University was preceded by the devotion of many people, among whom *Petre Meliqishvili* was one of the most prominent personalities. Petre Melikishvili was elected as the first Rector of the first Georgian University on January 13, 1918 at the first meeting of University Board of Professors. At that time, Melikishvili was the most famous scientist of all his colleagues. For almost two years, he managed the newly established school absolutely for free and willingly used all his knowledge, experience and authority for the benefit of the first Georgian University.

Petre Melikishvili - co-founder, first rector, head of organic chemistry department, dean of agronomic department in TSU and generally a great scientist. Works of Petre Melikishvili and his modern Georgian scholars paved the ways of science in Georgia. It is their achievement that we are involved in modern science, that we have great scholars today and that we can host such events as this one. His works are especially important for us, chemists.

I had researched extensively through various literature sources and translated them to put together a Biographic paper about Petre Melikishvili and his role in the Chemistry and Georgian Science. I want to let people know some specific parts of his life, such as: Early life and education, his scientific studies in organic and inorganic chemistry, his involvement in the foundation of Tbilisi state university and his role in the creation of Georgian chemical terminology.

Presenting his biography to the audience on this symposium will be a nice gesture to honor Petre Melikishvili and also way to inform foreigner guests about our great predecessors.

## **BIOACTIVE COMPOUNDS IN APPLES**

**G. Makasaragishvili**

San Diego State University Georgia, Faculty of Chemistry/Biochemistry  
5 Kostava Street, 0108 Tbilisi, Georgia

Science has still not discovered a full-proof treatment for many degenerative diseases like cancer or Alzheimer's, therefore, finding ways of preventing them is crucial for public health. Consumption of foods rich in bioactive compounds can help reduce the occurrence of these diseases<sup>1</sup>. It has been found that one of these foods are apples; although, different cultivars apparently contain different amounts of bioactive compounds. The aim of this study was to analyze concentrations of bioactive compounds in five apple cultivars and find links between their qualitative and quantitative characteristics. Phenolic compounds measurements were made by using the colorimetric Folin-Ciocalteu assay. Tissue TP measurements were made in a Shimadzu spectrophotometer set at 725 nm. Sugar and organics acids were quantified using high-performance liquid chromatograph. Antioxidant capacity was determined using three tests, which were 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical method<sup>1</sup>, ferric reducing antioxidant power (FRAP), and 2,2-azino-bis (ABTS)<sup>2</sup>. The study found that the highest concentration of phenolic compounds was in "GoldRush", which also had the highest antioxidant capacity along with "Crimson Crisp" based on ABTS and FRAP methods. As for sugar and acid concentrations,

“Pixie Crunch” showed the highest sugar content, followed by “Crimson Crisp” and “GoldRush”. Malic acid presented the highest concentrations between the four acids studied, tartaric acid presented the lowest. A significant correlation was found between the amount of polyphenols present and the antioxidant capacity; on the other hand, organic acids and fruit color showed much less significant correlation. The results of the study suggest that the breeding program should focus on total phenolics and antioxidant compounds.

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## BIOACTIVE COMPOUNDS AND ANTIOXIDANT ACTIVITY ANALYSIS DURING ORANGE VINEGAR PRODUCTION

**E. Aslanikashvili**

San Diego State University Georgia, Faculty of Chemistry/Biochemistry  
5 Kostava Street, 0108 Tbilisi, Georgia

Citrus fruits possess a significant concentration of bioactive compounds as well as high sugar content<sup>1</sup>. Because of their latter quality, making vinegar from alcoholic orange substrates is a possibility. In addition, new products could also have functional characteristics due to oranges being rich in bioactive compounds. The aim of this study was to analyze the changes that take place in ascorbic acid, total phenolics, carotenoids and antioxidant activity during orange vinegar processing. The alcoholic substrate used in acetification was prepared from Valencia Late oranges alcoholic fermentation<sup>1</sup>. Acetification was carried out in a laboratory NEW BRUNSWICK CIENTIFIC Co., Bioflo 2000 bioreactor<sup>1</sup>. In order to analyze the influence of acetification and aging in these characteristics, samples were taken in three stages: orange alcoholic substrate for acetification (SNA), young orange vinegar or recently obtained (Vn0) and orange vinegar after six month-aging in bottles (Vn6). For the analysis of L-ascorbic acid and total carotenoids, the method was reverse-phase HPLC, using a Hewlett Packard 1100

and a UV detector. The method for the analysis of total phenolics was based on the Folin-Ciocalteu reactive reduction.

Antioxidant activity was determined by ABTS and DPPH methods. The study found that antioxidant activity decreased along the process, but total phenolics and carotenoids remained constant during the aging period (Vn0-Vn6). The highest reduction was recorded during the acetification stage, possibly due to the oxidation process caused by continuous air flow to the system. A higher contribution to antioxidant activity was associated to ascorbic acid and phenolic compounds concentration.

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## HARMINE – A POTENT BIOACTIVE COMPOUND FOR TREATMENT OF VARIOUS TYPES OF CANCER

S. Mestvirishvili

San Diego State University Georgia  
5 Kostava Str. 3rd Floor Tbilisi 0108, Georgia  
smestvirishvili@sdsu.edu

Harmine is an alkaloid from a  $\beta$ -carboline class, which is naturally present in several plant species. There are no many researches done on this compound, however in recent years more and more studies are being done on effects of harmine on cancer cells and its development *in vitro* and *vivo*. So here I present the recent studies done on cultured human cells, which support the effectiveness of harmine in treatment of various cancer types. The first study focuses on ovarian cancer, which is the sixth most common cause in cancer related deaths among Western women. The study showed that harmine inhibited the growth of ovarian cancer cells induced by epidermal growth factor (EGF) and also suppressed the expression of vascular endothelial growth factor (VEGF) along with metalloproteinase family (MMP)<sup>1</sup>. The next study focuses on gastric cancer cells and finds out that harmine acts as potent inhibitor of gastric cancer cells, by inducing cell apoptosis and autophagy<sup>1</sup>. Another study investigates effects of harmine of thyroid

cancer. The authors found out that harmine inhibited the proliferation and induced apoptosis a of thyroid cancer cell line. Besides *in vitro* effects, study also examined effects of harmine on mice, where harmine dose-dependently inhibited the growth of a thyroid cancer<sup>1</sup>. The final study discusses effects of harmine on leukemia cells. The result of study suggests that harmine effectively halted leukemia cell proliferation by inhibiting and suppressing DNA methyltransferase 1 gene and therefore shutting down the DNMT 1-dependent pathways for tumor growth activation<sup>1</sup>. The one possible reason for bioactivity of harmine could be explained by its direct binding to DNA and interfering with topoisomerase activity. The study concludes that DNA binding activity of harmine and its derivatives is base pair-dependent. At last, the authors suggest that their study could help researches develop and design related bioactive compounds in future<sup>1</sup>.

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## THE BENEFITS OF PECTIN

**A. Rukhadze**

San Diego State University Georgia  
5 Kostava Str. 3rd Floor Tbilisi 0108, Georgia  
ani\_rukhadze@yahoo.com

Nowadays humanity faces many problems. One of them is increased level of heavy metals, caused by various sources. Heavy metals can be found in the paints of children's toys, in the polluted air, wastewater or even in the food that we consume. Another issue that many people encounter is cancerous diseases that are hard to fight. There are medicine that can help to overcome illness. However, they have harsh side effects, which may have drastic results on human health and well-being. Therefore, it is crucial to investigate a better way to resolve such problems; the solution, which will not have such harsh side effects and will be cheaper and available for everyone. The answer to this challenge may be pectin, which satisfies abovementioned requirements and gives us hopeful results from the various studies and researches. Pectin is known for slowing down the formation of cancer cells. In addition, it can be

used for strengthening the immune system or removing heavy metals from poisoned patients and from industrial waste [1,2].

Pectin is a polysaccharide (Fig.1), which is present in the cells of plants. It can be extracted and prepared from citrus peels (ex. lemon and lime contain 25-30% pectin), pomace of apple, sugar beets, sunflowers, etc. [3]

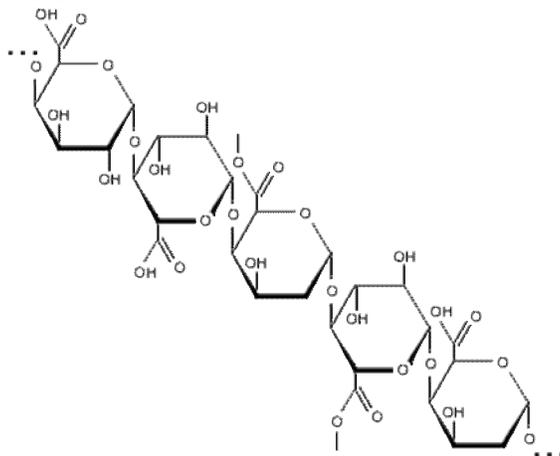


Fig.1. Pectin

The major use of pectin is in the confectionary production as a gelling, thickening and stabilizing agent. Pectin is used in desserts, jams, jellies, marmalades, sweet juices [4]. Pectin also has pharmaceutical usage. For instance, in the production of tablet matrix or film-coatings [3]. However, pectin has properties that can solve many other problems.

One of the most important values in the human life is health and well-being. Therefore, it is noteworthy that pectin not only helps to strengthen the immune system, but also has anticancer characteristics, that can be used in the prevention of the disease. Studies confirm that modified pectin has the potential to boost the effects of chemotherapeutic treatments.

Pectin possesses important and valuable characteristics that can be used in the advantage of human well-being and industrial work. In addition to this, it can be easily retrieved from various cheap sources, such as factorial waste. Therefore, it is important that we consider its benefits and find a way to incorporate use of pectin in the problem-solving methods.

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