Ministry of Education, Culture and Research
Institute of Chemistry

Scientific seminar with international participation

NEW FRONTIERS IN NATURAL PRODUCT CHEMISTRY

A DESTINY ON THE ALTAR OF RESEARCH

Dedicated to academician Pavel VLAD

Book of Abstracts

June 4, 2021
Chișinău, Republic of Moldova

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Online Event, www.ichem.md

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Acknowledgements. *The event is organized within the NARD State Program 2020-2023, project „New products with preventive and therapeutic potential basing on natural products of vegetal origin and modern methods of organic synthesis" (code 20.80009.8007.03).*

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Organizer: Laboratory of Chemistry of Natural and Biologically Active Compounds, Institute of Chemistry

Publisher: Institute of Chemistry, Academiei str. no. 3, MD-2028,
Chișinău, Republic of Moldova
www.ichem.md

DESCRIEREA CIP A CAMEREI NAŢIONALE A CĂRŢII DIN REPUBLICA MOLDOVA

"New frontiers in natural product chemistry", scientific seminar with international participation (6 ; 2021 ; Chişinău). Scientific seminar with international participation "New frontiers in natural product chemistry" : A destiny on the altar of research : Dedicated to academician Pavel Vlad, 6th edition, June 4, 2021, Chișinău : Book of Abstracts / editors: Aculina Arîcu, Veaceslav Kulcițki ; scientific committee : Aculina Arîcu (chair) [et al.]. – Chişinău : Institute of Chemistry, 2021. – 37 p. : fig.

Cerinţe de sistem: PDF Reader.

Antetit.: Ministry of Education, Culture and Research, Institute of Chemistry. – Referinţe bibliogr. la sfârşitul art.

ISBN 978-9975-3336-7-2 (PDF).

547(082)

N 62

DOI: http://dx.doi.org/10.19261/nfnpc.2021

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Note. The Authors of the Abstracts take the full responsibility for their content/originality.

Dear Colleagues and Friends,

It is our pleasure to welcome all the participants of the virtual Scientific Seminar „NEW FRONTIERS IN NATURAL PRODUCT CHEMISTRY" organized by the Laboratory of Chemistry of Natural and Biologically Active Compounds, Institute of Chemistry, Chișinău. The current event has been initiated in 2011 within a bilateral research project fulfilled with our colleagues from the Institute of Biomolecular Chemistry, Naples. We did our best to replicate this extraordinary event and now we are at its 6-th edition. This year we dedicate the seminar to the memory of the founder of our research laboratory, the illustrious scientist, academician Pavel VLAD, who would have celebrated the 85th anniversary on June 6, 2021.

The main aim of the seminar is establishing of an efficient communication between natural product researchers at national and international levels, as well as active promotion of this fascinating research field in the society.

The seminar is addressed to a broad circle of researchers, including young licence, master and PhD students from different fields of chemistry, biology, pharmacy and also to specialists from research and development areas of related chemical and pharmaceutical enterprises.

We are delighted to announce participation of several distinguished colleagues from international research institutions and laboratories who kindly accepted our invitation to provide oral presentations. We express our gratitude and appreciate your contributions.

Last but not least, we wish to thank our main sponsor – the National Agency for Research and Development (ANCD) of the Republic of Moldova who supports our research in consortium with the "Nicolae Testemitanu" State University of Medicine and Pharmacy of the Republic of Moldova within the project PLANTERAS.

We hope that the program will stimulate new ideas for collaboration and we can meet in person on other pleasant occasions, including the next edition of this seminar.

Dr. habilitate Aculina ARÎCU
Director of the Institute of Chemistry

Dr. habilitate Veaceslav KULCIȚKI
The Head of the Laboratory of Chemistry of Natural and Biologically Active Compounds

http://dx.doi.org/10.19261/nfnpc.2021.ab01 **Oral Presentation**

ACADEMICIAN PAVEL VLAD – A VERITABLE SCIENTIST OF OUR COUNTRY

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The name of the academician Pavel Vlad is associated with a number of remarkable fundamental and applied ideas. He has determined the priorities for research and some new lines in studies of terpenic compounds, in working out methods of investigation into fine organic synthesis. Under his guidance and with his direct contribution new approaches to determining the absolute configuration of a series of labdanic diterpenoids and of converting them into bi-, tri- and tetra- cyclic compounds have been designed [1]. Novel universal methods for synthesizing tetrahydrofurans from 1,4-glycols [2], olefins from tertiary alcoholic acetates, as well as dienones by means of photodehydrogenation of unsaturated cyclic ketons [3] have been developed by him. It has been established that the Swern reagent not only oxidizes the primary and secondary alcohols in the respective carbonyl compounds, but also dehydrates the tertiary alcohols [4]. The school founded by academician Pavel Vlad is the leader in the investigations of superacydic cyclisation reaction of terpenoids, and also of the regularities of the mentioned reaction in different classes of terpenic compounds, such as alcohols, their acetates, acids, esters, phenylsulphones [5]. Molecular transpositions were performed in the diterpene and sesquiterpene series [6]. Efficient ozonolytic methods for norlabdanic compounds preparation [7], as well as a new theory for evaluating the structure-ambra odor relationship have been also developed [8].

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab02 **Oral Presentation**

THE ROLE OF LIQUID-LIQUID CHROMATOGRAPHY IN NATURAL PRODUCT RESEARCH

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Support-free liquid-liquid chromatography (LLC), commonly referred to as countercurrent chromatography (CCC) or centrifugal partition chromatography (CPC), is considered a hybrid technique between liquid-liquid extraction (due to its partitioning separation mechanisms and high loading capacity) and solid-liquid chromatography (due to its very high selectivity). The ‘column’ in LLC is mounted either on a single axis rotor (in CPC) or double axis rotor (in CCC) and it is subjected to a centrifugal field that allows the stationary liquid phase to be kept inside the column, while the mobile liquid phase, immiscible with the first one, is pumped through it. Since there is no solid sorbent, no irreversible adsorption can practically occur, whereas the costs of purification are relatively low, as expensive solid stationary phases, time intensive column packing procedures or high-purity solvents are not required. The tailor-made mannerly preparation of the biphasic solvent systems as well as the numerous operating mode possibilities [classical ascending or descending elution, gradient elution, extrusion elution, recycling elution, continuous elution, (multiple) dual mode elution] make LLC a highly versatile and adaptable separation technique. As applications, examples in which LLC was integrated as a viable platform to isolate highly specific constituents from medicinal plants will be provided.

http://dx.doi.org/10.19261/nfnpc.2021.ab03 **Oral Presentation**

STEPS TOWARDS INCREASING INTERACTION BETWEEN CHEMICAL ECOLOGY AND PHARMACOLOGY

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Chemical ecologists are especially interested in exploring the chemical mechanisms by which living organisms obtain information about foods, dangers, predators, kin, sexual partners, and territorial boundaries, just to mention some of roles played by chemical communication. Conversely, pharmacologists are mostly interested in selecting bioactive natural products as promising candidates to address various kinds of human ailments. These different approaches to natural chemical diversity have led to two parallel and highly compartmentalized literatures, having their own publication outlets. Consequently, a number of questions still wait for answers, especially to clarify whether and how the properties that make natural products so important as drug candidates are closely related to their ecological roles. Exploiting the different and complementary expertise and interests at ICB, some of our researches evidently transcend the above disciplinary boundaries, and will be discussed to offer a synthetic point of view. Special emphasis will be placed on the crucial importance of animal models, such as the freshwater fish *Danio rerio* (zebrafish), to effectively approach the remarkable complexity of biological systems and to identify those molecular interactions underpinning both ecological roles and pharmacological activities.

http://dx.doi.org/10.19261/nfnpc.2021.ab04 **Oral Presentation**

BIOCHEMICAL TOOLS TO MONITOR ISOPRENOID BIOSYNTHESIS – THE CASE OF POLYPRENOL AND DOLICHOL

Agata Lipko [a], Adam Jozwiak [a], Magdalena Kania [b], Witold Danikiewicz [b], Marta Hoffman-Sommer [a], Liliana Surmacz [a], Michel Rohmer [c], Jaroslaw Poznanski [a], Ewa Swiezewska [a*]

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Isopentenyl diphosphate (IPP), the building block of isoprenoids, the most numerous class of secondary metabolites, is derived in plants from two pathways operating in parallel: the cytoplasmic mevalonate (MVA) and the plastidic methylerythritol phosphate (MEP) pathways. The cooperation of the two pathways (often called cross talk) is considered essential for plant adaptive responses to biotic and abiotic stresses. Elucidation of the isoprenoid metabolic pathways is indispensable for the rational design of plant and microbial systems for the production of industrially valuable terpenoids [1].

Numerous studies document that upon standard growth conditions majority of isoprenoids are made nearly exclusively via a single pathway, *e.g.* carotenoids and chlorophyll phytyl chains on the one hand and phytosterols on the other are derived from the MEP and MVA, respectively, while some other isoprenoids, including dolichols, are of mixed origin [2].

We have established methods, based on numerical modeling of mass spectra of metabolically labeled dolichols [3] and polyprenols, designed to quantitatively follow the cooperation of MVA and MEP *in Arabidopsis thaliana*. Our data indicate that in contrast to dolichols, which are 'mosaic' isoprenoids, polyprenols are predominantly derived from the MEP pathway. Interestingly, the relative contribution of both pathways to dolichol biosynthesis is reprogrammed upon environmental stress. Biological consequences of these observations will be discussed.

This contribution is dedicated to the memory of Professor Tadeusz Chojnacki, Founder of dolichology in IBB PAS and to the memory of Professor Pavel Vlad with thanks for the cooperation.

Acknowledgements
Financial support by a grant from the National Science Centre of Poland [UMO-2018/29/B/NZ3/01033] and "Frontier Research of Chemistry" (Strasbourg, France) foundation is kindly acknowledged.

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http://dx.doi.org/10.19261/nfnpc.2021.ab05 **Oral Presentation**

TERPENE BASED CHIRAL *N*-DONOR LIGANDS FOR TRANSITION METALS

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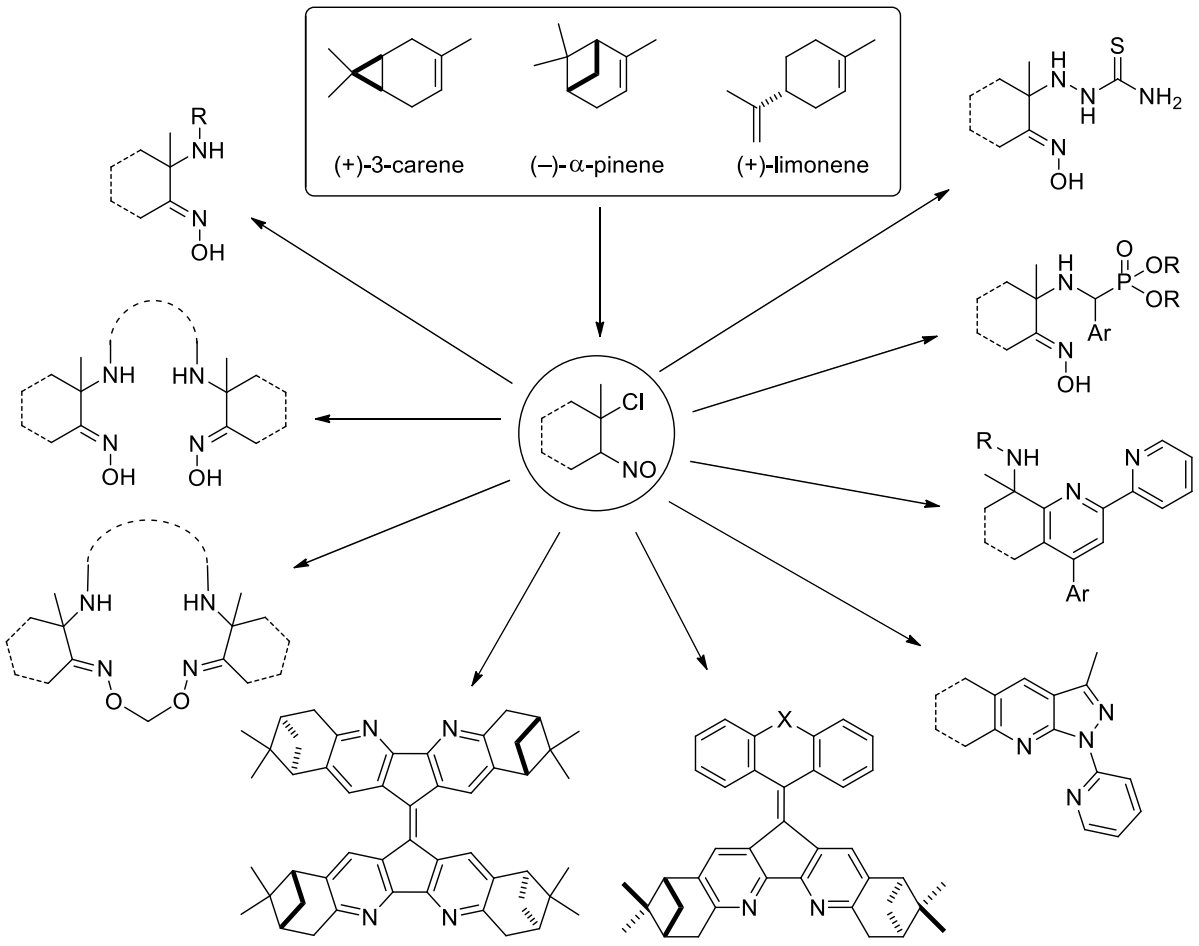
Natural monoterpenes of the carane, pinane and *para*-methane series are favourite starting compounds in design of wide diversity of chiral molecules of various properties. Chiral ligands based on natural product molecules are of special interest because of a set of promising properties.

The use of natural terpenes in synthetic pathways implies the primary modification of the starting compounds with the formation of heteroatomic derivatives. The report demonstrates synthetic approaches that make it possible to convert terpene nitrosochlorides into various *N*-donor ligands, which are promising reagents for coordination chemistry, for the selective extraction of metals, for the synthesis of luminescent materials and biologically active complexes, including those with antitumor activity.



The report gives examples of the dependence of the nature of complexation on the structure of the terpene fragment, discusses the features of establishing the spatial structure of the resulting ligands and complexes.

http://dx.doi.org/10.19261/nfnpc.2021.ab06 **Oral Presentation**

RECENT DISCOVERIES IN RADICAL CHAIN REACTIONS

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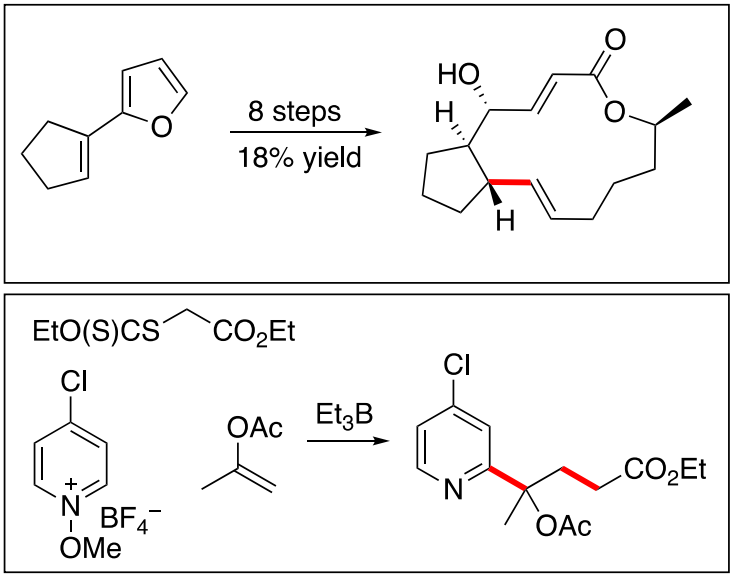
Radical chain reactions are particularly suitable for the formation of C–C bonds under mild conditions. This presentation will focus on the design of efficient chain reactions and their application in synthesis. To illustrate this approach, a short synthesis of (+)-brefeldin C [1] using a unique enantioselective and diastereoselective hydroalkynylation reaction will be presented as well as mild method for the monoalkylation of pyridines and related heterocycles [2].



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http://dx.doi.org/10.19261/nfnpc.2021.ab07 **Oral Presentation**

ANTIMICROBIAL AND ANTICANCER ACTIVITY OF SOME HYBRID AZINE/AZOLE DERIVATIVES

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Azine and azole heterocyclic derivatives has been reported as highly valuable scaffolds in medicine and pharmacy, being the core components of a large variety of drugs which posses a large variety of biological activity such as antiplasmodial and antimalarial, antitubercular, antibacterial, antifungal, anticancer, analgesic, antidepressant, anxiolytics, antihypertensive, anticoagulants, diuretics, *etc*. As a result, obtaining of such entities continues to arouse a strong interest from academia and industry.

As part of our ongoing research in the field of biologically active heterocyclic derivatives, we present herein some representative results obtained by our group in the field of azine/azole hybrid compounds with antimicrobial and anticancer activity. The methods of synthesis are straight and efficient, involving typical organic chemistry stuff: alkylation, acylation, estherification, etherification, Huisgen 3+n cycloadditions. Some of the new setup procedures were performed using environmentally friendly methods, by using microwave and ultrasounds technology. The antibacterial, antifungal, antituberculosis and anticancer activity of compounds was determined, some of the compounds having an excellent biological activity. For the most active compounds, a complete ADMET studies have been performed with very good results. The molecular docking experiments suggest important clues concerning the mechanism of actions of our nitrogen heterocyclic systems. Some of the obtained compounds are promising leading drug candidates.

Acknowledgements. Acknowledgment to Romanian Ministry of Education and Research, CNCS - UEFISCDI, project number PN-III-P4-ID-PCE-2020-0371.

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http://dx.doi.org/10.19261/nfnpc.2021.ab08 **Oral Presentation**

THE ELECTROCHEMICAL TRANSFORMATIONS OF METHYL BICYCLOHOMOFARNESOATES

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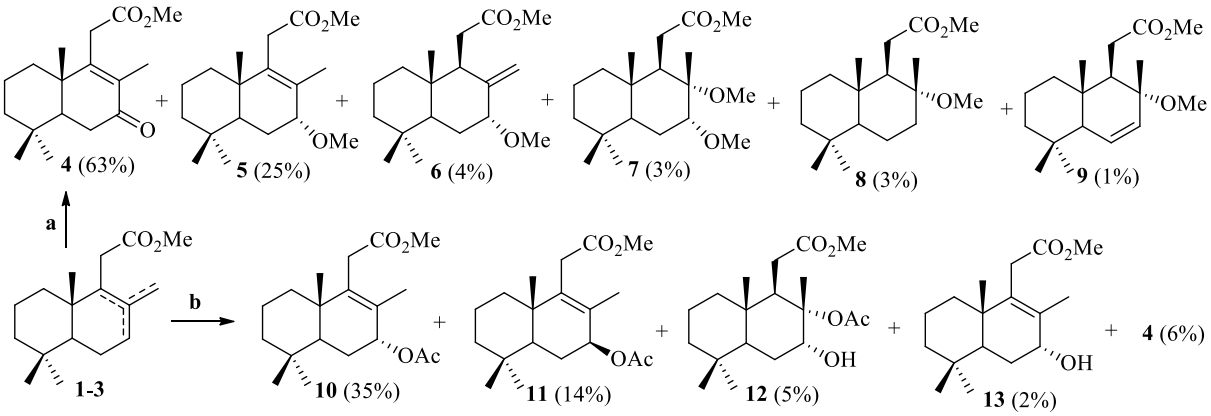
Electrochemical transformations have attracted much attention in synthetic organic chemistry, because they are cheap and environmentally friendly. Nowadays the interest for homodrimanic compounds increases substantially and frequently their syntheses were performed starting from known methyl bicyclohomofarnesoates **1-3**, which was obtained from commercially available (+)-sclareolide [1].

Methyl esters **1-3** were subjected to anodic oxidation in presence of lithium perchlorate as a supporting electrolyte. Additionally to previously reported compounds **4** and **5** [2], a series of minor compounds **6-9** were isolated from the reaction mixture and characterized [1].

The electrochemical oxidation of esters **1-3** depends significantly on the reaction conditions, in particular, on the supporting electrolyte and the solvent. In the case when the anodic oxidation of methyl esters **1-3** were performed in a mixture of AcOH-Ac_2O (5:1) and presence of AcONa, the products **4**, **10-13** were obtained in depicted yields (Scheme).

The structures of all synthesized compounds were fully confirmed by spectral methods of analysis (IR, ^1H and ^{13}C NMR and GS-MS).



Reagents and conditions: a. $LiClO_4$, MeOH, ē, 5h; b. AcONa, Ac_2O, AcOH glac., ē, 5h.

Scheme

The above examples confirm that electrochemical transformations are a suitable alternative for the synthesis of terpene compounds by processes belonging to the field of "green chemistry".

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab09 **Oral Presentation**

MOLECULAR ARCHITECTURE OF CHIRAL OXINDOLES AS A FACILE PLATFORM TO NEW DRUG CANDIDATES

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Oxindoles have been a rich source of leads in support of drug discovery efforts and many natural product derivatives have gone onto clinical development. Their rich structural and stereochemical characteristics make them valuable as templates for exploring novel molecular diversity. We have focused on the use of multi-component coupling strategies, due to the ease with which the heterocyclic core structures are formed, allowing both the directed synthesis of natural products and the parallel synthesis of analog libraries. A hybrid drug can have two or more partners, which are assembled covalently with or without a linker. Individual partners of the hybrids should act synergistically to improve the desired pharmacological activity and the hybrid design should follow an in-depth knowledge of the merits and drawbacks of individual partnering of drugs/functional entities with a view to improve the pharmacological efficacy and alleviate the toxicity through the new design. Quinolines are an important group of alkaloid natural products, due to their diverse range of biological activity and structural complexity. A similar strategy was employed for the synthesis of quinolines hybrids by variation of the oxindoles and natural terpene as well. We will present how structural hybridization of small molecule oxindoles has emerged as a promising tool to develop new generations of chiral drug candidates.

Acknowledgements

The author is grateful for the funding of this research under the Moldovan State Program (ANCD) project 20.80009.5007.17

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http://dx.doi.org/10.19261/nfnpc.2021.ab10 **Oral Presentation**

PHYTOCHEMICAL STUDY AND ANTIOXIDANT ACTION OF *LAVANDULAE ANGUSTIFOLIAE* RESIDUES

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Lavender industrial processing involves steam distillation of oil and vegetal residues are normally discarded unvalorized. Lavender wastes have been paid little attention from the point of view of secondary metabolites recovery. The available literature date report mostly on the quantification of phenolics and evaluation of antioxidant potential in crude or fractionated extracts [1]. Few data are available on the influence of pretreatment procedures of vegetal raw material on extraction yield, while triterpenic acids are totally overlooked in the characterization and application schemes [2]. The current work presents the chemical analyses of 2 lavender residues with different extraction methods and pretreatment procedures. The extraction yield and content of the secondary metabolites was evaluated. The content of ursolic and oleanolic acids has been demonstrated both chromatographically (TLC, GC-MS) and spectroscopically (NMR). The total phenolic content was determined by the Folin-Ciocalteu method and flavonoids (based on aluminum chloride complex) and measured by UV-visible spectrophotometer. Antioxidant activity was determined by three methods: DPPH, ABTS and metal chelating activity [3]. The results confirms that the residues can be used as a source of polyphenols and the *Lavandulae R-1* residue has a higher content of polyphenols expressed in gallic acid (2.19%) and flavonoids expressed in rutin (2.03%), followed by *Lavandulae R-2* residue, with a polyphenol content (1.12%) and flavonoids (1.43%) in correlation with the antioxidant action (Table 1). Lower absorbance of the reaction mixture indicated higher free radical activity for *Lavandulae R-1* residue.

Table 1. Antioxidant activity of *Lavandulae* residues.

Samples	*DPPH, IC_{50} µg/ml*	*ABTS, µM TEAC/g*	*Metal chelating activity, µM/g*
Lavandilae R1	96.651±0.121	27.556 ±0.012	75.145±0.016
Lavandulae R1	103.241 ±0.132	32.267±0.023	71.062±0.021
Trolox	5.032 ±0,003	-	-
EDTA	-	-	98.66

Acknowledgments

This work was funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova: projects PLANTERAS, code 20.80009.8007.03.

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http://dx.doi.org/10.19261/nfnpc.2021.ab11 **Oral Presentation**

MOLLECULAR REARRANGEMENTS IN THE SYNTHESIS OF BIOACTIVE TERPENOIDS WITH NEW CARBON SKELETONS

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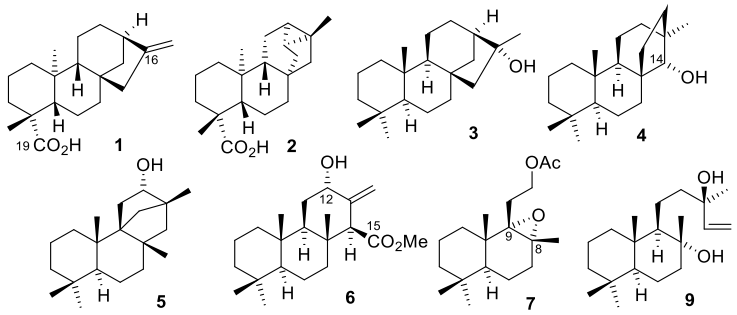
Diterpenoids represent one of the most numerous and important classes of natural terpenoids, both from theoretical and practical point of view. These are widespread all over the earth, including microorganisms and lower plants, aquatic and terrestrial organisms [1,2]. Many representatives have found vast applications in pharmaceutical industry, perfumery and cosmetics, as well as in food production.

An important path for accessing policyclic diterpenoids is represented by molecular rearrangements under the action of electrophilic agents, including both conventional and Lewis acids and also superacids. Molecular rearrangements of cyclic diterpenoids lead as a rule to diterpenic compounds with modified skeletons, including unprecedented ones. Basing on such strategies, a series of work has been demonstrated, leading to molecular rearrangements of a series of natural diterpenoids, such as *ent*-kaur-16-en-19-oic (**1**) and *ent*-trachiloban-19-oic (**2**) acids [3], as well as phillocladan-16-ol (**3**) [4], (1R,2S,7S,10S,12S)-2,6,6,12,12-pentamethyl-tetracyclo[10.2.1.01,10.02,7]-eicosan-11-ol (**4**) [5], hiban-14□-ol (**5**) [6], methyl 12-hidroxi-*ent*-isocopal-13(16)-en-15-oate (**6**) [7] and (5S,8R,9S,10S)-8,9-epoxi-12-acetoxybiciclohomofarnesane (**7**) [8,9] – diterpenoids obtained synthetically from (-)-sclareol (**9**). The possible mechanisms for the formation of new structures resulting from molecular rearrangement reactions have been hypothesized.



Acknowledgements. Authors express gratitude to the National Agency for Research and Development (ANCD) for financial support (project PLANTERAS, code 20.80009.8007.03).

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http://dx.doi.org/10.19261/nfnpc.2021.ab12 **Oral Presentation**

THE USE OF NON-CONVENTIONAL METHODS FOR THE ISOLATION OF CHROMATOGRAPHICALLY INSEPARABLE COMPOUNDS

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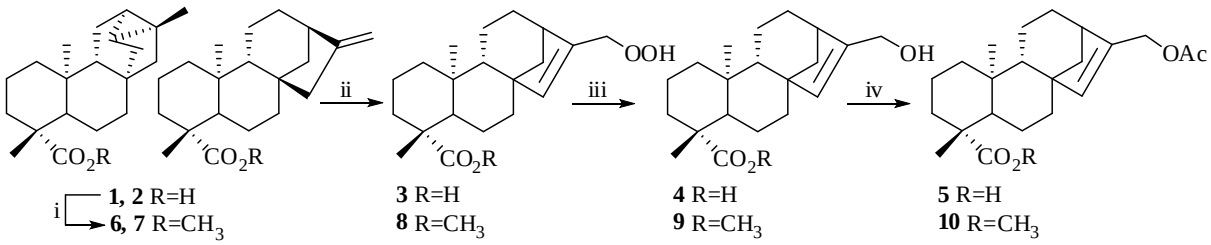
Frequently, in the case of extracts from natural sources, but also in the case of synthetic products, researchers face the problem of isolating some structures, which are inseparable chromatographically. For these cases, one of the solutions is their selective chemical separation, according to the model "*reactive-inert*" or their derivatization into separable reaction products.

The purpose of this study was to demonstrate the usefulness of unconventional chemical methods, especially of sensitized photooxidation in solving this problem.

Thus, *ent*-trahiloban-19-oic (**1**) and *ent*-kaur-16-en-19-oic (**2**) acids can be obtained in sufficient quantities from sunflower (*Helianthus annuus* L.) waste in the form of a mixture of ~1: 2, but isolating them in pure form is quite difficult [1,2].

For this reason, chemical separation of compounds **1** and **2** was attempted, applying sensitized photooxidation. In these conditions, only *ent*-kaur-16-en-19-oic (**2**) reacts, giving corresponding hydroperoxide **3**, in 61% yield (Scheme). Compound **3**, by a cascade of reaction was converted in alcohol **4** and its acetate **5**, in high yields. In such a way, the ratio on compound **1** and **2** after photooxidation reaction, according to GC-MS analysis, changed into ~2:1.



Reagents and conditions: i. CH_2N_2, Et_2O, 1 h, r.t., 99%; ii. O_2, TPP, hν, DCM, 7 h, 5°C, 61%; iii. Thiourea, MeOH, 5 h, r.t., 83%; iv. Ac_2O, Py, 24 h, r.t., 93%.

Scheme

The same transformations were done in a series of methyl esters **6** and **7** in comparable yields. Looking to the results, it much be concluded that sensitized photooxidation may be a useful tool for isolation of chromatographically inseparable compounds.

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab13 **Oral Presentation**

LATE STAGE FUNCTIONALIZATION OF UNACTIVATED C-H BONDS IN TERPENES – A FRUITFUL FIELD FOR FREE RADICAL CHEMISTRY

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Terpenoids are a large group of natural products with a broad structural diversity which are biosynthetically produced in living cells over a multistep sequence of events. The expansion of terpenoids structures, which are based on similar elementary building blocks, is due to an array of isomerizations and selective functionalizations/degradations of isoprenic chains, leading to cycles, chiral centers and heteroatomic functional groups. These transformations can be hardly reproduced synthetically and free radical processes represent an efficient tool to trigger both cyclization and functionalization events.

The current communication will present our results on application of free radical chemistry in order to achieve selective late stage C-H functionalizations in higher terpenes. Radical relay processes proved efficient for remote functionalization of sesterterpenes of scalarane family. An alternative approach relates to the well-known Atom Transfer Radical Addition (ATRA), which turned out to be an excellent opportunity for long range remote functionalization under different reaction settings. It occurs through a parallel Hydrogen Atom Transfer (HAT), which allows free radical migration to both primary and tertiary positions. Different HAT sequences have been observed, including an unprecedented 3-fold 1,5-HAT, leading to a distal functionalization of *epi*-manoyloxide. Application of visible light fotoredox catalysis showed compatibility with ATRA-HAT sequence, demonstrating the free radical character of fotoredox processes. The steric factors have been found to be crucial for a successful application of ATRA-HAT strategy. Functionalized derivatives of both manoyloxide and *epi*-manoyloxide have been obtained.

Acknowledgements. This work has been partially funded by the National Agency for Research and Development (ANCD), project PLANTERAS, code 20.80009.8007.03 (VK, CC, OM, VG and NU). Authors were partly supported by the Swiss National Science Foundation, project IZ73Z0_152346/1 (SCOPES program).

http://dx.doi.org/10.19261/nfnpc.2021.ab14 **Poster**

BENZO[*F*]QUINOLINIUM SALTS: ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

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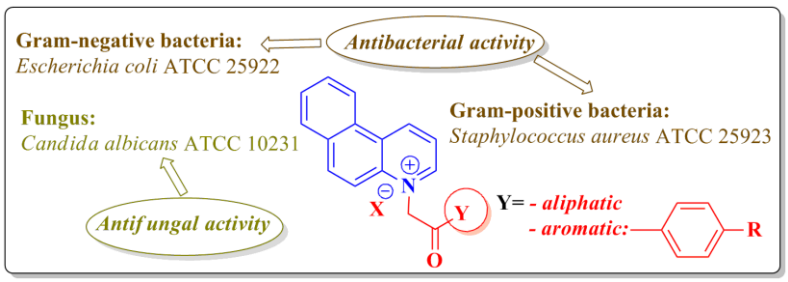
Infectious diseases, especially those caused by bacterial (*Gram positive* and *Gram negative*) and fungal microorganisms, have become a serious threat to the global health system, being responsible for about a quarter of all deaths worldwide. Benzo[*f*]quinoline and their derivatives, some of them being structurally analogues to the steroid skeleton, are very useful compounds in various fields of chemistry, including biological and pharmacological chemistry, as well as promising candidates for use in organic light emitting diodes [1-4].

Having in view the above mentioned, our main goal was to synthesize, characterize and testing of antimicrobial properties of novel benzo[*f*]quinolinium salts. Using a Bruker Avance III 500 spectrometer equipped with a 5 mm PABBO detection probe, operating at 500.1 MHz for ^{1}H and 125 MHz for ^{13}C, the structures of newly quaternary salts were proved by NMR experiments (^{1}H, ^{13}C, COSY, HMQC, HMBC).



The *in vitro* antimicrobial activity of benzo[*f*]quinolinium salts was determined by the method Kirby-Bauer disk diffusion, using nutrient agar medium: Mueller Hinton agar for antibacterial tests and Sabouraud agar for antifungal tests. The strain bacteria used for the antibacterial and antifungal activity are illustrated in the figure.

Acknowledgements. This work was supported by a grant of the Romanian Ministry of Education and Research, CNCS-UEFISCDI, project number PN-III-P4-ID-PCE-2020-0371, within PNCDI III. We also thank to CERNESIM Research Centre from Alexandru Ioan Cuza University of Iasi, for the NMR experiments.

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http://dx.doi.org/10.19261/nfnpc.2021.ab15 **Poster**

SYNTHESIS OF HYDRAZIDE CONTAINING TRINORLABDANE DERIVATIVES

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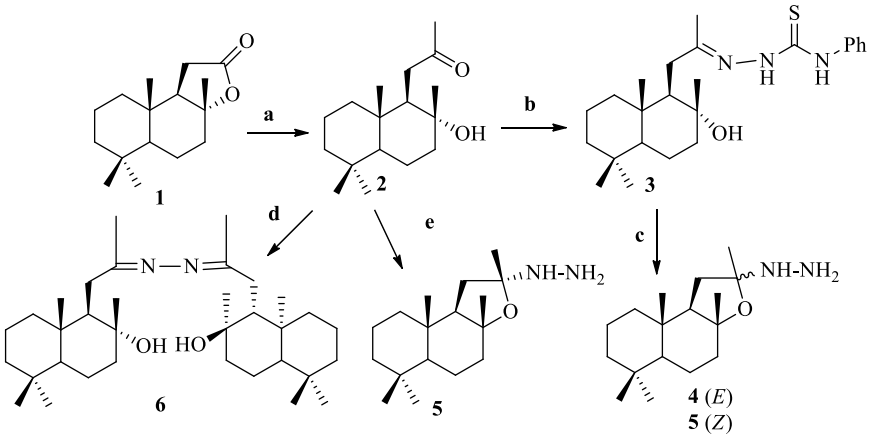
The starting material for the synthesis of trinorlabdane compounds with hydrazide fragments was used hydroxyketone (**2**) which was obtained from commercially available sclareolide (**1**). Ketone (**2**) was coupled with 4-phenylthiosemicarbazide in ethanol, to afford compound (**3**) (Scheme) [1]. Subsequently, instead of obtaining the coordination compound with thiosemicarbazone (**3**) and Co(II) salt in the presence of hydrogen peroxide, a mixture of two hydrazides (**4**) and (**5**) was obtained.



Reagents and conditions: *a*. CH_3Li/Et_2O, r.t., 15 min., 65%; *b*. $NH_2NHCSNHC_6H_5$, EtOH, 6 h, 60°C, 76%; *c*. $CoCl_2 \cdot 6H_2O$, MeOH, H_2O_2 30%, r.t., 5 min, **(4)** 10%, **(5)** 30%; *d*. $N_2H_4 \cdot H_2O$, CH_3OH, Δ, 10 h, 80%; *e*. $N_2H_4 \cdot H_2SO_4$, MeOH, Δ, 50 min, H_2O_2 30%, 10 min, 60%.

Scheme

For this reason, the ketone (**2**) was treated with $N_2H_4 \cdot H_2SO_4$ in methanol, but in this case, only hydrazide (**5**) was obtained. In another case, hydroxyketone (**2**) was treated with $N_2H_4 \cdot H_2O$ in methanol, giving azine (**6**) described in [2].

The structure of obtained compounds have been established using modern methods of analysis (ATR-FTIR, ^1H, ^{13}C and ^{15}N NMR and GS-MS).

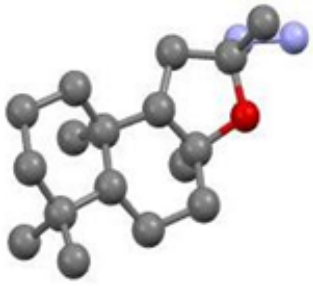


Figure 1. Molecular structure of compound **(4)**.

The structure and stereochemistry of the compound (**4**) was confirmed by X-ray diffraction on monocrystal (Figure 1).

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab16 **Poster**

NEW HYBRID QUATERNARY SALTS WITH PYRIDINE/BENZIMIDAZOLE SKELETON

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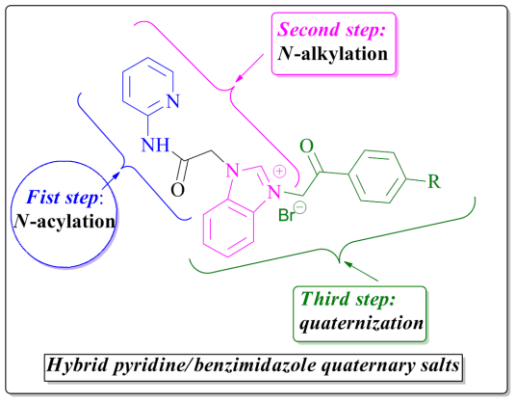
Pyridine and pyridine-derived skeletons represents an invaluable scaffolds in drug designing, and also an essential functionality for organic chemists [1]. Over the years, the chemistry of hybrid compounds containing imidazole/benzimidazole and pyridine moieties is developing, due to the fact that novel derivatives have important biological properties such as: anticancer, antimicrobial (antibacterial, antifungal, antitubercular), antimalarial, anti-inflammatory, antidepressant, analgesic, antihypertensive *etc.* [2-4].

Considering the above, our main objective was to synthesize and characterize novel hybrid quaternary salts with pyridine/benzimidazole skeleton adopting a general and straightforward strategy, involving three steps: I) *N*-acylation of 2-aminopyridine; II) *N*-alkylation of benzimidazole; II) quaternization reactions with halogenated derivatives with increased reactivity: *p*-substituted acetophenones. The structures of newly hybrid pyridine/benzimidazole quaternary salts were proved using NMR experiments (^{1}H, ^{13}C, 2D-correlations). The NMR apparatus (Bruker Advance III 500 spectrometer) is equipped with a 5 mm PABBO detection probe, operating at 500.1 MHz for ^{1}H and 125 MHz for ^{13}C.



Acknowledgements. This work was supported by a grant of the Romanian Ministry of Education and Research, CNCS-UEFISCDI, project number PN-III-P4-ID-PCE-2020-0371, within PNCDI III. We also thank to CERNESIM Research Centre from ”Alexandru Ioan Cuza” University of Iasi, for the NMR experiments.

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http://dx.doi.org/10.19261/nfnpc.2021.ab17 **Poster**

PYRROLO-FUSED HETEROCYCLIC DERIVATIVES: DESIGN, SYNTHESIS AND ANTICANCER EVALUATION

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Natural compounds with quinoline and isoquinoline scaffolds have demonstrated numerous biological activities and have found use in both medical research laboratories and clinical practice throughout the world [1]. In particular, semisynthetic pyrroloquinoline derivatives are currently widely accepted as first line treatments for anticancer therapy, including camptothecin derivatives irinotecan and topotecan, with many others currently being investigated as potent antiproliferative agents [2]. In addition to pyrrolo(iso)quinolines, which unsurprisingly lie at the center of various synthetic organic chemisty efforts for further improvement of biological activity, including our own group’s [3], other heterocyles can be considered for pyrrole fusion in order to maximize selectivity to targets and improve biological effects, including benzo[*f*]quinoline, pyrazine and pyrimidine [4].

We describe herein the design, synthesis and anticancer evaluation of novel pyrrolo-fused heterocycles based on quinoline, isoquinoline, benzo[*f*]quinoline, pyrazine and pyrimidine. We furthermore show that the most active compound from the whole series (pyrrolo[1,2-*a*]quinoline **10a**) inhibits tubulin polymerization *in vitro* and we describe the *in silico* molecular interactions with tubulin in order to understand the mechanisms behind its antiproliferative activity.

Acknowledgements. This work was supported by a grant of the Romanian Ministry of Education and Research, CNCS-UEFISCDI, project number PN-III-P4-ID-PCE-2020-0371, within PNCDI III. The authors also thank Romanian Ministry of Research and Innovation, Program 1 - Development of the national R&D system, Subprogram 1.2 - Institutional performance - RDI excellence financing projects, Grant no. 34PFE for financial support and CERNESIM Research Centre from “Al. I. Cuza” University of Iasi, for NMR experiments.

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http://dx.doi.org/10.19261/nfnpc.2021.ab18 **Poster**

GC-MS ANALYSIS OF THE ESSENTIAL OIL OF *MENTHA PIPERITA L.* OF VIETNAM ORIGIN

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For the first time the results of GC-MS analysis of special simple of the *Mentha piperita* L. oil from Vietnam origin product from year 1975 are reported.

The analysis was carried out on an Agilent Technologies 7890A system with 5975C MSD equipped with split-splitless injector (split, 250°C, split ratio 1:50, 0.1 μL) and HP-5 ms capillary calibrated column (30 m x 0.25 mm x 0.25 μm); The carrier gas: helium 1.1 mL/min; oven: 70°C - 2 min, 5°C/min - 200°C - 20 min - 300°C - 5 min; MSD in scan 30 - 300 amu, 15 min, 30 - 450 amu.

The obtained chromatogram was compared to the results from the literature [1,2], and it differs by composition (mass spectra) and the ratio (A%) of the identified compounds. The major compounds detected by mass-spectometry are: (-)-Menthone (5.47%); Neoisomenthol (7.69); (-)-Menthol (52.25%); (+)-*iso*-Menthol (0.94%); *iso*-Menthol acetate (2.11%); Myristic acid (1.05%); Isopropyl myristate (9.97%) and new discover compounds: Ciclohexanol, 5-methyl-2-(1-methylethyl)-sulphite (2:1) (0.53%); Acetylene dicarboxilic acid, di-(-)-menthyl- (0.53%); *p*- Menthone; 3-allylperoxy (6.79%); Diazoacetic acid, 2-isopropyl-5-methylciclohexyl ester (0.44%).

The obtained results show that during long storage (about 45 years) under normal conditions sealed at room temperature, the oil will be altered due to catalytic and oxidative processes (photocatalysis, peroxidase and others).

Acknowledgements

I.D. acknowledges financial support of the National Agency for Research and Development (ANCD) of the Republic of Moldova, project PLANTERAS, code 20.80009.8007.03.

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http://dx.doi.org/10.19261/nfnpc.2021.ab19 **Poster**

NEW CYTOTOXIC *ENT*-KAURANES WITH UNPRECEDENTED PHARMACOPHORES

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The cytotoxicity of *ent*-kauranic derivatives functionalized with azide, lactam and pyrrolidine fragments has been demonstrated. The inverstigated compounds showed relevant activity against Capan-1 (pancreatic adenocarcinoma), Hap-1 (chronic myeloid leukemia), HCT-116 (colorectal carcinoma), NCI-H460 (lung carcinoma), DND-41 (acute lymphoblastic leukemia), HL-60 (acute myeloid leukemia), K-562 (chronic myeloid leukemia), and Z-138 (non-Hodgkin lymphoma) cancer cell lines. The selectivity index was demonstrated by higher IC_{50} values in normal retina cells (hTERT RPE-1).

The *ent*-kauranic azides **1** and **2** have been synthesized by radical carboazidation reactions using two different methods: first with hexabutylditin as radical transfer reagent and di-*tert*-butyl hyponitrite (DTBHN) as radical initiator and the second with triethylborane in the presence of air [1, 2]. Compounds **1** and **2** were converted to lactams **3** and **4**, the lactam **3** was reduced to pyrrolidine **5**.

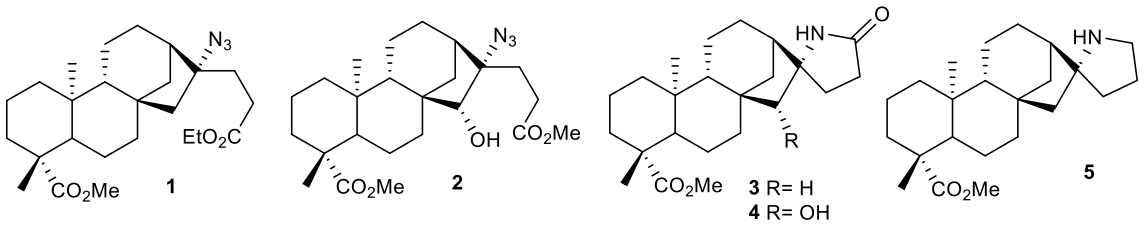

Figure 1

Compounds **1** - **5** presented in Figure 1 are air- and moisture stable, soluble in DMSO and other organic solvents.

Acknowledgments

This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development (ANCD).

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http://dx.doi.org/10.19261/nfnpc.2021.ab20 **Poster**

FREE RADICAL FUNCTIONALIZATIONS OF LABDANES AND RELATED DITERPENOIDS

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Free radical transformations are intensively explored nowadays as efficient synthetic tools provided the broad range of potential transformations, mild reaction conditions and high functional group tolerance.

Synthesis and structural modification of natural products provide a fruitful field for atom transfer radical addition (ATRA) methodology and in our opinion this potential is underexplored. There is still prevalence in the scientific publications of ionic processes reported for assembling C-C bonds in complex molecular frameworks, although successful examples involving ATRA are also known in natural product synthesis [1]. Sometimes radical additions represent the only solutions to overcome synthetic challenges connected to substrate reactivity and stereochemistry issues [1].

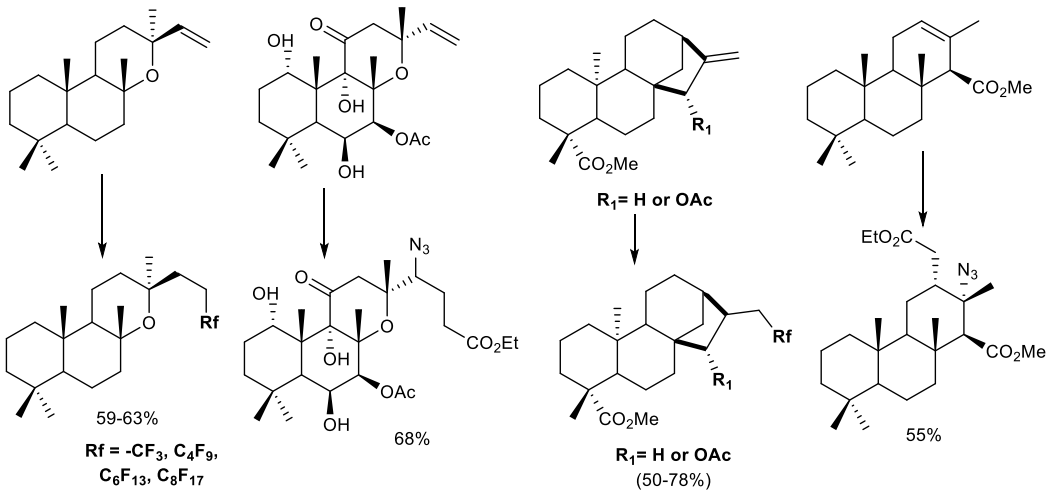

Figure 1. Radical transformation of labdane diterpenoids.

ent-Kauranic, isocopalic and labdane derivatives (Figure 1) were modified *via* ATRA processes. An array of functionalized derivatives, including azides and fluorinated compounds have been obtained in good yields and will be further involved in biological activity testing.

Acknowledgments

This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab21 **Poster**

EXTRACTION OF PHARMACEUTICAL GRADE LIGNINS AND THEIR OZONOLYTIC CLEAVAGE IN A DEEP EUTECTIC SOLVENT

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Lignins are currently considered promising biomaterials for pharmaceutical industry [1,2]. The main advantages they offer, relate to natural origin, biocompatibility and biodegradability. This is connected to their potential use as both enterosorbents and efficient drug careers. Besides, lignins alone possess antioxidant, antimicrobial, antiviral activities and low cytotoxicity.

From the structural point of view, lignins represent oxygenated hetoropolymers with a highly heterogeneous tridimensional cross-linked network of aromatic monomers. This is the main reason of their recalcitrance and low solubility in most solvents. In order to dissolve lignin, the polymeric network must be disassembled, that is usually achieved by harsh chemical action. As a result, the target biopolymer integrity is severely affected and its practical use limited.

We present in the current communication our results on the isolation of natural lignins from the wastes of agricultural and forestry production, including common spruce (*Picea abies*) bark and de-fated grape (*Vítis vinífera*) seeds, and their following ozonolytic cleavage leading to new analogues with improved properties.

The selected extractive agent and ozonolysis media was a nontoxic deep eutectic solvent (DES) composed of choline chloride and 1,2-propyleneglycol. DESs are considered green solvents and are especially suitable for lignin dissolution due to their high boiling points that makes possible extractions to be efficiently run at elevated temperatures.

The lipophilic and low-molecular weight polyphenolic compounds have been extracted with suitable solvents prior to lignin recovery. The pretreated materials have been suspended in the DES and kept at 160^{o}C for 4 hours on continuous stirring. The obtained lignin solution was filtered while hot through a steel course filter in order to separate insoluble polysaccharides and tar. The homogenous solution was used either for unmodified lignin sedimentation or ozonolytic treatment. It was performed on ozone bubbling at 0–5^{o}C for 60 minutes.

The resulting polymeric fractions have been investigated by spectral methods (IR and NMR). In particular, heteronuclear HSQC and DOSY experiments allowed to draw important conclusions on structural changes of native lignin after ozonolysis. The partial degradation of polymeric structures has been demonstrated.

Acknowledgments

This work was funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova, project PLANTERAS, code 20.80009.8007.03.

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http://dx.doi.org/10.19261/nfnpc.2021.ab22 **Poster**

THE USE OF qNMR SPECTROSCOPY FOR ANALYTICAL EVALUATION OF NATURAL EXTRACTS. THE CASE OF APPLE POMACE

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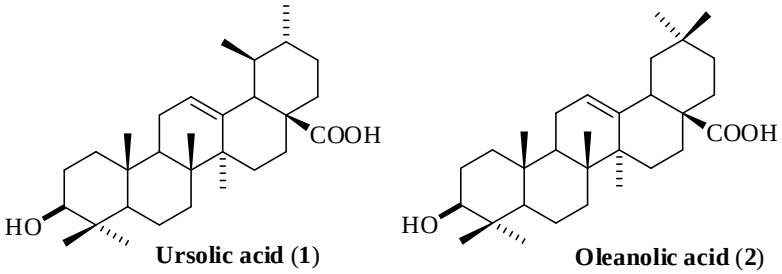
NMR spectroscopy is a convenient method for structural identification of both individual compounds and complex natural products mixtures. The main advantages of this powerful analytical tool are, among others, high resolution power, as well as simultaneous qualitative and quantitative evaluation of the investigated sample [1].

The current work presents the determination of ursolic **1** and oleanolic **2** acids content in apple pomace extracts basing on fast and reliable 2D NMR correlations [2]. Both triterpenic acids are present in the apple skins [3] and their biological activity spectrum is well known. Due to very similar chemical structure, simultaneous determination of acids **1** and **2** by routine techniques poses significant challenges which requires additional efforts and complex solutions.



Ursolic acid (1) **Oleanolic acid (2)**

The crude apple pomace was air dried in shade, grinded into a fine powder and extracted with EtOAc on combining cyclic passive macerations with ultrasonic irradiations on heating. Total extraction time did not exceed 3 hours. An aliquot of the crude extract was submitted to preparative chromatography on silica gel in order to isolate a pure mixture of **1** and **2** (cca. 30 % of total extract).

The content of individual acids **1** and **2** was determined basing on the 2D NMR (^{1}H-^{13}C HSQC) quantitative experiment on integration of 2D-plots of diagnostic signals corresponding to individual acids. Methyl paranitrobenzoate was used as internal standard and the calibration plots have been drawn separately for each acid. Basing on these data, determination of **1** and **2** was performed in both purified fractions and crude EtOAc-extracts from apple pomace. Obtained results showed identical data with parallel GC-MS experiments.

Acknowledgments

This work was funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova: projects PLANTERAS, code 20.80009.8007.03 (MG, NU and VK) and RedoxPro, code 20.80009.5007.27 (AB and GD).

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http://dx.doi.org/10.19261/nfnpc.2021.ab23 **Poster**

STUDIES OF STARFISH POLAR STEROIDS: STRUCTURES, BIOLOGICAL ACTIVITY, AND METABOLIC PROFILING

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Starfish (class Asteroidea, phylum Echinodermata) are a rich source of polar steroids, diverse in their chemical structure, which differ significantly from steroid metabolites of land plants and other animals, including those of marine origin, which indicates unusual pathways of their biosynthesis. In continuation of our studies of biologically active secondary metabolites of marine invertebrates, our research group over the past few years isolated several dozen new polar steroids of various structural classes from Far Eastern and tropical starfish and established their structure, including absolute stereochemistry. For a number of these compounds different type of biological activity was investigated.

In particular, substances belonging to rare structural types were found. Thus, rare cyclic glycosides luzonicosides B–E were isolated from the starfish *Echinaster luzonicus*. Their isolation almost doubled the number of representatives of this unique structural group of polar steroids. Rare anthenosides were found in starfishes of the genus Anthenea, for example, anthenosides L–U from *Anthenea aspera*, and their cancer-preventive activity was studied. A unique glycoside granulatoside C was isolated from the starfish *Choriaster granulatus*, which combines the characteristic structural features of several different types of polar steroids from different marine invertebrates. New asterosaponins, pentaregulosides B and C, with furostanic aglycones, characteristic of terrestrial plants, but not previously found in marine oligoglycosides, were discovered from the starfish *Pentaceraster regulus*. Pentareguloside C was shown apparent immunomodulatory effects. New conjugates, esters of polyhydroxysteroids with long-chain fatty acids, were isolated from the deep-water Far Eastern starfish *Ceramaster patagonicus.* These compounds effectively suppressed colony formation and migration of human cancer cell lines.

Our experience in structural studies of polar steroids of starfish allowed us to carry out metabolic profiling method for investigation of metabolite profiles of polar steroids of some Far Eastern starfishes. We demonstrated that LC-ESI MS and LC-ESI MS/MS approach are quite applicable for the profiling of starfish polar steroid compounds in such complex mixtures as starfish extracts and useful for searching of new structures, comparing metabolomic profiles of different marine animal species and populations for ecological, dietary and biosynthesis studies.

http://dx.doi.org/10.19261/nfnpc.2021.ab24 **Poster**

IN VITRO EVALUATION OF *LAVANDULA AUGUSTIFOLIA* AND *HIPPOPHAE RHAMNOIDES* EXTRACTS ON PROMOTION OF BONE MARROW MESENCHYMAL STEM CELLS PROLIFERATION

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Chemical substances of natural origin represent an efficient cell proliferation tool and a lot of studies have been reported in this direction [1]. In particular, natural terpenoids showed effective in numerous studies on wound healing and other tissue engineering [2]. Lavender (*Lavandula Augustifolia*) and sea-buckthorn (*Hippophae rhamnoides*) are two plants broadly used in folk medicine for wound healing and other therapeutic and preventive purposes, predominantly in the form of essential or fatty oils [3,4]. Few studies report on the cell proliferative effect of other extracts derived from these abundant natural sources.

The aim of this investigation is to test in vitro the action of extracts of *Lavandula Augustifolia* wastes and *Hippophae rhamnoides* seeds in concentration of 500 µg/mL, 100 µg/mL, 20 µg/ml and 4 µg/mL on mesenchymal stem cells from rabbit bone marrow. The cells isolation was performed according to the method proposed by Cobzac and the authors [1] with the positive opinion of the Etics Committee of 14.12.2016, no.31. Cell viability was determined by the MTT test after Mosmann [2].

According to the results of the MTT test, in all extracts compared to the control, the highest cell viability is attested at concentration of 4 µg/ml at interval of 24, 48 and at 72 hours the viability exceeds 100% which denotes a potential positive effect on cell viability over time. It should also be noted that the least cytotoxic action has the extract of *Hippophae rhamnoides* both at concentrations of 4 µg/mL and 20 µg/mL compared to other extracts, which would allow their more detailed research on *in vivo* model.

Acknowledgments

This work was funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova: projects PLANTERAS, code 20.80009.8007.03.

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http://dx.doi.org/10.19261/nfnpc.2021.ab25 **Poster**

SYNTHESIS OF SOME HOMODRIMANE SESQUITERPENOIDS WITH DIHYDRAZIDE FRAGMENT FROM NORAMBREINOLIDE

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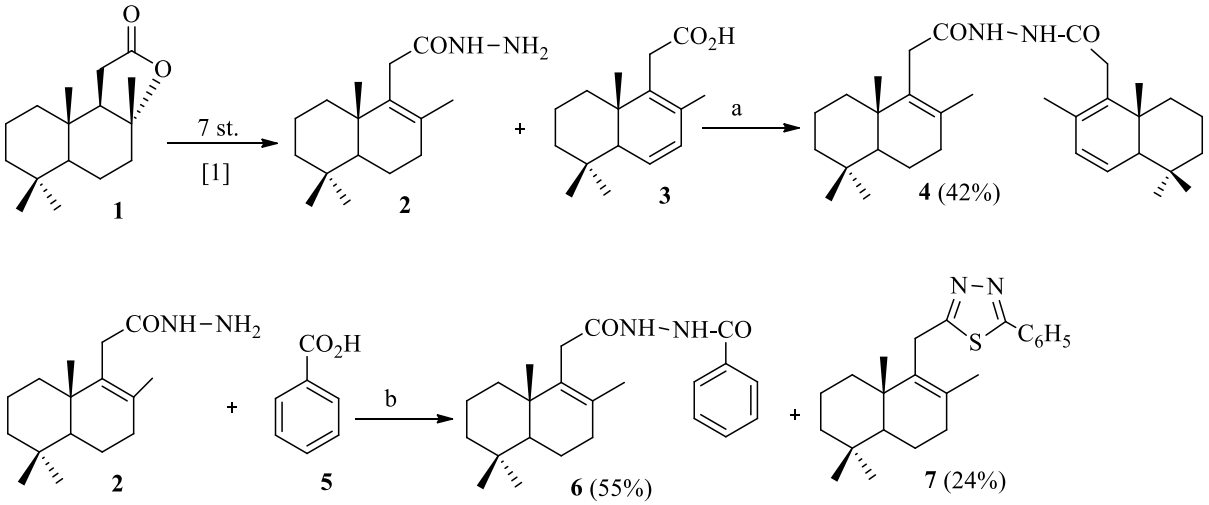
In a search of new biologically active compounds, in the present communication we describe the synthesis of N-(Δ^8-bicyclohomofarnesenoyl)-N′-Δ(^{6,8}-bicyclohomofarnesenoyl)-hidrazine (**4**), N-(Δ^8-bicyclohomofarnesenoyl)-N′-benzoyl-hidrazine (**6**) and 2-phenyl-5-(Δ^8-bicyclohomofarnesenyl)-1,3,4-thiadiazole (**7**) from commercially available norambreinolide (**1**), according to the scheme:



Reagents and conditions: a. P_2S_5, Et_3N, T3P, EtOAc, Δ, 10 h; b. Vilsmeier reagent, Et_3N, Lawesson′s reagent, THF, 20°C, 20 h.

Dihydrazide (**4**) was obtained by interaction of Δ^8-bicyclohomofarnesoic acid hydrazide (**2**) with $\Delta^{6,8}$-bicyclohomofarnesoic acid (**3**). Reaction of hydrazide (**2**) with benzoic acid lead to dihydrazide (**6**) and 2-phenyl-5-(Δ^8-bicyclohomofarnesenyl)-1,3,4-thiadiazole (**7**).

The structures of the newly obtained compounds were established on the basis of their spectral date (IR, ^{1}H- and ^{13}C-NMR, mass-spectra).

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab26 **Poster**

SYNTHESIS OF SOME NEW HOMODRIMANE DERIVATIVES OF BENZOTHIAZOLE FROM NORAMBREINOLIDE

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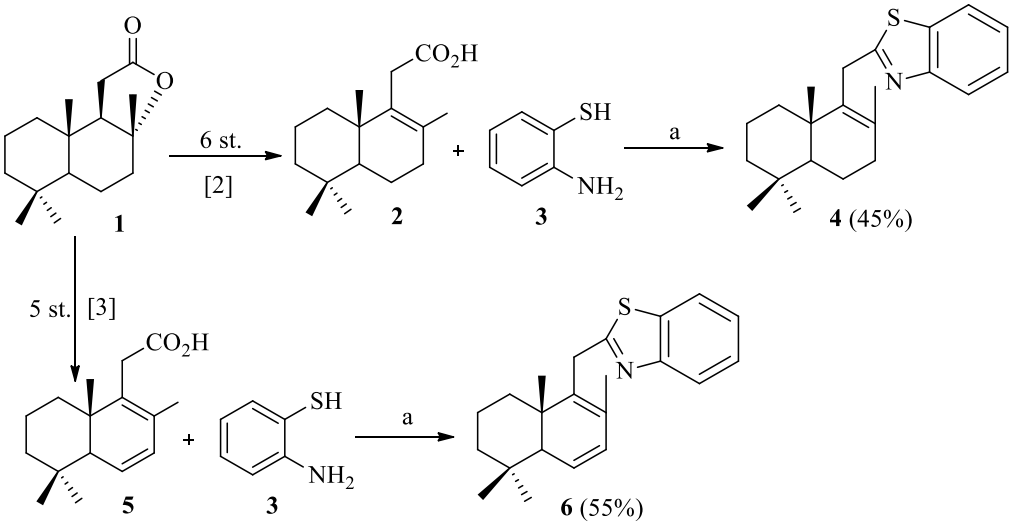
Many drimane and homodrimane sesquiterpenoids, including those containing nitrogen, are known to exhibit a variety of biological activities [1]. The search of new biologically active compounds prompted us to synthesize homodrimane sesquiterpenoids (**4**) and (**6**), containing benzothiazole fragment. Starting Δ^8-bicyclohomofarnesoic acid (**2**) and $\Delta^{6,8}$-bicyclohomofarnesoic acid (**5**) were obtained from commercially available norambreinolide (**1**). Reaction of these acids with 2-aminothiophenole (**3**) produce 2-(Δ^8-bicyclohomofarnesyl)-benzothiazole (**4**) and 2-($\Delta^{6,8}$-bicyclohomofarnesyl)-benzothiazole (**6**), accordingly.



Reagents and conditions: a. Ph_3P, Et_3N, CCl_4, Δ, 4 h.

The structures of the newly obtained compounds were established on the basis of their spectral date (IR, ^{1}H- and ^{13}C-NMR, mass-spectra).

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab27 **Poster**

SELECTIVE SYNTHESIS OF 13-*epi*-MANOYL OXIDE

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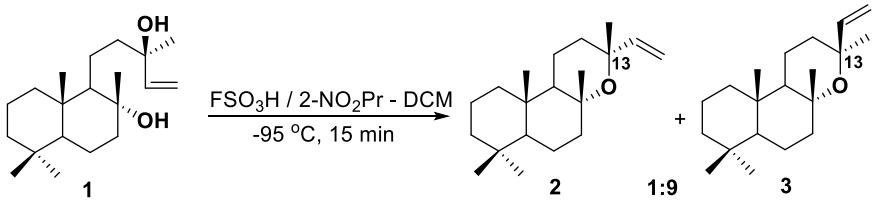
Labdane-type diterpenes are excellent examples of natural products with important pharmaceutical activities. Besides, several labdanes are quite abundant in nature and/or are commercially, such as sclareol **1**. Hence, they are useful starting materials for chemical transformations.

On the other hand, manoyl oxide **2** and 13-*epi*-manoyl oxide **3** are labdane compounds with skeleton identical to forskolin – a secondary metabolite isolated from *Coleus forskohlii* plant and showing a myriad of therapeutic activities [1], and other relevant natural compounds reported in structure-activity relationship (SAR) [2,3]. We have also demonstrated recently a free-radical procedure for structural modification of both forskolin and manoyl oxides [4,5] leading to an unusual distal functionalization of *13-epi-* framework. In order to explore the full potential of such late-stage functionalization, one needs reliable sources of *13-epi*-manoyl oxide **3**, which ideally is made available via selective synthesis.

The current work presents the selective one-step synthesis of *13-epi*-manoyl oxide **3** basing on a low-temperature superacidic cyclization of sclareol **1** (Scheme 1). An older contribution of some of us reported an equimolar mixture of epimers [6]. Now, the reaction conditions have been finely tuned in order to achieve a 9:1 ratio in favor of the desired *13-epi*-oxide **3**. The preparative value of the elaborated procedure was convincingly demonstrated.



Scheme 1

Acknowledgments

This work was funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova: projects PLANTERAS, code 20.80009.8007.03 (OM, MS, NU and VK) and RedoxPro, code 20.80009.5007.27 (AB and GD).

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http://dx.doi.org/10.19261/nfnpc.2021.ab28 **Poster**

CHEMICAL COMPOSITION OF ESSENTIAL OIL OF DILL (*ANETHUM GRAVEOLENS* L.) GROWING IN REPUBLIC OF MOLDOVA

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The species *Anethum graveolens* L., commonly known as Dill, includes annual herbs belonging to the family *Umbelliferae*. This plant is native to the Mediterranean and Western Asia, having a long history of cultivation and use as a spice and medicinal plant, and now its area has spread to all continents [1]. In Republic of Moldova, the Dill is cultivated on small areas, and due to its high multiplication capacity, it often appears as a spontaneous plant [2].

Essential oil and extracts from *A. graveolens* plants have various biological activities, such as antibacterial, antifungal, antioxidant, insecticide, anti-inflammatory, antidiabetic, anticancer, antispasmodic, hypolipidemic, hypotensive etc. [1,3]. The essential oil obtained from *A. graveolens* plants are mainly used in the food industry for flavoring and seasoning [4].

The Dill essential oil can be extracted from the green plant with unripe fruits and from the dry fruits. Its composition can vary from 20 to 60 constituents, a mixture that gives the oil its characteristic perfume and aroma.

The essential oil of *A. graveolens* is obtained by hydrodistillation, with a yield of 0.4-1.2% from the green plant and 2.5-4% from the dry fruits. Dill essential oil is a colorless or yellowish liquid, with a characteristic aromatic, herbaceous odor, reminiscent of the smell of cumin [3].

According to the GC-MS analysis in the essential oil of *A. graveolens*, industrially produced in the Republic of Moldova, twenty-six components were detected, which represents 99.40% of its total composition. The terpenic fraction (99.40%) includes monoterpenic hydrocarbons (51.287%), among which α-phellandrene (21.47%) and *D*-limonene (26.96%) are highlighted. Their oxygenated derivatives constitute (47.80%), the main components being dill ether (12.16%) and *S*-(+)-carvone (31.72%). The least numerous are sesquiterpenoids (0.32%), the most abundant being D-germacrene (0.13%).

The variations of the main components of the essential oil of Dill depend on the raw material harvesting period, the growing conditions and the method of production. The differences between the essential oil of Dill produced industrially in the Republic of Moldova and these of Indian, Turkish, Egyptian origin are quantitative.

Acknowledgements. This work is part of the project PLANTERAS 20.80009.8007.03 within the State Program (2020-2023) financed by the National Agency for Research and Development.

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http://dx.doi.org/10.19261/nfnpc.2021.ab29 **Poster**

SYNTHESIS OF HYBRID MOLECULES BY INTERACTION OF 2-HYDROXY JUGLONE WITH TERPENOID ALDEHYDES

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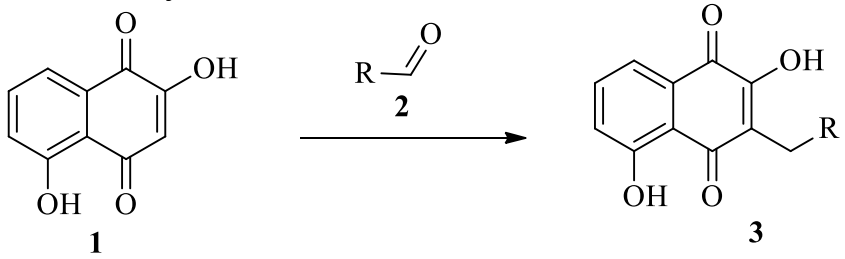
Currently, so-called "hybrid" molecules are of particular interest. The combination of some structure fragments with different biological properties in one molecule can lead to attractive results. For example, the effect of a drug may be enhanced, the range of its use may be expanded, side effects or resistance to it may be reduced.

In this work, we will focus on the synthesis of derivatives that will simultaneously contain in their structure the skeletal block of juglone and various terpenoids derivatives.

It is well known that juglone has a wide spectrum of biological activity, including antibacterial and antifungal properties [1]. Juglone containing ointments are used as anti-inflammatory, antibacterial and antifungal remedies [2]. Anticancer properties have been also detected for juglone by some researchers [3]. On other hand plant terpenoids are used for their aromatic qualities and play a role in traditional herbal remedies [4].

The main goal of this research was to study the reaction of 2-hydroxy-juglone **1** with terpenoid aldehydes **2** (citronellal, hydroxycitronellal, derivatives of sclareolactone) to obtain various hybrid molecules (Scheme). Reaction was performed in the presence of the Hantzsch ester and L-proline as catalysts.



Scheme. The synthesis of compounds 3.

The products were separated with application of the column chromatography. The structures of the obtained compounds were confirmed by application of different physico-chemical methods of analysis. The identity of the compounds has been established by various ^{1}H-, ^{13}C-NMR experiments including those bi-dimensional (COSY, HSQC, HMBC, NOE).

Acknowledgements. The work was carried out within the project 20.80009.5007.17 of the National Agency for Research and Development of Moldova (NARD).

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June 4, 2021
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Book of Abstracts
ISBN 978-9975-3336-7-2 (PDF)
DOI http://dx.doi.org/10.19261/nfnpc.2021