Ministry of Education and Research
Moldova State University
Institute of Chemistry

Scientific seminar with international participation

NEW FRONTIERS IN NATURAL PRODUCT CHEMISTRY

Book of Abstracts

October 12-13, 2023
Chișinău, Republic of Moldova

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VIIth edition

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VIIth edition

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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 Scientific Seminar „NEW FRONTIERS IN NATURAL PRODUCT CHEMISTRY" organized by the Laboratory of Chemistry of Natural and Biologically Active Compounds, Institute of Chemistry, Moldova State University. The 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 7-th edition.

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 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. This year we offer the seminar stage to younger researchers, actively involved in projects performed in the Institute of Chemistry and other partner research centers. Promoting the event in hybrid format is envisioned as an efficient tool for a larger audience, including local and international colleagues.

We are delighted to announce participation of several distinguished scholars 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 on other pleasant occasions, including the next editions of this seminar.

Dr. hab. Aculina ARÎCU
Director of the Institute of Chemistry,

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

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HYBRID AND CHIMERIC NITROGEN HETEROCYCLES WITH BIOLOGICAL ACTIVITY

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Nitrogen heterocycles, especially azine and azole derivatives, are highly valuable scaffolds in medicinal chemistry, being the core components of a large variety of drugs with variously 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 area of nitrogen heterocyclic derivatives, we present herein some representative results obtained by our group in the field of hybrid and chimeric azahetrocycles compounds with antimicrobial and anticancer activity. Chemistry, anticancer, antibacterial, antifungal and antituberculosis activity of compounds is presented. Some of the hybrid and chimeric structures possess a good anticancer and/or antimicrobial activity.

Acknowledgements. The authors are thankful for financial support to Romanian Ministry of Research, Innovation and Digitization, within Program 1—Development of the national RD system, Subprogram 1.2—Institutional Performance—RDI excellence funding projects, Contract no.11PFE/30.12.2021, and to CNCS - UEFISCDI, project number PN-III-P4-ID-PCE-2020-0371.

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PHOTOCHEMICAL TRANSFORMATION OF SOME (+)-LARIXOL DERIVATIVES

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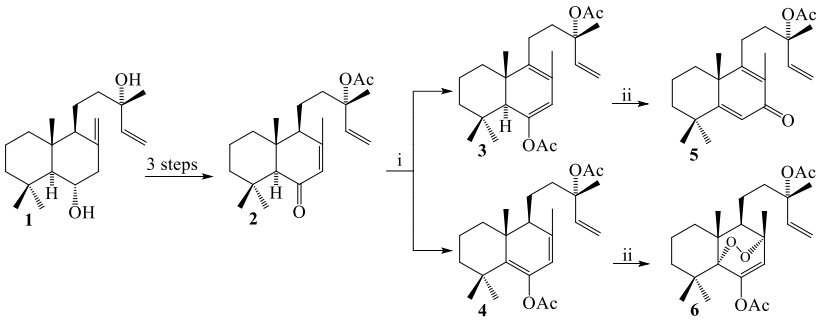
In terms of synthetic potential, (+)-larixol **1** outperform other labdanic diterpenoids due to the hydroxyl group at the C_6 position. Over the years, various chemical transformations have been performed on the basis of this compound, selectively or on both hydroxyl groups, or by modifying of the side chain [1-4]. Unlike the syntheses mentioned above, only a few are known with the preservation of the side chain or its rearrangement and functionalization in cycle B [5,6].

Herein, the syntheses of (+)-larixol **1** derivatives with an advanced degree of functionalization of the B cycle and preservation of the side chain will be described, by combining classical and nonconventional methods, such as sensitized photooxidation.

Starting from (+)-larixol **1**, in three steps the intermediate ketoacetate **2** was obtained in 86% overall yield. Next, compound **2** was subjected to the enolacetylation reaction, which led to undescribed before enolacetates **3** and **4** in depicted yields (see Scheme). Compounds **3** and **4**, due to their conjugated diene systems, were subjected to photochemical transformations. As result, α,α-dienone **5** was obtained as product of photooxidative dehydrogenation and endoperoxyde **6** as product of [4+2] cycloaddition of singlet oxygen.

The structures of all synthesized compounds were fully proved by spectral methods of analysis (IR, ^{1}H and ^{13}C NMR) and for compound **6**, additionally confirmed by XRD analysis.



Reagents and conditions: **i**) ≥-OAc, *p*-TsOH, N_2, 109°C, 13h, 49%, 41%.

ii) O_2, hν, H_2tpp, DCM, 12h, 82% and 78%.

Acknowledgements: This work is part of the project PLANTERAS 20.80009.8007.03 "New substances with preventive and therapeutic potential based on natural compounds of plant origin and modern methods of organic synthesis" within the State Program (2020-2023) financed by the National Agency for Research and Development

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https://doi.org/10.19261/nfnpc.2023.ab03 **Oral Presentation**

SYNTHESIS OF 1,3-PHENYL(PYRIDYL)PROPENONES WITH THIOSEMICARBAZIDIC GROUPS

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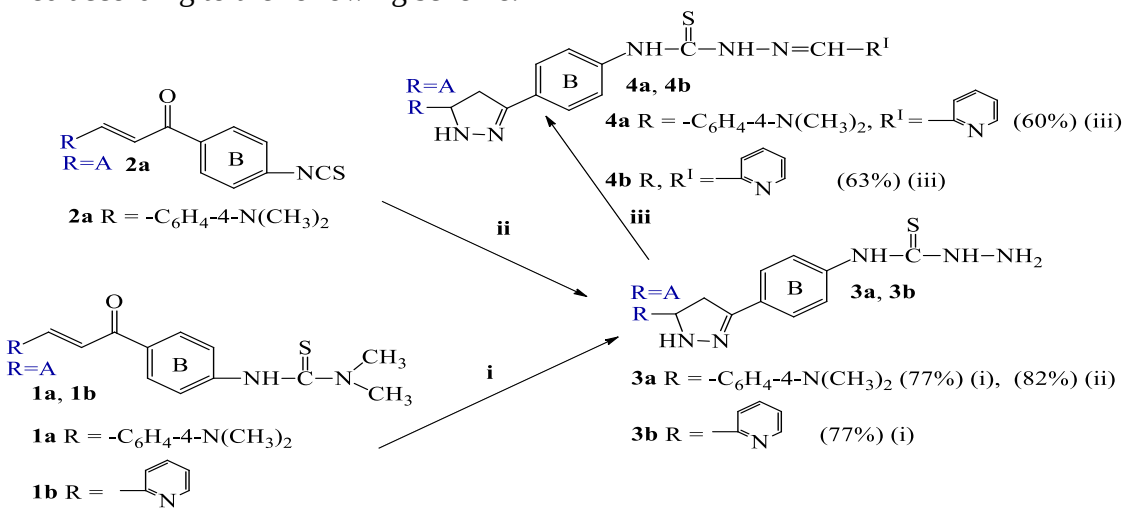
The bibliographic studz of chalcones of the type 1,3-aryl(heteryl)propen-2-one with thiosemicarbazidic 4- and 1,4-disubstituted and thisemicarbazonic groups respectively gives us the information that they have a wide spectrum of biological activity, but methods of their synthesis are less described in the literature, and they became our object of study.

4,5-Dihydro-1-*H*-(pyrazol-3-yl)phenylhydrazinecarbothioamides **3a** and **3b** were obtained according to the following scheme:



Reagents and reaction conditions: i, ii) 2-Py, 25ºC – 24h, 90-95ºC – 3h, 77-82%;
iii) DMF, CH_3COOH, 70-80ºC, 2-3h, 60-63%.

Figure 1. Synthesis of chalcone derivatives 3a, 3b, 4a and 4b.

Initially N,N-dimethylthioureas **1a** and **1b** with hydrazine hydrate from hydrazones in pyridine at room temperature, which without being isolated upon heating cyclize to pyrazole derivatives (Fig. 1.) as described in the literature, and in parallel, dimethylamine is substituted by the hydrazine group [1] with the formation of compounds **3a** and **3b**, with a yield of 77%. Compound **3a** was also obtained by an alternative route from isothiocyanatophenylpropen-2-one **2a** and hydrazine hydrate at room temperature, then on heating in pyridine (Fig. 1.). It is possible to from the same intermediates, which turn in to the finished product **3a**, the yield is 82%. Compounds **4a** and **4b** were obtained from products 3a and 3b by boiling in ethanol with 2-pyridinecarboxyaldehyde. The antiproliferative activity of N-(4-(5-(pyridine-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl)-2-(pyridine-2-ylmethylene)hydrazinecarbotioamide towards HL-60 leukemia cells were patented [2].

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IN VIVO STUDIES OF LAVENDER EXTRACTS FOR HEALING THERMAL INJURY IN RATS

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In recent years, herbal extracts obtained from medicinal plants have gained increasing interest in treatment of wounds. About 450 plant species having wound healing properties have been identified. The present knowledge of the wound healing process comprises coagulation, inflammation, proliferation, formation and accumulation of fibrous tissues, collagen deposition, epithelialization, contraction of wound with formation of granulation tissues, remodeling and maturation [1].

The selection of research methods was carried out in accordance with objectives of the work: determining of regeneration properties of *Lavandula angustifolia* extract fractions with assessment of the influence on the regeneration of thermal injuries of the epithelium in laboratory animals, through the evaluation, when they are administered in different fractions.

Sodium carboxymethylcellulose gels containing 5% lavender extracts were investigated in this study for regenerative properties in thermal injury repair in laboratory rats. "Levomicol" ointment was administered as a control.

Gel formulations were administered daily to lesions in white rats. Animals were divided into 6 groups of 3 individuals. After the observation period (of 7 days) the animals were euthanized and the epithelium harvested for the study of regeneration indices.

As a result of this study, the histological sections studied in hematoxylin and eosin (HE) staining showed partial regeneration both at the epithelial and dermal levels. Regeneration indices have shown that gels containing lavender extracts can increase the proliferation of epithelial cells, the inflammatory processes being decreased.

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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SYNTHESIS AND STUDY OF THE SAME HYDRAZINCARBOTHIOAMIDES AS PRIVILEGE PHARMACOPHORES IN PHARMACOLOGY

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Hydrazinecarbothioamides represent a privileged class of pharmacophores in pharmacology, thanks to an impressive number of derivatives that exhibit outstanding antimicrobial, anticancer and antifungal properties [1]. The presence of electron donor atoms such as N(nitrogen) and S(sulfur) substantially widen the spectrum of use.

In the framework of theoretical studies on the structure of biologically active compounds with valuable properties were highlighted following common structural elements such as substitution of a hydrogen atom from the nitrogen atom (N) with the benzene ring, the introduction of electron-donating substituents, the presence of the atom of sulfur and condensation with carbonyl compounds from the pyridine series but also with benzaldehyde derivatives [2].

At the initial stage called "ab initio", all compounds selected for synthesis were evaluated by the computational method of correspondence to Lipinski's rule [3]. Results suggest that the evaluated compounds fall within the theoretical parameters. A simulation of their interaction with an anticancer biological target such as RR (ribonucleotide reductase, the protein responsible for the synthesis of cellular DNA) was performed. Hydrazinecarbothioamides condensed with carbonyl compounds were highlighted as having a powerful anticancer potential due to their substantially lower binding energy than of free hydrazinecarbothioamides.

A new series of N-(methylphenyl)hydrazinecarbothioamides were obtained starting from corresponding methylanilines. These compounds were subsequently condensed with aromatic carbonyl compounds and heterocyclics.

The research of the anticancer properties was carried out *in vitro*, on a series of cancer cell lines: cervical adenocarcinoma (HeLa), human pancreatic adenocarcinoma (BxPC-3), muscle tissue myosarcoma (RD) and human leukemia (HL-60). The toxicity of the compounds was evaluated on the normal renal epithelial cell line (MDCK).

The results of the *in vitro* evaluation of anticancer properties revealed that N-(2,4-dimethylphenyl)-2-(2-hydroxybenzylidene)-hydrazinecarbothioamide inhibits the proliferation of HL-60 cancer cells in proportion of 90-98%, at both concentrations of 10 μM and 0.1 μM. This compound exhibits a higher activity than DOX (doxorubicin), drug used in cancer chemotherapy.

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https://doi.org/10.19261/nfnpc.2023.ab06 **Oral Presentation**

SYNTHESIS AND STRUCTURE OF COMPOUNDS OBTAINED FROM THE INTERACTION OF (+)-3-CARENE MONOTERPENE WITH POTASSIUM PERMANGANATE

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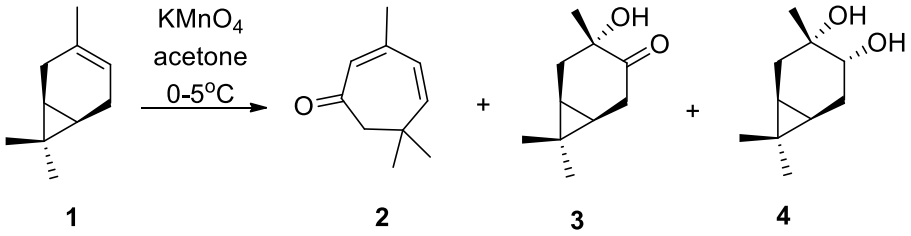
At present one of the main features of the chemistry of natural cyclopropanes is determined by the great diversity/variability of their structures and properties. However, the low content of most optically active cyclopropanes obtained from natural sources is a priority and requires the urgent development of readily applicable methods for synthesis from available natural substances, e.g. (+)-3-carene monoterpene **1**. A distinctive structural feature of (+)-3-carene is the presence in its molecule of a bicyclic bridge system consisting of methylcyclohexane, 2,2-dimethylcyclopropane moieties and a reactive C-C double bond.

The main aim of the work is to obtain oxygen-containing functional groups in the (+)-3-carene **1** molecule, thus the oxidation properties of (+)-3-carene with permanganate in an acetone solution were studied.



It was found that after 3 hours of mixing of the reagents a mixture of products (TLC data) was formed, which allowed the isolation by SiO_2 column chromatography of three predominant substances. Less polar was substance **2**, in the IR spectrum of which there are characteristic stretching vibration frequencies for the unsaturated ketone (1660 cm-1), for methyl (1370 and 1385 cm^{-1}). In the 1*H* NMR spectrum, the singlet signals of six protons and three protons of two single methyl groups in a strong field are complemented by one proton signals of three vinyl protons and a two proton signal of the methylene group. These data, combined with 13C NMR data, indicate the structure of (2Z,4Z)-3,6,6-trimethylcyclohepta-2,4-dienone **2**. (1R,4S,6S)-4-hydroxy-4,7,7-trimethylbicyclo[4.1.0]heptane-3-one **3**. The most polar substance was cis-diol (1S,3S,4R,6R)-3,7,7-trimethylbicyclo[4.1.0]heptan-33,4-diol **4**.

Thus, it was found that the interaction of monoterpene (+)-3-carene 1 with KMnO4 occurs with the introduction of both one and two oxygen-containing functional groups, and involves both change and conservation of the carene "scaffold".

Acknowledgments: The authors are grateful for the funding of this research under the Moldovan State Program (2020–2023), Project Nr. 20.80009.5007.17 “Hybrid materials functionalized with carboxyl groups based on plant metabolites with activity against human and agricultural pathogens”.

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SIMULTANEOUS IDENTIFICATION AND QUANTIFICATION OF ROSMARINIC, OLEANOLIC, URSOLIC AND POMOLIC ACIDS IN *LAMIACEAE* PLANTS BY qNMR METHOD

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qNMR spectroscopy is a convenient analytical method for the investigation of particular components in complex mixtures such as plant extracts, allowing simultaneous qualitative and quantitative determination. Hence, this method was applied to evaluate the rosmarinic and triterpenic acids content in different plant sources as follows *Lavandula angustifolia*, *Melissa Officinalis*, *Mentha Piperita*, *Salvia Officinalis*, *Salvia Sclarea*, *Rosmarinus Officinalis*, *Origanum vulgare* and a subspecies of the latter *Origanum hirtum*.

The utilization of selective ultrasound assisted extraction, employing 70% aqueous ethanol, has proven to be effective in obtaining enriched extracts containing triterpenic and rosmarinic acids. The quantification of these compounds was carried out basing on 2D HSQC experiments and calibration curves were drawn for rosmarinic, oleanolic, ursolic and pomolic acids using an internal standard. Rosmarinic acid, initially isolated from lemon balm, was found to be present at higher concentrations in the investigated extracts, ranging from 4% to 6%. In contrast, terpenic acids content showed lower values in comparison with their known amount in the investigated plants species.

The demonstrated analytical protocol offers several advantages, including a simple and cost-effective extraction method, the use of non-toxic reagents and the application of a versatile method for identification and quantification.

Acknowledgments: This study was supported by the research project PLANTERAS, code 20.80009.8007.03., funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova.

https://doi.org/10.19261/nfnpc.2023.ab08 **Oral Presentation**

THE ALKYLATION OF THE AMIDES OF DEHYDROABIETIC ACID

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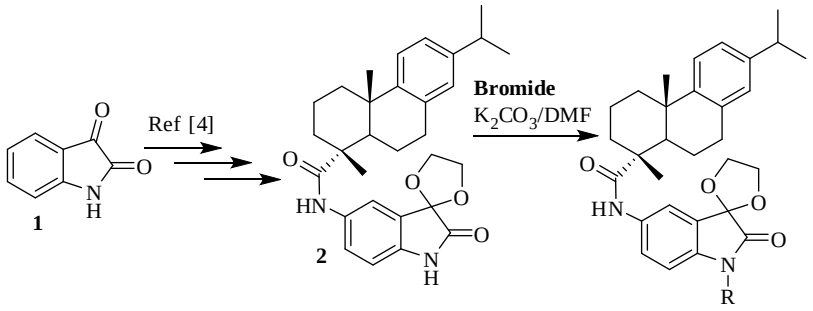
In this abstract is being discussed the synthesis of new substituted amides of dehydroabietic acid with different bromides in system K_2CO_3/DMF.

It is known fact that many compounds, such as famous isatine **1**, have the amide group in its molecule. There is no point in talking about it, because everything is known regarding chemical properties. However, what if there are two amide groups in the molecule at once? Let us see…

For our investigation, we used the model of well-known alkylation reaction [1]. As starting material, we used two types of bromide: aliphatic and aromatic – bromoacetone [2] and phenacyl bromide [3], respectively, which reacted with dioxalane **2** [4] in above described conditions [4].



The first approach was started from slight excess of corresponding bromide (1.2-1.3 eq.) and the full conversion observed after 3 hours at 40-50^{0}C. According to NMR spectrum, the isolated white solids are monosubstituted products – **3** and **4**, respectively [4]. Increasing the amount of bromide to 3-4 equivalents didn't change the situation – the TLC showed only monosubstituted compounds. And the last approach was in significantly increasing the amount of bromide (up to 10 equivalents) and heating the reaction mixture above 100^{0}C for several days, resulting a significant drop in the yield of the desired products and the formation of by-products that could not be isolated and characterized. The formation of monosubstituted products can be explained by steric factors – the close location of methyl and carbonyl group to the reaction center at the nitrogen atom in dehydroabietic fragment.

Acknowledgements: The research supported by NAIR of the Republic of Moldova under project No. 20.80009.5007.17.

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https://doi.org/10.19261/nfnpc.2023.ab09 **Oral Presentation**

INHANCED ANTIFUNGAL ACTIVITY WITH THE JOINT USE OF DEHYDROABIETIIC ACID AND 2-*TERT*-BUTYL-3-(1H-1,2,4-TRIAZOL-1-YL)-2*H*-CHROMENE-2-OL

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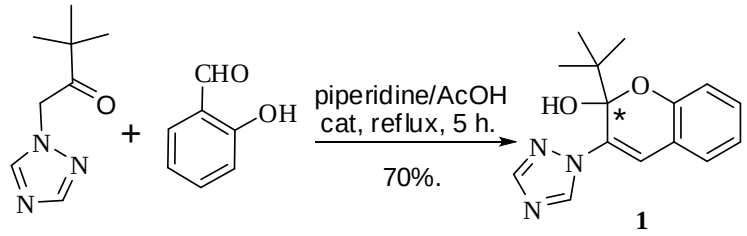
The wide potential of resin acids as bioactive agents gave rise to a growing effort in the search for new applications of the natural forms and semisynthetic agents [1]. From the other hand, chromenes are widespread in natural products and have attracted much attention from a researchers in medicinal chemistry [2]. From the point of view of bioactivity, the hybrid system of 1,2,4-triazol and chromenol is an interesting subject for study [3].



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To obtain the co-crystalline particles of dehydroabietinic acid and 2-*tert*-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromen-2-ol, two different sets of conditions were tried: co-precipitation and the kneading method, which is relatively simple and consists of precisely weighing the acid and chromen **1**, stirring and grinding them in the dry phase for a few minutes, followed by the addition of some H_2O. The mixture of dehydroabietic acid and 2-*tert*-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromene-2-ol becomes a paste that has been triturated for 1.5 hours and finally resulting product is dried.

The antifungal activity of dehydroabietic acid, 2-*tert*-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromene-2-ol and microparticulate system was evaluated against different species: *Candida albicans, Saccharomyces cerevisiae. Aspergillus fumigatus, A. versicolor, A. ochramensis, Trichoderma viride* respectively. All the tested compounds exhibited good antifungal activity which was higher compared to the parent components and reference drugs (ketoconazole and bifonazole).

Acknowledgements: The research supported by NAIR of the Republic of Moldova under project No. 20.80009.5007.17.

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https://doi.org/10.19261/nfnpc.2023.ab10 **Poster**

SYNTHESIS OF NEW MOLECULAR HYBRIDS WITH PHENOTHIAZINE FRAGMENT FROM NORAMBREINOLIDE

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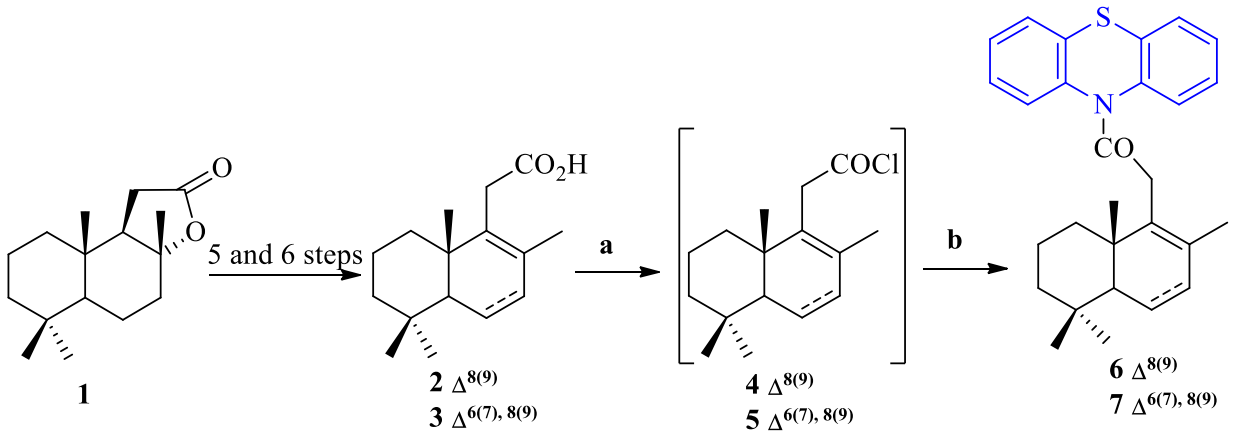
The known phenothiazine derivatives exhibit a wide spectrum of biological activities, including such as antiparasitic, antioxidant, anticancer, antiproliferative, antineoplastic, antimicrobial, etc. [1]. For this reason, terpeno-phenothiazine molecular hybrids represent one of the priority strategies of organic synthesis in the design of new bioactive compounds.

Here are reported the results of the synthesis of new homodrimane hybrids with a phenothiazine fragment. Starting from (+)-sclareolide **1** the $\Delta^{8,13}$-bicyclohomofarnesoic acid **2** and 11-homodrim-6(8)-dien-12-oic acid **3** were synthesized in 6 and 5 steps in 62% and 81% overall yields, respectively [2,3]. Intermediate acyl chlorides **4** and **5** were generated *in situ* by treating acids **2** and **3** with oxalyl chloride in anhydrous benzene and then coupled with phenothiazine in the presence of triethylamine in methylene chloride on stirring to give hybrid phenothiazines **6** and **7** in depicted yields (see Scheme).

The structures of all synthesized compounds were fully confirmed by spectral methods of analysis (IR, ^{1}H, ^{13}C and ^{15}N NMR).



Reagents and conditions: **a.** $(COCl)_2$, C_6H_6, r.t., 1h, Δ, 1h;
b. Phenothiazine, Et_3N, CH_2Cl_2, Δ, 8h, (40% and 45%).
Scheme. Synthesis of terpeno-phenothiazine hybrid compounds**.**

Acknowledgements: This work is part of the project PLANTERAS 20.80009.8007.03 “*New substances with preventive and therapeutic potential based on natural compounds of plant origin and modern methods of organic synthesis*” within the State Program (2020-2023) financed by the National Agency for Research and Development.

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https://doi.org/10.19261/nfnpc.2023.ab11 **Poster**

THE DYNAMICS OF LAVENDER AND CLARY SAGE VOLATILE OILS ADULTERATION ON-AIR EXPOSURE

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Industrially produced Lavender (*Lavandula angustifolia* L.) and Clary sage (*Salvia sclarea* Mill.) essential oils are frequently used as ingredients in aromatherapy, traditional medicine, perfumery and cosmetics [1]. The chemical composition of both fresh volatile oils is mainly determined by unsaturated sesquiterpenic hydrocarbons and their oxygenated derivatives, but the main constituents are linalool **1** (22-34%) and linalyl acetate **2** (34-62%). The quality of volatile oils depends a lot on the storage conditions. Their adulteration can be caused by autooxidation, especially of terpenic unsaturated hydrocarbons and the resulted hydroperoxides are harmful, and can cause skin conditions, including cancer [2].

The aim of this study was the determination of the dynamics of mentioned essential oils adulteration on-air exposure, compared to the linalool **1** and linalyl acetate **2** standards, under ambient conditions (25-30ºC) for 20 weeks. During this time, both standards oxidized completely, but in the case of linalool and linalyl acetate in analysed oils the rates of oxidation are insignificantly (~8%) (see Fig.).

Also, the results showed that the content of hydrocarbons decreased 16.9%→0.8% (Lavender oil), 7.9%→0.9% (C. sage oil), and that of oxygenated derivative increased 82.5%→98.6% and 82.5%→96.4%, respectively (see Table). The visible difference between the oxidation dynamics of linalool and linalyl acetate from the composition of volatile oils and standard samples is influenced by the competition with mono- and sesquiterpene components for molecular oxygen.

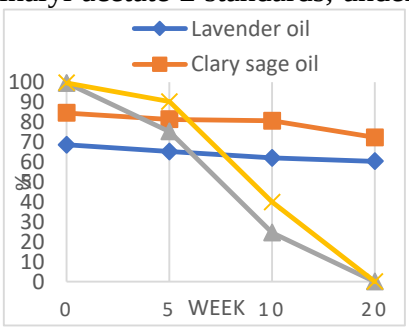

Figure. The dynamics of autooxidation of standards and linalool/linalyl acetate in Lavender and Clary sage volatile oils.

Tabel. Chemical composition of fresh Lavender and Clary sage essential oils and after autooxidation on-air exposure (GC-MS analysis).

Subclass of Terpenic compounds	*Lavender oil (%)*			*Clary sage oil (%)*		
	Fresh oil	*10 weeks*	*20 weeks*	*Fresh oil*	*10 weeks*	*20 weeks*
Monoterpene hydrocarbons	8.7	1.5	0.2	2.1	0.7	0.1
Oxygenated monoterpenes	82.0	91.8	94.6	90.3	93.2	93.9
Sesquiterpene hydrocarbons	8.2	3.3	0.6	5.8	1.7	0.8
Oxygenated sesquiterpenes	0.5	2.7	4.0	0.3	1.9	2.5
Oxygenated diterpenes	-	-	-	0.5	0.6	0.6
Total	99.4	99.3	99.4	99.0	98.1	97.9

Acknowledgements: This work is part of the project PLANTERAS 20.80009.8007.03 “*New substances with preventive and therapeutic potential based on natural compounds of plant origin and modern methods of organic synthesis*” within the State Program (2020-2023) financed by the National Agency for Research and Development.

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https://doi.org/10.19261/nfnpc.2023.ab12 **Poster**

LATE STAGE FUNCTIONALIZATION OF CYCLIC TERPENOIDS BY ATOM TRANSFER RADICAL ADDITION. A CONVENIENT ROUTE TOWARDS NITROGEN HETEROCYCLES

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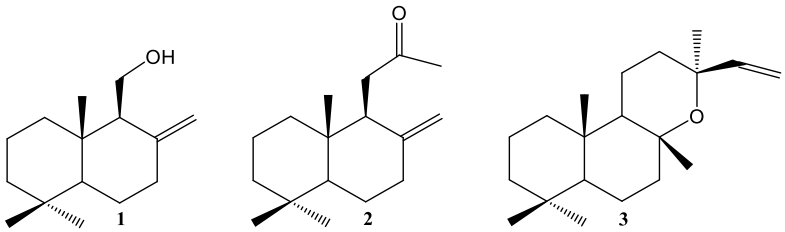
Terpens are a class of widely spread natural compounds with a broad range of biological properties, showing ‘drug-like’ chemical properties, including lipophilicity, interesting molecular geometry, alkylating center reactivity etc [1]. Nevertheless, nitrogen-containing terpens, which can show diverse functionality and biological activity in living cells, are rare in natural sources.

We present in this communication the atom transfer radical additions performed on relevant terpene derivatives of labdane and drimane framework, compounds **1**-**3**, and resulting in a series of azido-compounds. Carboazidation of correspomding terpenic olefins was carried out with ethyliodoacetate under specific conditions using di-tert-butyl hyponitrite (DTBHN) as free radical initiator and phenylsolfonylazide as the azide radical source [2]. The addition products formed with excellent yields. Subsequent modifications to the azide group, such as catalytic hydrogenation, led to spontaneous lactamization, resulting in the formation of γ-lactam products. Our investigations revealed that stereochemical constraints play an important role in these transformations, both at addition and reduction steps.

Following assessment of the interactions of these compounds with biomolecular targets is under way.



Acknowledgments: This study was supported by the research project PLANTERAS, code 20.80009.8007.03., funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova.

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https://doi.org/10.19261/nfnpc.2023.ab13 **Poster**

DOCKING AND ADMET STUDIES OF MANOILOXIDE DERIVATIVES

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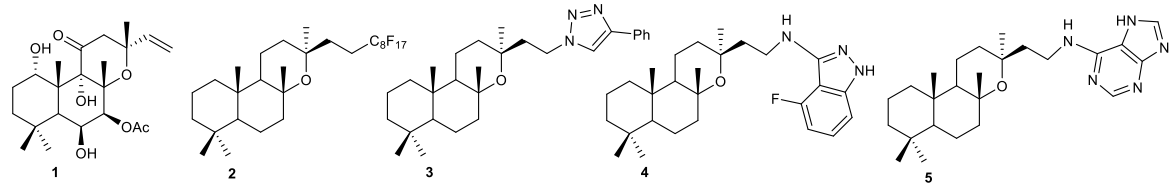
Manoiloxide is a labdane type diterpenoid that can be synthesized from commercially available sclareol. Derivatives of this substance contain the scaffold of forskolin **1** and potentially bind to the active site of adenylate cyclase (PDB 1ab8) showing cytotoxic and cytostatic activity. We report in the current communication the use of Autodock vina and Molegro Virtual Docker software packages for the prediction of the approximate values of binding affinity to the active site of this protein of a series of manoyloxide derivatives. The prediction of the probable adsorption, transportation and toxicity of the synthesized as well as virtually modelled substances was computed on two online resources - SwissADME and ADMET labs. The main aim of the research was to identify with computational methods what are the rationales for the substances available in the laboratory to be addressed within biological activity studies and to perform a lead optimization in order to obtain a library of substances feasible for synthetize.



Scheme 1. Manoiloxide derivatives

The results of docking studies showed promising binding affinities for compounds **1-5**, which also showed acceptable pharmacological parameters (Table 1). Compounds **2** and **3** have been obtained by synthesis and their biological activity studies are in progress.

Table 1 Docking and ADMET results[1]

Substance	Autodock kkal/mol	Molegro kj/mol	BBB	HIA	PGB	CYP3A4	CYPC9	Herg blockers	H-HT	LD-50
1	-10	-95.8	no	yes	yes	yes	no	0.257	0.722	2.618
2	-10.9	-85.4	no	low	yes	no	no	0.428	0.778	3.378
3	-10.8	-113.7	no	low	yes	no	no	0.545	0.590	3.117
4	-11.6	-117.2	no	low	yes	no	no	0.525	0.708	3.246
5	-11.4	-107.6	no	yes	yes	yes	no	0.522	0.664	3.067

[1]BBB: blood-brain barrier penetration ability; HIA: gastrointensional tract absorption ability; PGB: P-glycoprotein affinity; CYP3A4/CYPC9: CYP family enzymes affinity; Herg blockers: K-channel modulator index; H-HT: hepatotoxicity index; LD-50: oral toxicity index.

Acknowledgements: This study was supported by the research project PLANTERAS, code 20.80009.8007.03., funded by the National Agency for Research and Development (ANCD) of the Republic of Moldova.

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https://doi.org/10.19261/nfnpc.2023.ab14 **Poster**

POMOLIC ACID FROM APPLE POMACE: QUANTITATIVE DETERMINATION BY HETERONUCLEAR TWO-DIMENTIONAL QNMR AND PREPARATIVE ISOLATION

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Pomolic acid (PA) is a pentacyclic triterpenic acid isolated from apples by Brieskorn and Wunderer in 1967 [1]. Its highly relevant biological activity profile came recently into focus and there have been many reports on the content of PA in different plant sources [2]. Quite surprisingly, the general perception of low PA content in plants persists and this information hinders its broader investigation as a compound of pharmaceutical and nutraceutical potential. The main aim of the current work was quantitative determination of pomolic acid in apple pomace by two-dimensional heteronuclear NMR correlation spectroscopy.

The dried and grinded apple pomace was extracted with solvents of moderate polarity, including ethanol, ethylacetate and dimethylcarbonate under conditions of ultrasound assisted extraction. The overall extraction time did not exceed 3 hours. Fractionated extracts were obtained on the separation of acidic and neutral part, followed by selective extraction with solvent series of increasing polarity (petroleum ether, dichloromethane, ethylacetate).

The content of PA in the obtained extracts was determined basing on 2D NMR HSQC experiment according to a recently elaborated protocol [3]. The quantification was based on integration of cross peaks corresponding to selected protons of PA and methyl 2,4-dinitrobenzoate as internal standard. The results showed that the highest content of PA was observed in ethylacetate (13.7%) and dimethylcarbonate (9.5%) extracts. Ethanol extracts displayed lower PA content (4.6%) in extracts and higher material recovery as expressed in percentage PA of dry weight. It was also demonstrated that selective extracts fractionations can provide enriched PA samples on avoiding the laborious chromatographic separations. The broad availability of apple pomace as a by-product of apple juice production ensures an excellent perspective for the preparative isolation of pomolic acid which could be a valuable raw material for the food and pharmaceutical industries.

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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https://doi.org/10.19261/nfnpc.2023.ab15 **Poster**

THE SPIROCYCLOPROPANE WITH FRAGMENTS OF DEHYDROABIETIC ACID AND AMINOOXINDOLE

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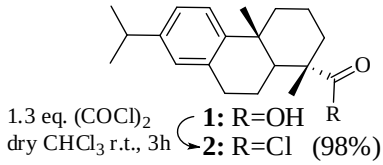
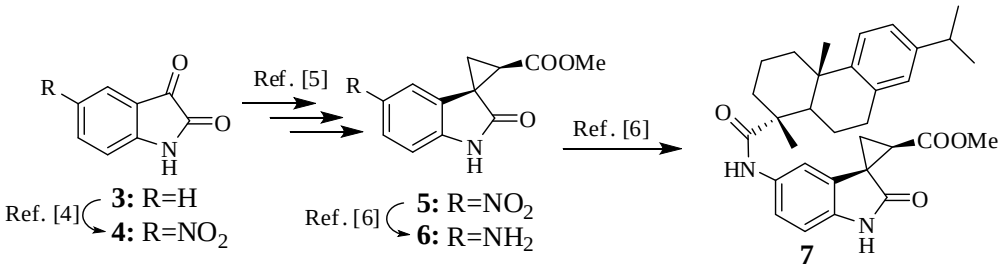
The abstract presents the synthesis of new highly functionalized spirocyclopropane with the fragment of natural compound – dehydroabietic acid **1** (DAK), which can be potentially active against some diseases.



It is a known that spirocyclopropanes have anti-HIV activity [1]. From the other side there are a lot of natural and synthetical oxindoles with various biological activities [2]. And the last fact – that the high optical purity and the molecular structure of tricyclic diterpenoid **1** make it an attractive object for studying new various properties, such as the synthesis of new derivatives with the natural skeleton preservation [3]. Firstly, our approach was to isolate the DAK from natural sources and to transform into chloride **2**.

The next stage was the obtaining of 5-aminooxindole **6**, which started from isatine **4**, according to a known method [4]. The sequential three-stage synthesis of oxindole **5** [5] followed by classical reduction with hydrogen and 5 mol% of palladium on activated carbon [6] succeeded with 98% yield. And the final stage was the reaction of aminooxindole **6** with chloride **2** in dry chloroform, using as acceptor the excess Et_3N. According to NMR spectrum, the desired product **7** is the mixture of diastereomers in ratio 1:1.



Acknowledgements: The research supported by NAIR of the Republic of Moldova under project No. 20.80009.5007.17.

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https://doi.org/10.19261/nfnpc.2023.ab16 **Poster**

THE AMIDES OF DEHYDROABIETIC ACID IN SYNTHESYS OF SPIROPYRANES WITH THE PARTICIPATION OF CARBONYL COMPOUNDS

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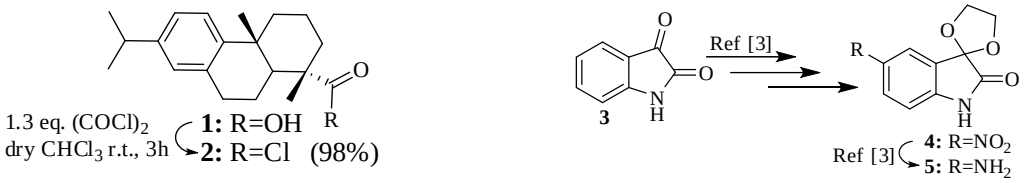
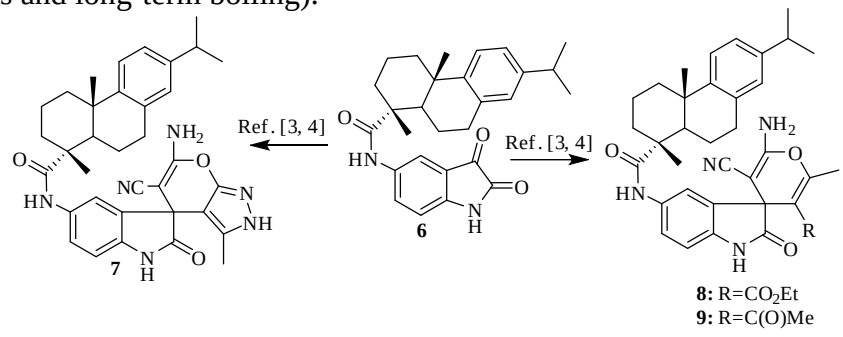
The abstract presents the synthesis of new spiropyranes from substituted 5-aminoisatin **6** in multicomponent reaction with different carbonyl compounds.

It is known that spiropyranes have various activities, which depend from spatial structure and substituents [1]. From the other side, previously mentioned dehydroabietic acid **1** [2] is interesting object to study due to its molecular structure, chemical and biological properties.



Initially, our strategy was to obtain the substituted isatine **6** from easily accessible isatine **3**. To implement that approach, previously obtained [2] 5-nitroisatine reacted with fivefold excess of ethylene glycol [3] using 10 mol% p-toluenesulfonic acid in boiling toluene to give **4** in good yield. Next, the obtained dioxalane **4** was introduced into the reduction reaction, where the best yield was reached using the fivefold excess of tin (II) chloride [3] as reducing agent. The amidation reaction between 5-aminodioxalane **5** and chloride **2** took place in dry chloroform, using as acceptor the moderate excess Et_3N [3]. During the deprotecting essay of dioxalane cycle [3] the best conditions were aqueous acetone (1:3) and 96% sulfuric acid at 35^0C, leading to desired isatine **6** with 75% yield. The final stage was famous three component reaction [4] between the desired isatine **4**, malononitrile and carbonyl compound. The first example [3] started from pyrazoline-2-one, yielded 57% the desired compound **7**. Another carbonyl compound – acetoacetic ester gave the compound **8** with 66% yield [3]. But in case of 2,4-pentanedione the reaction haven't succeeded in different conditions selection (various solvents and long-term boiling).



Acknowledgements: The research supported by NAIR of the Republic of Moldova under project No. 20.80009.5007.17.

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https://doi.org/10.19261/nfnpc.2023.ab17 **Poster**

PHENOLIC COMPOUNDS IN *AGRIMONIA EUPATORIA* L. ETHANOLIC EXTRACT EVALUATED BY HPLC

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Agrimonia eupatoria L. (Rosaceae fam.) is widespread in temperate regions. In folk medicine, this species has been used for its astringent, analgesic and anti-inflammatory, as well as in gastrointestinal disorders. As these biological properties have been linked to its phenolic composition, this plant species could be an interesting source of bioactive compounds with therapeutic potential [1].

For the evaluation of chemical compounds in *A. eupatoria* extract, the aerial parts were harvested in the flowering period from the collection of the Scientific Practical Centre in the Field of Medicinal Plants of “Nicolae Testemițanu” State University of Medicine and Pharmacy. The dry extracts were concentrated using a rotary evaporator-Laborota 4011. The analysis was performed on Shimadzu LC-20AD chromatograph with SPD-20A UV detector [2], under the following conditions: stationary phase - Zorbax Exlipse Plus C18 (4.6x250 mm, 5 microns); 2 mobile phases: solvent mixture: methanol: water (40:60) with gradient elution and orthophosphoric acid 0.5%: acetonitrile (80:20) with isocratic elution mode; detection at wavelengths of 280, 325 and 360 nm.

The solvent system that achieved optimal separation of the phenolic compounds was the mixture of 0.5% orthophosphoric acid:acetonitrile (80:20) at a wavelength of 325 nm.
The extract of *A. eupatoria* was found to be richer in tannins (catechin-3.68%, epicatechin-2.59%); in flavonoids (rutin-1.71%, quercetin-0.199%, luteolin-0.184%, kaempferol-0.162%, apigenin-0.078%, with a lower content of hydroxycinnamic acids (chlorogenic, caffeic, cycoric and ellagic).

The HPLC method with UV-VIS detection can be successfully used in the identification and quantitative determination of chemical compounds in *Agrimonia eupatoria* extracts for the development and standardization of new pharmaceutical forms.

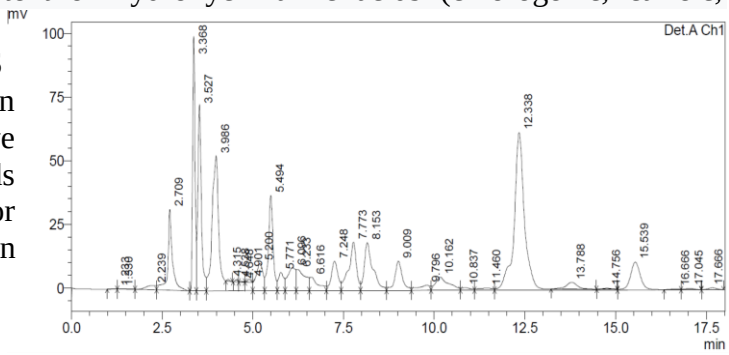

Figure. 1. Cromatograme of *Agrimonia eupatoria* extract

Acknowledgments:
The research was carried out within the project of the State Program 20.80009.8007.24.

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https://doi.org/10.19261/nfnpc.2023.ab18 **Poster**

DIASTEREOSELECTIVE SYNTHESIS OF A NOVEL CYCLIC DERIVATIVE BASED ON 2,3-INDOLINEDIONE

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Generally, organic synthesis is renowned for its predictability in determining results. Nevertheless, there are situations where instead of the expected products, unexpected compounds with unique structures may arise. This report is a presentation of one such remarkable cyclic compound with four chiral centres prepared by diastereoselective dimerization of Morita-Baylis-Hillman (MBH) adducts of acrylonitrile to 5-chloro-indole-2,3-dione.

MBH adducts are very popular in organic chemistry. They are synthesized by the addition of an activated alkene and a carbon electrophile in the presence of a nucleophilic catalyst, such as a tertiary amine or phosphine. The product is densely functionalized, joining the alkene at the α-position to a reduced form of the electrophile with a new carbon-carbon bond. In cases where indol-2,3-dione acts as an electrophile in such reactions, literature examples are found only with N-substituted isatins [1-3].

We attempted to carry out this reaction using unsubstituted 5-chloroindol-2,3-dione. As a result, a series of products were isolated, among which several similar compounds of particular interest were observed, with NMR spectra showing a double set of signals. The overall yield of these compounds was insignificant, and their chromatographic separation proved to be very labour-intensive. In order to enhance the stereo-selectivity of the reaction and consequently increase the yield of the desired compound, conditions were optimized in which the corresponding MBH adduct was used as the starting substrate. In the presence of DABCO and acetic ether as catalysts, primarily, a single substance with an unusual cyclic structure was formed (Figure 1).

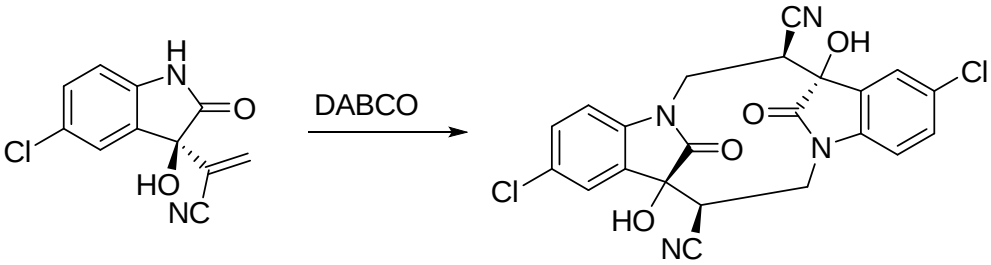

Figure 1. The synthesis of cyclic dimer.

NMR spectra were consistent with the proposed structure. To confirm it, X-ray structural analysis was conducted

Acknowledgements: The research was partially supported by NAIR of the Republic of Moldova under projects No.23.00208.5007.04/PDI.

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https://doi.org/10.19261/nfnpc.2023.ab19 **Poster**

NUCLEOPHILIC ADDITION OF PYRIDINE AMINES TO THE DOUBLE BOND OF *IN SITU* GENERATED MORITA-BAYLIS-HILLMAN ADDUCTS FROM INDOLE-2,3-DIONE

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This report will present the results of addition reactions of indole-2,3-dione to methyl or nitryl acrylate and amino-methyl-pyridine. The addition of an activated alkene like methyl acrylate and nitryl acrylate to a carbon electrophile in the presence of a nucleophilic catalyst is named Morita-Bailys Hillman (MBH) addition. Such adducts are very popular in organic chemistry [1-3].

As a result of screening various substances in search of new catalysts in MBH reactions, substances were discovered that not only catalyzed the addition of olefin to a carbonyl compound but also acted as a reagent themselves, leading to the formation of fundamentally new substances (Figure 1). After analyzing NMR spectra, conclusions were drawn about the structure of the substance, which was subsequently confirmed by X-ray structural analysis.

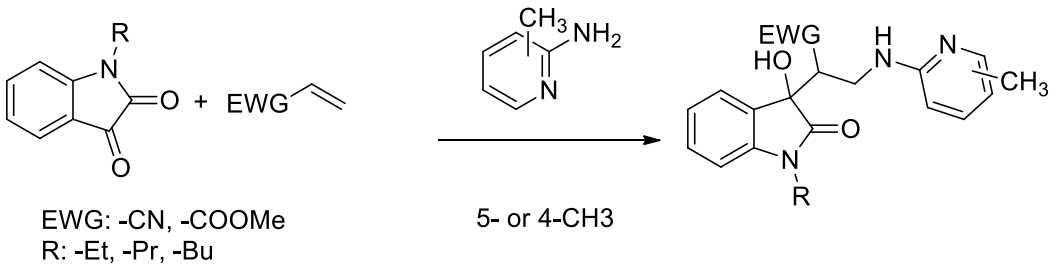

Figure 1. General scheme of nucleophilic addition of pyridine amines to the double bond of *in situ* generated Morita-Baylis-Hillman adducts

It should be noted that methyl acrylate reacts better under these conditions, and the reaction proceeds faster than acrylonitrile. In all cases, the yield was around 70%, and the reaction proceeded regioselectively, forming only one diastereomeric pair of enantiomers. It is also worth noting that the complex ether product hydrolyzes during the reaction, forming the corresponding acid. Even when the reaction is carried out under practically absolute conditions, up to 30% of the final product yield is attributed to the acid.

Acknowledgements: The research was partially supported by NAIR of the Republic of Moldova under projects No.23.00208.5007.04/PDI and No. 20.80009.5007.17.

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https://doi.org/10.19261/nfnpc.2023.ab20 **Poster**

TOTAL CONTENT OF FLAVONOIDS IN SPECIES OF THE GENUS HEICHRYSUM

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The genus Helichrysum (Asteraceae) comprises about 600 species of perennial or annual plants distributed in Europe, Asia, and Africa, which are an abundant source of secondary metabolites, such as flavonoids, chalcones, phenolic acids, coumarins, pyrones, and terpenes [1]. In the Republic of Moldova only one species *H. arenarium* (L.) Moench-(popularly known as everlasting), occurs sporadically on the cliffs of the right bank of the Nistru River, in the landscape reserve "Climăuții de jos", in the Steppe Hills steppes, on the limestones of Naslavcea, with a declining population [2]. Another species *H. italicum* L. is recently introduced (2021) in the collection of the Scientific Practical Centre in the Field of Medicinal Plants of “Nicolae Testemițanu” State University of Medicine and Pharmacy.

We proposed identification and assay of flavonoids from species of the genus Heichrysum (*H. arenarium* and *H. italicum).* Aerial parts and flowers of *H. arenarium* were collected from wild flora, and for *H. italicum* - from the collection. Flavonoids were identified by specific reactions as well as by thin layer chromatography. Determination of flavonoids was performed with aluminium chloride using a Metertech UV/VIS SP 8001 spectrophotometer.

By colour reactions and CSS in the aerial parts and flowers of *H. arenarium* were identified: apigenin, luteolin, rutozide, quercetin, quercitrin, while in *H. italicum*: apigenin, rutozide, luteolin. The flavonoid concentration (mg/ml), expressed as rutin (λ=430nm) shows a higher content in the *H. arenarii flores* (1.46), followed by the *H. italici flores* (1.31), while the flavonoid content in the aerial parts is lower and varies from 0.80 for *H. italicum* to 0.89 for *H. arenarium*. Where the total flavonoid content (mg/ml), expressed as quercetin (λ=425nm) is higher and shows 10,69 in *H. arenarii flores;* 9,87 in *H. italici flores*, followed by aerial parts (2,76 for *H. italicum* to 3,62 for *H. arenarium)* with a maximum extraction in ethanol of 50% for all products.

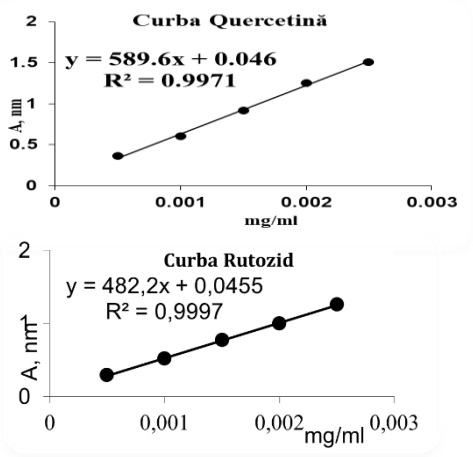

Figure. 1. Calibration curves of rutozid (1) and quercetin

Conclusions: The study shows that the flowers of Helichrysum species are a richer source of flavonoids than the aerial parts for both species (*H arenarium* and *H.italicum*) and represent a perspective for the development of new pharmaceutical forms.

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https://doi.org/10.19261/nfnpc.2023.ab21 **Poster**

IDENTIFICATION OF PHENOLIC COMPOUNDS FROM EXTRACT OF *GALIUM VERUM*

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The species *Galium verum* has a long history as a traditional healing herb and attracted attention for intense investigation in recent years as it proves to be a safe, affordable and effective natural health remedy as a choleretic, diuretic or spasmolytic [1]. There is detailed research showing a complex and rich content of phytochemicals in the flowers and leaves of *G. verum*, with the highest total composition of phenols and flavonoids [2]. For the determination of phenolic compounds, the plant extract was obtained from *Galii veri herba*, collected during the flowering period and treated with 60 % hydro-ethanol solution (ratio of 1:10). The extraction was performed using a water bath, followed by the removal of solvent with rotary evaporator Laborota 4011. Identification of phenolic compounds was carried out by thin layer chromatography (TLC) in three systems: Ist system– butanol-glacial acetic acid-water (4:1:2), IInd system– chloroform-ethyl alcohol (9:1) and IIIrd system–formic acid-water-ethyl acetate (6:9:90).

Table 1. Identification of phenolic compounds in extract of *Galii veri herba* by TLC

Sample and reference solutions	I system	II system	III system	Spot colour
G. veri herba	0,43;0,88;0,80; 0,77; 0,82; 0,65	0,36;0,89;0,86; 0,79; 0,84; 0,68	0,23;0,92;0,89; 0,90; 0,82; 0,91	
rutosid	0,43	0,36	0,23	orange-brown
quercetin	0,88	0,89	0,92	light yellow
isoquercetin	0,80	0, 86	0,89	yellow
apigenin	0,77	0,79	0,82	intense yellow
quercitrin	0,82	0,84	0,91	orange
hyperosid	0,65	0,68	0,72	yellow-brown

In the chromatographic study of the extract from *G.veri herba*, in all three systems, identified compounds of phenolic nature including four hydroxycinnamic acids (caffeic, chlorogenic, p-coumaric and gallic) and six flavonoids (rutosid, hyperosid, quercetin, isoquercetin, apigenin, quercitrin) with a more successful separation in the chloroform-ethyl alcohol system (9:1). The extract of *Galii veri herba* is rich in phenolic compounds and can be used for further preclinical and clinical studies.

Acknowledgments:
The research was carried out within the project of the State Program 20.80009.8007.24.

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https://doi.org/10.19261/nfnpc.2023.ab22 **Poster**

TRANSFORMING THE FIVE-MEMBERED RING D IN A PREGNENOLONE DERIVATIVE INTO A SIX-MEMBERED RING THROUGH SKELETAL REARRANGEMENT

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In pursuit of obtaining steroid derivatives containing a triazole moiety in their structure, a series of reactions was conducted (Figure 1). In these reactions, an intermediate compound was the corresponding azide **3**, which was subsequently involved in a reaction with the required alkyne to form a 1,2,3-triazole. In click chemistry reactions, it is well-known that catalysts are one-valent copper salts, which can be generated in situ from copper(II) salts. However, the NMR spectra of the main product, isolated from the reaction mass, did not match the expected results.

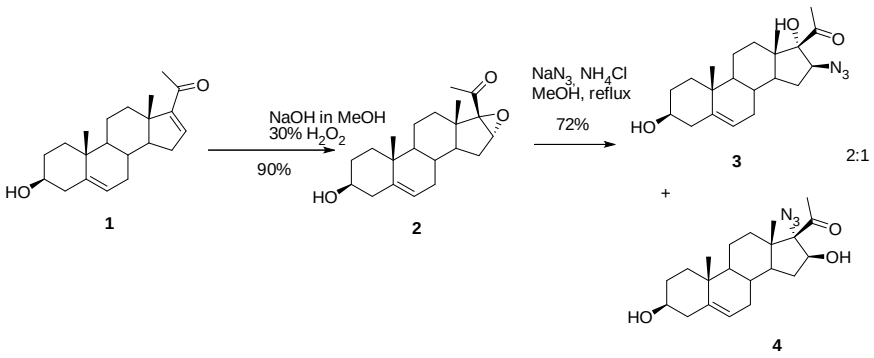

Figure 1. The procedure for synthesizing azides 3 and 4

Upon analyzing the collected data from ^{1}H, ^{13}C, ^{15}N, HSQC, HMBC, and DEPT spectra, it was concluded that under these conditions, a skeletal rearrangement occurs, where the five-membered ring D expands to a six-membered one, forming a new compound. To confirm this hypothesis, the starting compound **3** was mixed under similar conditions without the addition of a reagent. As a result, the same compound was isolated, and its spectral data corresponded to the structure of **5**, which was confirmed through X-ray structural analysis too.

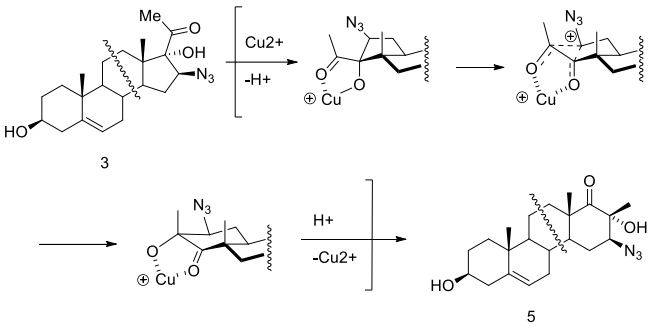

Figure 2. The mechanism of the skeletal rearrangement

The mechanism of the skeletal rearrangement of steroid derivatives in the presence of copper(I) ions is presented in Figure 2.

Acknowledgements: The research was partially supported by NAIR of the Republic of Moldova under projects No.23.00208.5007.04/PDI and No. 22.80013.8007.1BL.

https://doi.org/10.19261/nfnpc.2023.ab23 **Poster**

THE OPENING OF DEHYDROPREGNENOLONE EPOXIDE LEADING TO THE NON-SATURATED SKELETAL REARRANGEMENT PRODUCT

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This report presents a compound that emerges as a product of the skeletal rearrangement following the opening of dehydropregnenolone epoxide (Figure 1).

The opening of the epoxy cycle in dehydropregnenolone epoxide **1** in the presence of hydrochloric acid leads to the formation of two chromatographically inseparable diastereomers **2** and **3** (Figure 1).

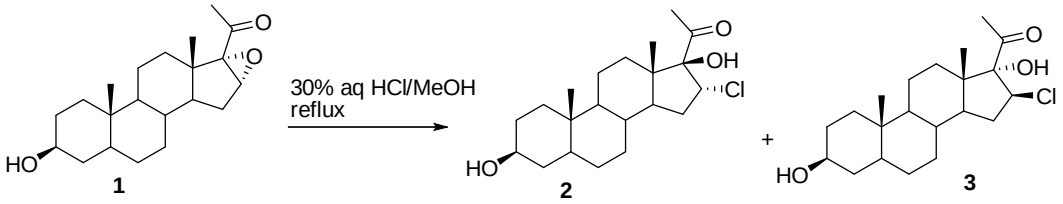

Figure 1. Scheme of the formation of diastereomers 2 and 3

In the literature, there is an example of the epoxide opening in absolute methanol. Thus, according to Girdhar *et al* [1], the reaction of compound **1** with dry HCl in dry MeOH at low temperatures resulted in the formation of a major product, which was isolated and characterized as 21-chloro-3b-hydroxy-pregn-5,16-dien20-one (**4**, > 85%), along with a dimeric product that could not be characterized (Figure 2).

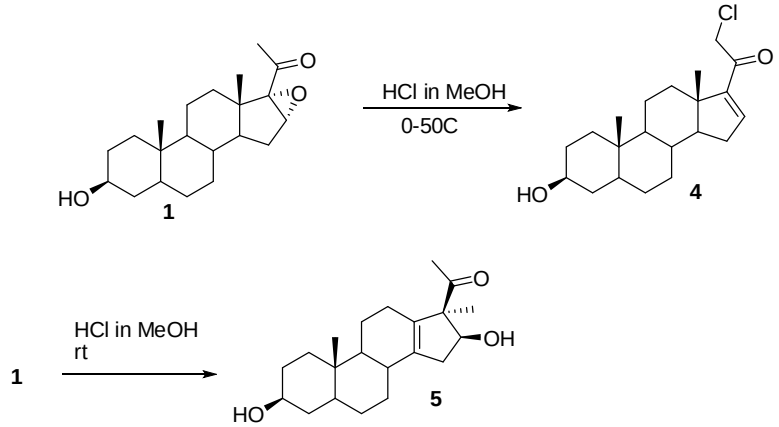

Figure 2. The epoxide ring opening of 1 with dry HCl in dry MeOH

We also conducted a similar synthesis and isolated a byproduct. The structure of compound **5** was assigned based on detailed spectroscopic analysis (^{1}H, ^{13}C, DEPT, HMBC, HSQC, COSY NMR, IR, and mass). It was shown that the formed product is not a dimer but rather a hardly separable mixture of diastereomers formed as a result of skeletal rearrangement. The presupposed structure was proved by X-ray analysis. It has been attained conditions under which compound **5** becomes the main product of the reaction, up to 45%.

Acknowledgements: The research was partially supported by NAIR of the Republic of Moldova under projects No.23.00208.5007.04/PDI and No. 22.80013.8007.1BL.

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https://doi.org/10.19261/nfnpc.2023.ab24 **Poster**

TARGETING THE BIOACTIVE DIHYDROPYRIMIDINES BY ECOFRIENDLY PROCEDURE OF BIGINELLI REACTION: STUDY CASE OF MONASTROL

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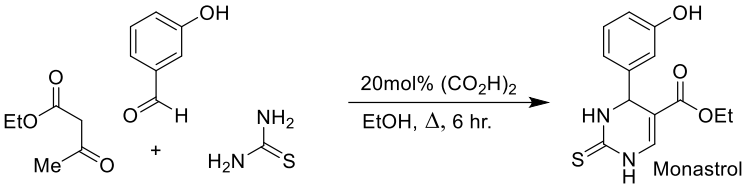
Biologically active compounds decorated with dihydropyridine moiety are counted amongst the numerous broad-spectrum therapeutic agents that explain the increasing role of this scaffold in rational drug design [1]. The Biginelli reaction is a multicomponent reaction of aldehyde, (thio)urea, and ß-ketoester, involving Mannich reaction in the first step, which produces multifunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones and related heterocyclic compounds [2]. The attractiveness of this acid-catalyzed one-pot condensation reaction lies in the simplicity of grafting the substituent into the structure of the products, which can later be transformed into different functional groups that are required for subsequent syntheses. Monastrol, the most representative Biginelli adduct in anticancer drug development, proved to be a cell permeable molecule whose mechanism of action on cancer cells involves the selective inhibition of the motility of the mitotic motor enzyme kinesin Eg5 [3]. Thus the remarkable therapeutic and pharmacological potential of it maintains expressive interest of chemists, some green synthesis approaches being recently reported, as well [4,5].

In continuation of our research line [6], we herein report on a facile ecofriendly synthesis of (±)-M, based on the use of oxalic acid (20mol/%) as green catalyst instead of toxic Lewis acids. The proposed procedure also offers the advantage of shortening the reaction time twice, in comparison with the classic reaction, producing the racemic target compound in 60% yield, m.p. 182-184ºC (crystallized from ethyl acetate), rep. 182-184ºC [4,5].

The prepared (±)-monastrol has shown antifungal activity against *Candida albicans* and *Saccharromyces cerevisiae* at concentrations 8 times lower than reference antifungal agent Nystatin.



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https://doi.org/10.19261/nfnpc.2023.ab25 **Poster**

SYNTHESIS AND ANTICANCER PROPERTIES OF NEW INDOLIZINIC DERIVATIVES

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Natural compounds with indolizine scaffolds have demonstrated numerous biological activities and have found use in medical research laboratories. Thys, the unique indolizine scaffold became an important system for the development of new drug candidates in medicinal chemistry. [1,2] Several indolizines with excellent anticancer activity and tubulin polymerization inhibitory potency have been reported recently, and our group contributed also to the field. [1,3]

The goal of this study was the design, synthesis and anticancer evaluation of several new derivatives with symmetrical or unsymmetrical substituted 7,7’-(ethene-1,2-diyl)bisindolizine structure, and several new 6-, 7- or 8-substituted indolizine derivatives. Mono and bisindolizines were synthesized in good yields via [3+2] dipolar cycloaddition of the *in situ* generated ylides, from corresponding N-pyridinium salts to ethyl propiolate. Part of the new derivatives were tested for their anticancer activity by screening against NCI’s 60 human tumour cell lines panel and the results are presented herein. *In vitro* experiments regarding tubulin interaction were performed for the active compounds.

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QUINOLINE - SULFONAMIDE - COMPLEXES WITH ANTIMICROBIAL ACTIVITY

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Quinoline-sulfonamide-complexes with variously metals, especially M^{2+}, are a relatively new class of compounds with potential practical interest as fluorescent materials (having fotoluminiscent properties) and also as drugs (having a large variety of biological activities such as antibacterial, antifungal, antiprotozoals, etc.).

The emphasis of this work was to obtain hybrid quinoline – sulfonamide - complexes with antimicrobial activity. The synthesis of the hybrid derivatives is direct and efficient, in two steps: acylation of variously amino-quinoline followed by metal complexation with different metals M^{2+} (Zn^{2+}, Cu^{2+}, Co^{2+}, Cd^{2+}, Ni^{2+}, Pd^{2+}). Following this experimental setup several series of synthetic hybrid quinoline – sulfonamide - complexes was obtained. The hybrid complexes were characterized by IR and NMR spectroscopy, elemental analysis and X-ray diffraction on single crystal. The antibacterial and antifungal activity was determined against gram positive bacteria Staphylococcus aureus ATCC25923, gram negative bacteria Escherichia coli ATCC25922 and fungus Candida albicans ATCC10231. The obtained data from the antimicrobial assay reveal that some of the obtained hybrids have a very good antimicrobial and antifungal activity.

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1,3-DIPOLAR CYCLOADDITION REACTIONS OF BENZIMIDAZOLIUM-YLIDES TO AN ACTIVATED SYMMETRIC ALKYNE

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The cycloaddition reactions represent an important way to obtain cyclic structures and take place between two or more reactants containing double or triple bonds in the molecule. After Huisgen, the addition of 1,3-dipole to a dipolarophile, takes place through a concerted mechanism, when two σ bonds are formed. [1,2]

The purpose of this research is to study the Huisgen [3+2] dipolar cycloaddition reactions carried out in a conventional way (stirring at room temperature) and non-conventional way (ultrasonic irradiation), between benzimidazolium-ylides and an activated symmetric substituted alkyne - dimethyl acetylenedicarboxylate (DMAD) - as dipolarophile. [3-5] The Huisgen 3+2 dipolar cycloaddition reaction of benzimidazolium ylides to dymethyl acetylenedicarboxilate (DMAD) afford generating of three types of hybrid quinoline-benzimidazole cycloadducts and, according with the source of energy and solvent used the reactions pathway could be conducted selective.

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ANALYTICAL STUDIES ON THE FRACTIONATION PRODUCTS FROM LAVENDER EXTRACTS

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Lavender (*Lavandula angustifolia*) is a widespread aromatic plant exploited globally for essential oil production. It is known that the remaining wastes after industrial processing are rich in secondary metabolites with relevant biological activities [1]. In particular, triterpenic acids have recently attracted the interest of scientific community because of their broad activity spectrum which makes them very attractive for the use in cosmetics and healthcare products as functional compounds.

The aim of this study was isolation and analytical studies on different fractions obtained from *Lavandula angustifolia* ethanolic extracts. The vegetal plant material represented wastes generated on the extraction of essential oil at industrial scale.

The obtained integral extracts were mixed with different organic solvents of different polarity in acid and basic medium, thus obtaining a series of fractions with different content of secondary metabolites. The fractions with a high content of triterpenic acids were selected by using thin layer chromatography.

The analytical experiments included determination of total polyphenols with the Folin-Ciocâlteu reagent, quantitative determination of flavonoids, FRAP reducing capacity test and qNMR determination of oleanolic, ursolic, pomolic and rosmarinic acids.

According to the obtained results fractions showing higher total polyphenols (495.59 mg EGA/g of extract) were also rich in flavonoids (343.01 mg catechin equivalent/g of extract) demonstrating relevant reducing capacity (386.67 mg EGA/g of extract) and high rosmarinic acid content (cca. 250 mg/g of extract). The triterpenic acids have been found to predominate in less polar fractions.

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