Ministry of Education, Culture and Research
Institute of Chemistry

Scientific seminar

NEW FRONTIERS IN NATURAL PRODUCT CHEMISTRY

A DESTINY ON THE ALTAR OF RESEARCH
Dedicated to academician Pavel VLAD

Poster presentations

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Benzo[*f*]quinolinium salts: antibacterial and antifungal activities

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Introduction

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].

Aim of the work

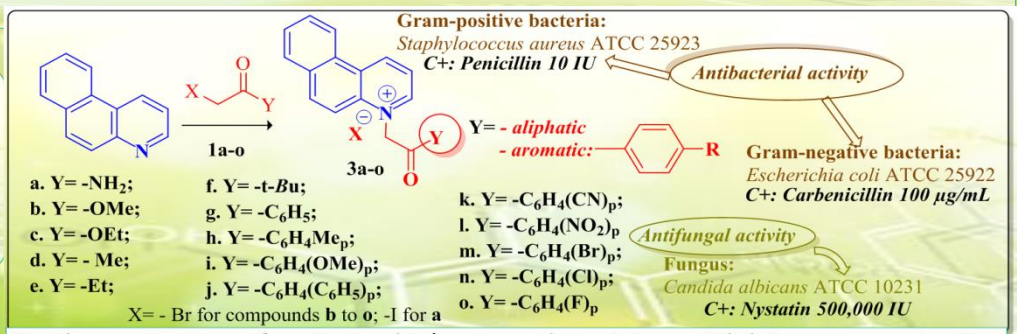
Having in view the above mentioned, our main goal was to synthesize, characterize and testing of antimicrobial properties of novel benzo[*f*]quinolinium salts. The *in vitro* antimicrobial activity of benzo[*f*]quinolinium salts was determined by the method Kirby-Bauer disk diffusion, using nutrient agar medium: Mueller Hinton agar for antibacterial tests and Sabouraud agar for antifungal tests.

Experimental

The synthesis of salts was done by perform the quaternization reaction of benzo[*f*]quinoline **1** with variously activated α-halocarbonyl compounds **2a-o**, such as: 1-bromo-alkyl-2-one, 2-iodoacetamide, (un)substituted phenacyl bromides. 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 **3a-o** were proved by NMR experiments (^{1}H, ^{13}C, COSY, HMQC, HMBC).

The *in vitro* antimicrobial activity was evaluated different bacteria and fungus. As negative control (C-) were used sterile filter paper disks (with no antimicrobial compounds). The obtained results were expressed as diameters of inhibition zones (mm). The larger the diameter of the inhibition zones is, the more active the compounds are as antimicrobials and and antifungal.

Cpd / Y	[a]Diameter of inhibition zone (mm)		
	S. aureus ATCC 25923	*E. coli ATCC 25922*	*C. albicans ATCC 10231*
3a / -NH_2	0	0	10.5±0.5
3b / -OMe	19.5±1.5	17±1.73	**20±1.5**
3c / -OEt	**20±1**	18.5±1.5	**22±1.25**
3d / -Me	16±1	11± 1	**20±1.80**
3e / -Et	17±1.73	12.5±1.5	**30±2**
3f / -t-Bu	**20±1**	15.5±2	**27.5±1.5**
3g / -C_6H_5	18±1.5	13±1.5	**20±1.8**
3h / -$C_6H_4(Me)_p$	**20.5±1.5**	17±2	**21.5±1.8**
3i / -$C_6H_4(OMe)_p$	**21.5±1.73**	18±1.73	**22±1**
3j / -$C_6H_4(C_6H_5)_p$	15±1.5	13±1.73	17±1
3k / -$C_6H_4(CN)_p$	15±2.5	12.5±1.25	15±1.73
3l / -$C_6H_4(NO_2)_p$	15±2	14±2.6	17±1
3m / -$C_6H_4(Br)_p$	16±1.5	12±1.5	19±1.5
3n / -$C_6H_4(Cl)_p$	**21±1.5**	18±1.32	**22.5±1**
3o / -$C_6H_4(F)_p$	14±1.5	10.5±1.5	14±0.5
C+	44±1	46±1.33	21±1



In the next step of antimicrobial assay, the minimum inhibitory concentration (MIC) of the most active 10 (ten) salts (namely **3b-e**, **3g-k**, **3n**) were determined, using the standardized broth microdilution assay procedure. The resulted MIC value is defined as the lowest concentration of the antimicrobial salts under investigation, which prevents visible growth of the tested microorganism.

Strain	MIC (μg/mL)									
	3b	**3c**	**3d**	**3e**	**3g**	**3h**	**3i**	**3j**	**3k**	**3n**
S. aureus	1.56	0.39	1.56	0.78	0.195	0.195	**0.00304**	0.39	1.19	*0.0975*
E. coli	1.56	0.78	1.56	0.78	0.195	0.195	**0.00152**	0.78	1.39	0.195
C. albicans	3.12	0.78	3.12	3.12	0.139	0.195	**0.0575**	0.78	0.81	0.195

Conclusions:

The antifungal activity is significant more pronounced in the aliphatic series **3a-f** comparative with the aromatic one **3g-o**, which demonstrate a certain influence on activity of the aliphatic substituent of carbonyl group. In the aromatic series **3g-o**, compounds **3n** [Y= -$C_6H_4(Cl)_p$] and **3i** [Y= -$C_6H_4(OMe)_p$] have the higher antifungal activity, which also indicate an influence of the substituent (chlorine or methoxy) from the *para* position of phenyl ring.

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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NEW HYBRID QUATERNARY SALTS WITH PYRIDINE/BENZIMIDAZOLE SKELETON

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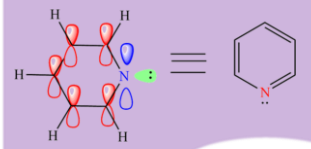
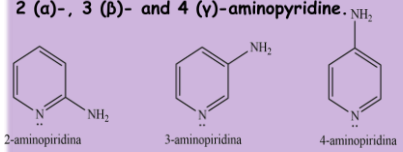
Introduction

Pyridine structure



Pyridine and pyridine-derived skeletons represents an invaluable scaffold 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].

In the series of aminopyridines there can be 3 derivatives, position isomers: 2 (α)-, 3 (β)- and 4 (γ)-aminopyridine.

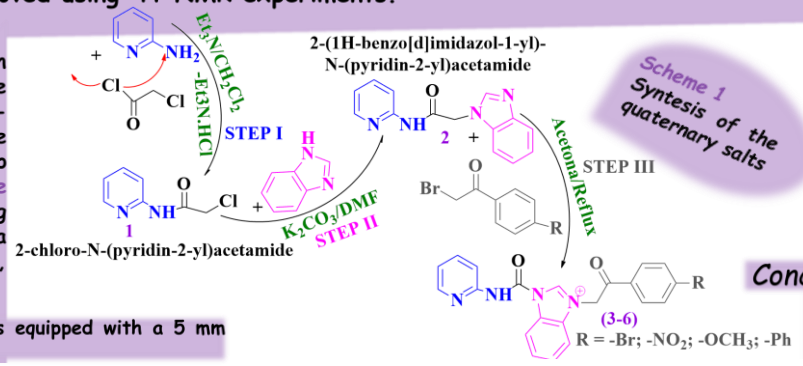


Aim of the work

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 new compounds were proved using ^{1}H-NMR experiments.

Experimental

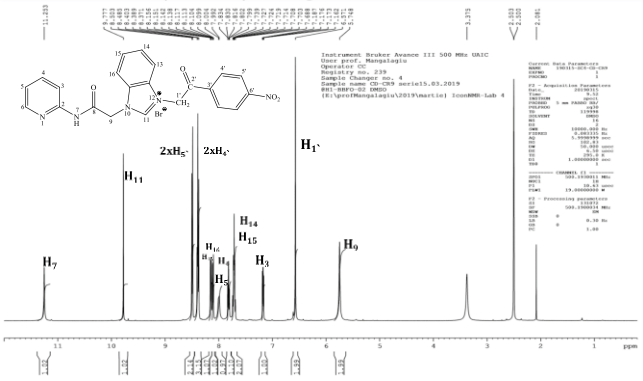
In the first step (*N*-acylation) occurred between 2-aminopyridine and α-chloroacetyl chloride, giving the corresponding acylated compound (1). The second step (*N*-alkylation of benzimidazole) was done using K_2CO_3 as a base and compound 1 obtained previously.The third step consisted of the hybrid pyridine-benzimidazole derivative (2) was subjected to the quaternization reaction using bromoacetophenones differently substituted in the para position. The quaternary salts obtained are new compounds, not mentioned in the literature.

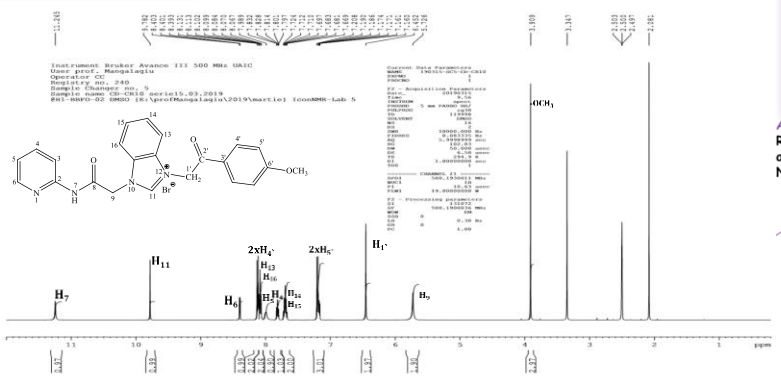


Scheme 1 Syntesis of the quaternary salts

Quaternary salt when R is:	Yield (%)	Melting Point
-Br	80	232 - 234 °C
-NO_2	70	234 - 235 °C
-OCH_3	50	190 - 192 °C
-Ph	80	220 - 223 °C

❖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 nucleus.





Conclusions:

Aminopyridines, due to the reactivity and variety of reactions they can give, forming derivatives with various actions on biological systems, are the perfect candidates for the synthesis of active substances that are part of drugs. The wide range of drugs discovered, synthesized and marketed that contain pyridine nucleus and / or aminopyridine derivatives demonstrates their applicability in the pharmaceutical and medical field.

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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SELECTIVE SYNTHESIS OF 13-*epi*-MANOYL OXIDE

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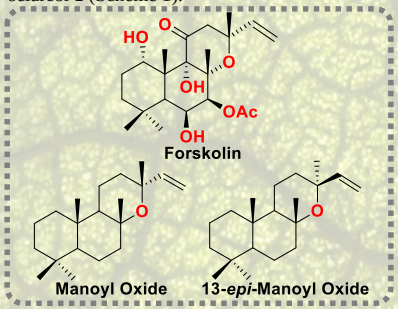
Introduction

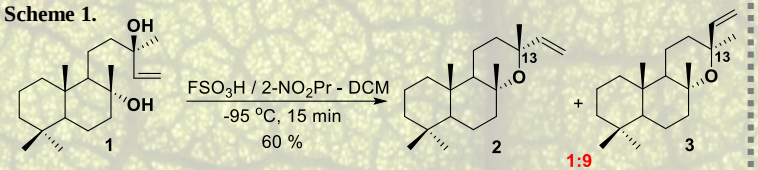
Labdane-type diterpenes are excellent examples of natural products with important pharmaceutical activities. Besides, several labdanes are quite abundant in nature and/or are commercially, such as sclareol **1**. Hence, they are useful starting materials for chemical transformations. On the other hand,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



Results

Scheme 1.



An older contribution of some of us reported an equimolar mixture of epimers [6]. Optimization experiments basing on the published cyclization conditions (5 molar excess of FSO_3H at -78 °C), showed a specific dependence of the reaction outcome on experimental conditions, including reagent addition procedure, reaction temperature and the amount of cyclization agent (Table 1). Estimation of the reaction course relied upon the GC-MS analysis of the worked-up reaction mixtures and separate integration of peaks, providing a relative content of oxides **2** and **3**, starting diol **1** and all other reaction byproducts taken together.

Table 1.

No	Procedure	Reaction temperature	FSO_3H, mole equiv.	Reaction products, % by GC-MS				3/2
				Recovered 1	Secondary products	2	3	
1	P1	-85	5	-	4	37	59	61/39
2	P1	-85	3	-	4	51	45	47/53
3	P1	-85	1.5	26	5	42	27	39/61
4	P2	-85	3	-	2	59	39	40/60
5	P3	-85	3	2	1	55	42	43/57
6	P5	-85	3	-	2	55	43	44/56
7	P2	-85	5	-	1	53	46	46/54
8	P4	-85	5	-	2	50	48	49/51
9	P5	-85	5	-	3	37	60	62/38
10	P5	-90	5	-	7	18	75	81/19
11	**P5**	**-95**	**5**	**-**	**17**	**8**	**75**	**90/10**
12	P5	-100	5	-	28	6	66	92/8
13	P5	-105	5	-	33	5	62	93/7
14	P5	-110	5	-	45	6	49	89/11

The optimal conversion-selectivity reaction conditions are achieved at -95 °C, with 5 equiv. reagent excess and addition of the dissolved substrate in one batch (Table 1, entry 11). A parallel preparative experiment was performed witch included isolation of reaction products *via* column chromatography. The mixture of oxides **2** and **3** was obtained with an acceptable 60 % yield and the prevalence of the desired oxide **3** was exactly the same as determined in the optimization experiment (GC-MS and NMR data).

Thus, a careful optimization of reaction conditions for low temperature cyclization of (-)-sclareol allowed a highly selective synthesis of 13-*epi*-manoyl oxide – a labdanic compound with a carbon skeleton similar to different natural products and derivatives with relevant biological activity. The optimized procedure opens the path for a broader investigation of similar compounds in SAR studies basing on commercially available starting materials.

Acknowledgments

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

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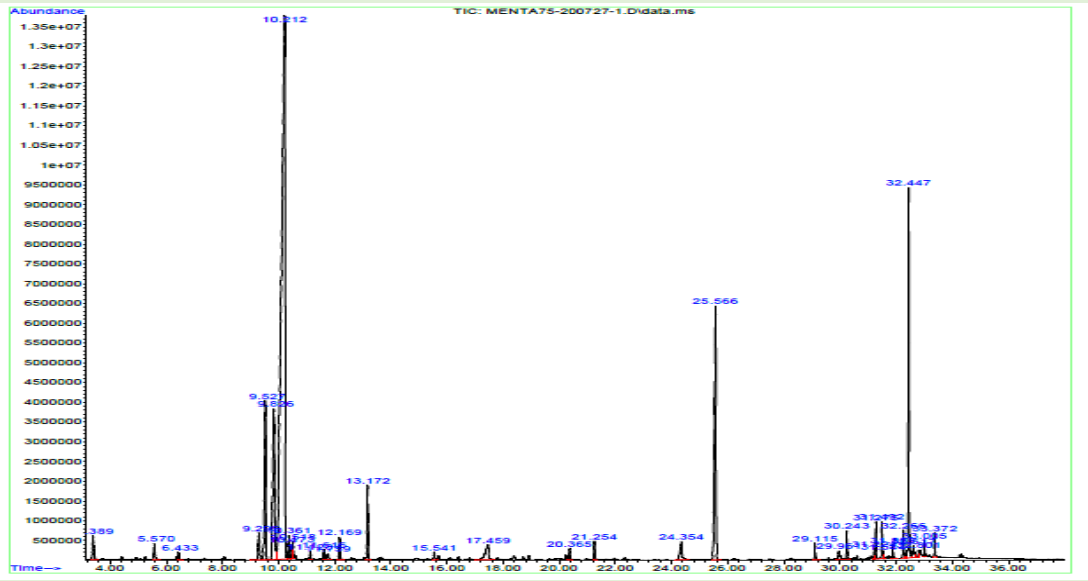
For the first time the results of GC-MS analysis of special simple of the *Mentha piperita* L. oil from Vietnam origin product from year 1975 are reported. The analysis was carried out on an Agilent Technologies 7890A system with 5975C MSD equipped with split-splitless injector (split, 250°C, split ratio 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.

Nr. pic	Component	Rt, min	Area %		Nr. pic	Component	Rt, min	Area %
1	1-Butanol,3-methyl-, acetate	3.389	0.96		20	β-Caryophyllene	16,459	0.10
2	a-Pinene	4,407	0.09		21	5-Undecen-4-one	17,463	1.21
3	b-Pinene	5,254	0.07		22	(+)d-Cadinene	18,920	0.14
4	3-Octanol	5,570	0.54		23	(-)-Spathulenol	20,260	0.15
5	Eucaliptol	6,433	0.21		24	Caryophyllene oxide	20,396	0.36
6	L-Isopulegol	9,295	0.99		25	Isopropyl dodecanoate	21,254	0.52
7	(-)-Menthone	9,528	5.47		26	Myristic acid	24,356	1.05
8	Neoisomenthol	9,827	7.69		27	Isopropyl myristate	25,568	9.97
9	(-)-Menthol	10,216	52.25		28	Isopropyl hexadecanoate	29,115	0.35
10	(+)-Isomenthol	10,361	0.94		29	Kauran-13-ol	29,961	0.23
11	Cyclohexanol, 1-methyl -4-(1-methylethyl)-	10,473	0.34		30	Cyclohexanol, 5-methyl-2-(1-methylethyl)- , sulphite(2:1)	30,243	0.53
12	α-Terpineol	10,518	0.43		31	Acetylenedicarboxilic acid, di-(-)-menthyl-	31,279	0.65
13	Cis-3-hexenyl isovaleriate	11,616	0.27		32	Ethyl chrysantemate	31,492	0.67
14	Menthylacetate	11,715	0,14		33	Myristyl myristate	31,884	0.27
15	Pulegone	12,182	0.20		34	Linalyl butirate	32,266	0.69
16	Piperitone	12,245	0.70		35	p-Menthone, 3-allylperoxy-	32,447	6.79
17	Iso-Menthylacetate	13,172	2.11		36	Diazoacetic acid, -2-isopropyl- 5-methylciclohexyl ester	33,371	0.44
18	a-Bourbonene	15,573	0.24					
19	(-)-b-Elemene	15,702	0.13					



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).

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

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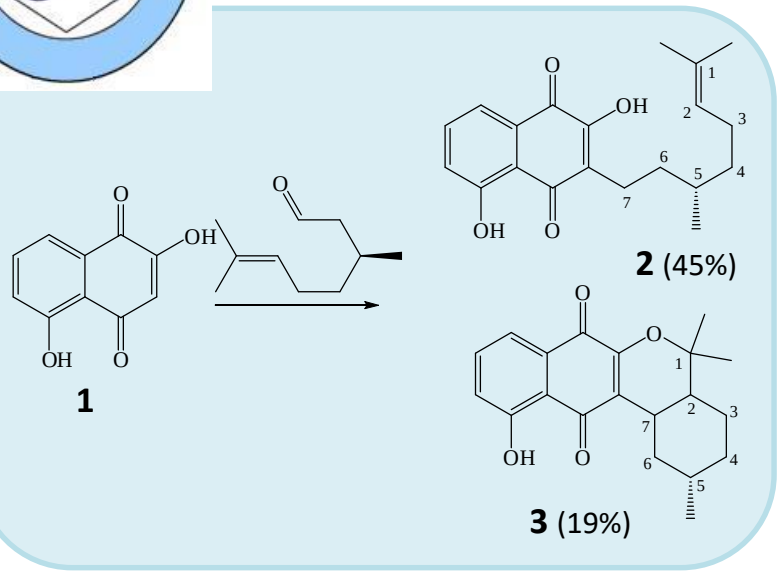
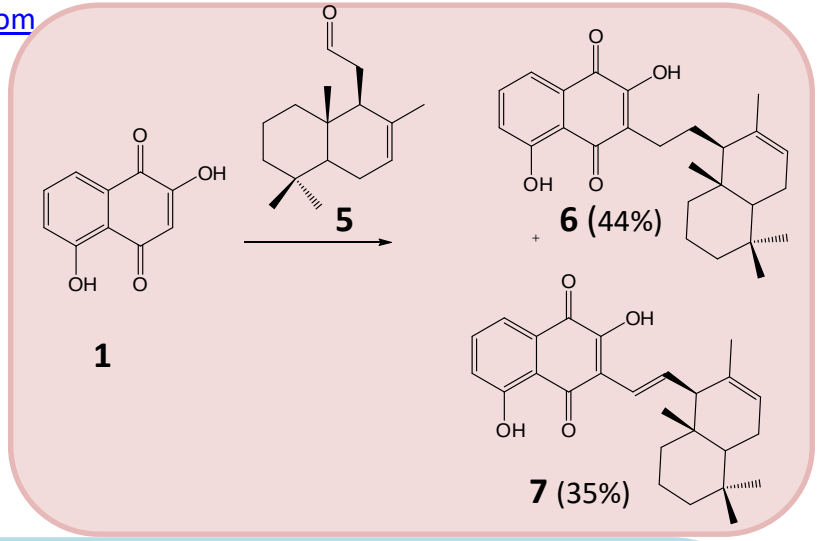
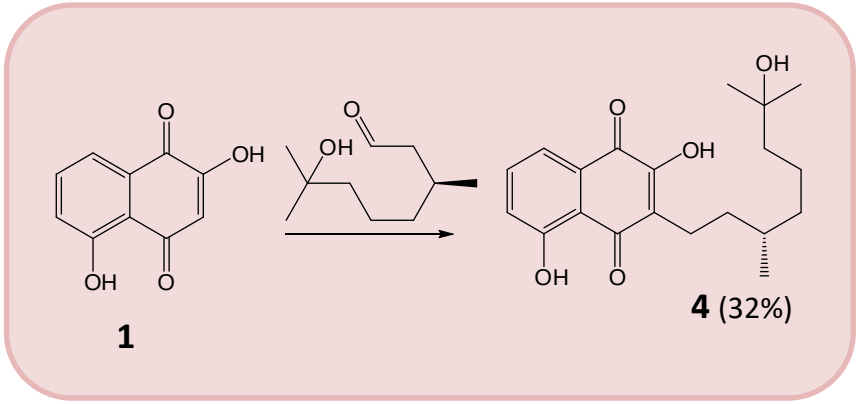
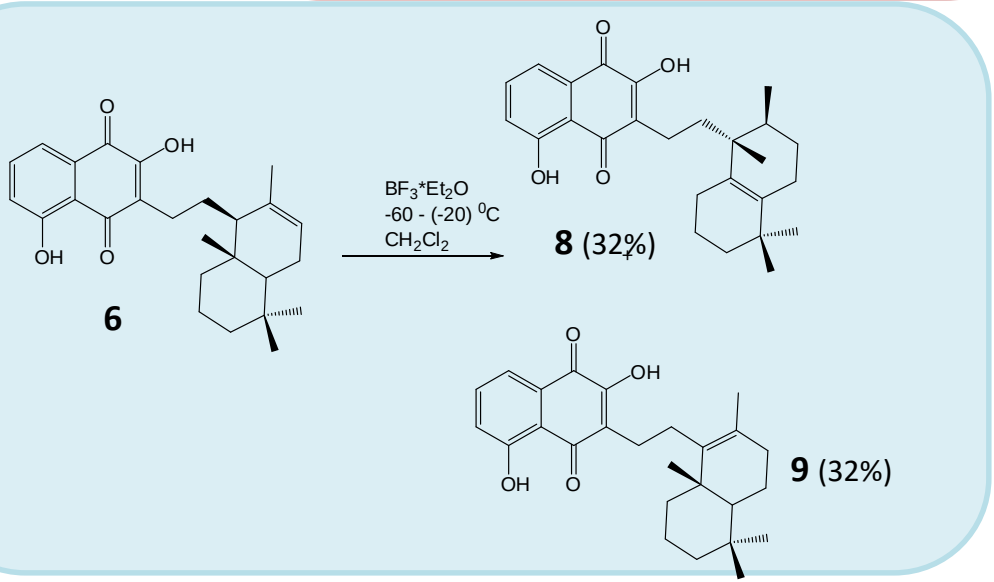


Conditions:
Hantzsch ester
L-Prolin
CH_2Cl_2, reflux







NEW CYTOTOXIC ENT-KAURANES WITH UNPRECEDENTED PHARMACOPHORES

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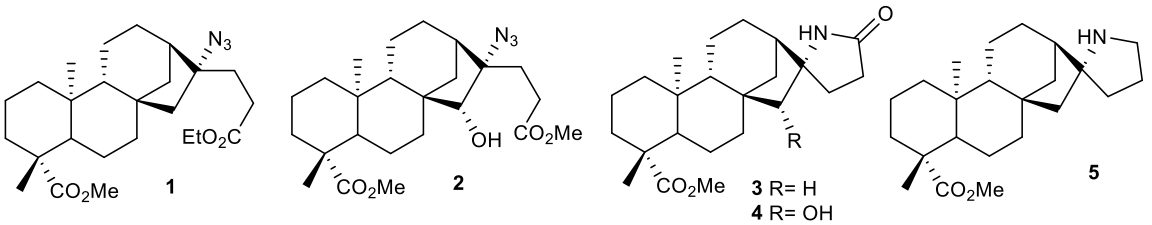
The cytotoxicity of *ent*-kauranic derivatives functionalized with azide, lactam and pyrrolidine fragments has been demonstrated. The inverstigated compounds showed relevant activity against Capan-1 (pancreatic adenocarcinoma), Hap-1 (chronic myeloid leukemia), HCT-116 (colorectal carcinoma), NCI-H460 (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**.



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

Compound	Conc. unit	IC_{50}								
		hTERT RPE-1	Capan-1	Hap-1	HCT-116	NCI-H460	DND-41	HL-60	K-562	Z-138
1	µM	1.8±0.4	1.7±0.5	4.4±2.7	1.0±0.4	1.3±0.1	1.4±0.3	3.0±1.4	8.8±2.2	0.5±0.2 SI=3.6
2	µM	25.9±0.3	8.3±1.1	40.4±8.6	9.9±2.7	0.6±0.2 SI=43.2	6.6±1.3	41.1±15.9	36.9±0.2	21.6±5.4
3	µM	7.6±0.5	1.2±0.7	2.1±0.4	0.8±0.2 SI=9.5	1.4±0.1	21.4±10.1	38.3±17.8	36.4±11.5	52.0±33.4
4	µM	27.7±4.3	3.7±1.7 SI=7.5	1.1±0.6 SI=25.2	4.0±3.7	1.9±0.2	8.3±2.0	38.0±11.8	56.5±2.8	39.8±10.9
6	µM	32.2±2.0	11.5±1.0	9.2±3.3 SI=3.5	11.6±0.5	1.0±0.1 SI=32.2	6.1±1.1 SI=5.3	8.3±1.3 SI=3.9	3.2±1.0 SI=10.1	9.5±0.9 3.4
DT	nM	18.7±4.8	4.2±1.8	4.5±1.5	2.2±0.8	5.5±1.3	4.7±1.2	4.3±1.6	5.2±1.2	3.7±0.7
SP	nM	1.0	6.2±1.8	1.3±0.2	1.5	2.2±0.8	8.6±1.5	9.1±1.6	27.9±3.2	6.7±4.4

Table 1. Antiproliferative activity of selected *ent*-kauranic derivatives. SI – selectivity index; **DT –** Docetaxel; **SP** – Staurosporine.

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 (ANCD).

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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].

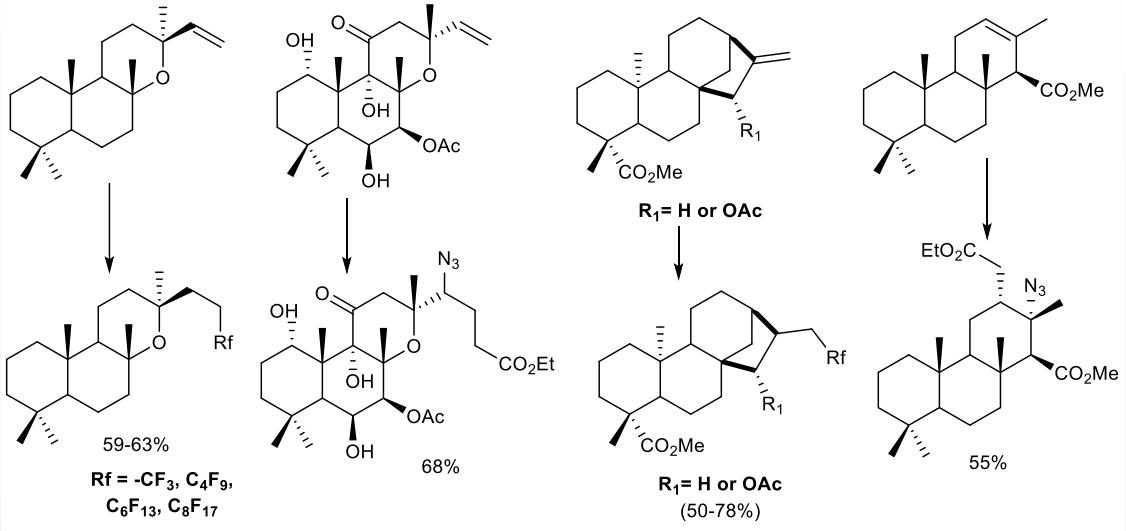

Figure 1. Radical transformation of labdane diterpenoids.

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.

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

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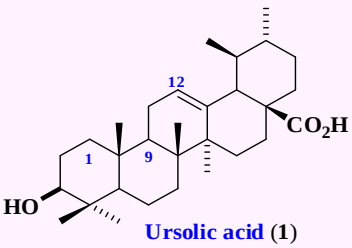
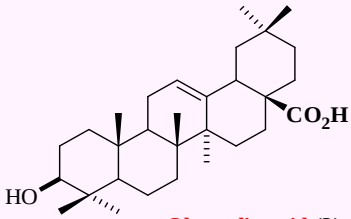
NMR spectroscopy is a convenient method for structural identification of both individual compounds and complex natural products mixtures. The main advantages of this powerful analytical tool are, among others, high resolution power, as well as simultaneous qualitative and quantitative evaluation of the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



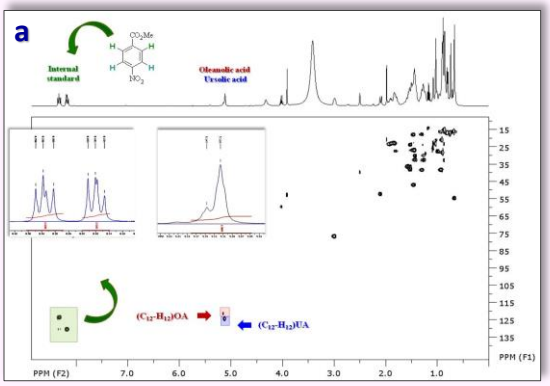
Ursolic acid (1)

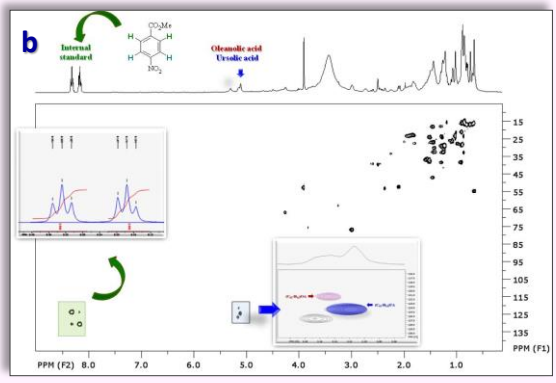


Oleanolic acid (2)

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 (*fig. 1; a, b*). Methyl *para*-nitrobenzoate (MPNB) was used as internal standard and the calibration plots have been drawn separately for each acid (*fig. 1, c*). 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.





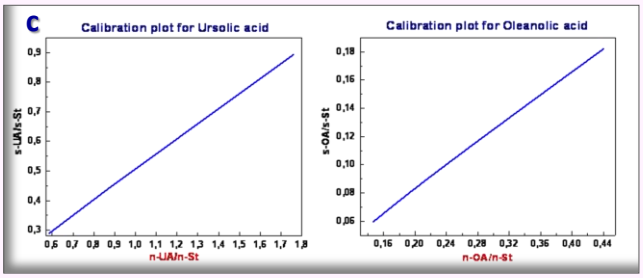


Fig. 1. (*a*) 400 MHz ^{1}H–^{13}C HSQC spectrum of the pure mixture of oleanolic (OA) and ursolic acid (UA) (ns = 32, experimental time: 1 h; (*b*) ^{1}H–^{13}C HMBC spectrum of the crude EtOAc-extract from apple pomace (ns = 32, experimental time: 1 h; (*c*) Calibration plots for triterpenic acids determination with MPNB as internal standard.

Acknowledgments

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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 defatted grape (Vítis vinífera) seeds, and their following ozonolytic cleavage leading to new analogues with improved properties (Fig. 1).

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 ˚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 ˚C for 60 minutes.

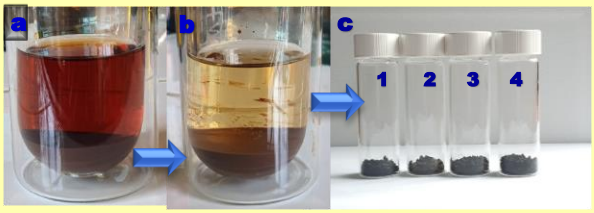

Fig.1. Picture of isolated (**a**), washed (**b**) and dried (**c**) lignins: ***1)*** spruce (Picea abies) lignin (**PA-L**); ***2)*** PA-L modified analog (**O-PA-L**); ***3)*** deffated grape (Vitis vinifera) seeds lignin (**VV-L**); ***4)*** VV-L modified analog (**O-VV-L**).

The resulting polymeric fractions have been investigated by spectral methods (IR and NMR). In particular, heteronuclear HSQC (Fig. 2) 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.

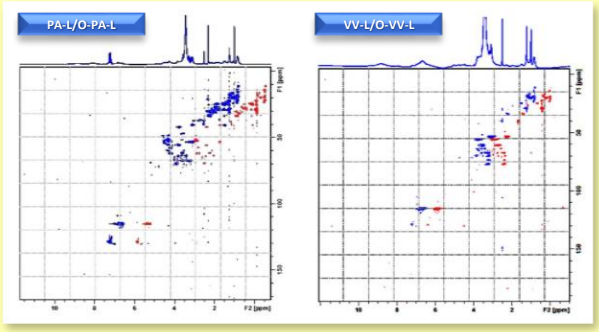

Fig.2. The HSQC NMR spectra of natural lignins in DMSO-d_6 before (blue color) and after (red color) ozonolysis in DES (for illustration and comparison purposes, the signals of the modified analogs were shifted).

Acknowledgements

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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SYNTHESIS OF SOME NEW HOMODRIMANE DERIVATIVES OF BENZOTHIAZOLE FROM NORAMBREINOLIDE

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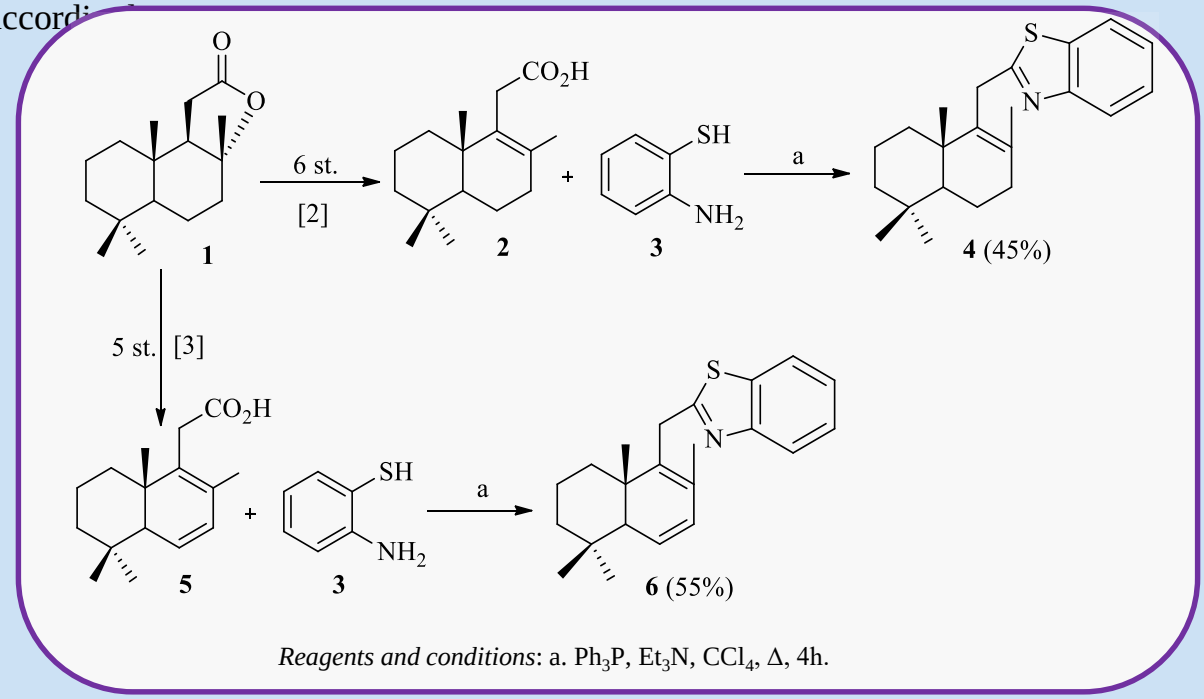
Many drimane and homodrimane sesquiterpenoids, including those containing nitrogen, are known to exhibit a variety of biological activities [1]. The search of new biologically active compounds prompted us to synthesize homodrimane sesquiterpenoids (**4**) and (**6**), containing benzothiazole fragment. 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**), accordi



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

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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SYNTHESIS OF SOME HOMODRIMANE SESQUITERPENOIDS WITH DIHYDRAZIDE FRAGMENT FROM NORAMBREINOLIDE

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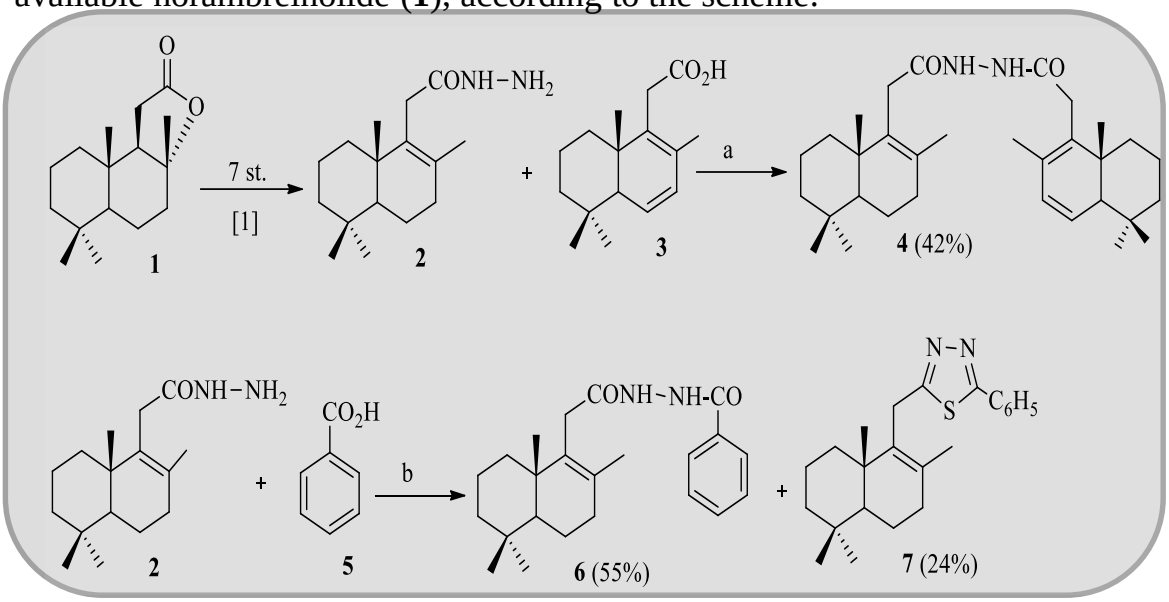
In a search of new biologically active compounds, in the present communication we describe the synthesis of N-(Δ^8-bicyclohomofarnesenoyl)-N′-Δ(^{6,8}-bicyclohomofarnesenoyl)-hidrazine (**4**), N-(Δ^8-bicyclohomofarnesenoyl)-N′-benzoyl-hidrazine (**6**) and 2-phenyl-5-(Δ^8-bicyclohomofarnesenyl)-1,3,4-thiadiazole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



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

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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SYNTHESIS OF HYDRAZIDE CONTAINING TRINORLABDANE DERIVATIVES

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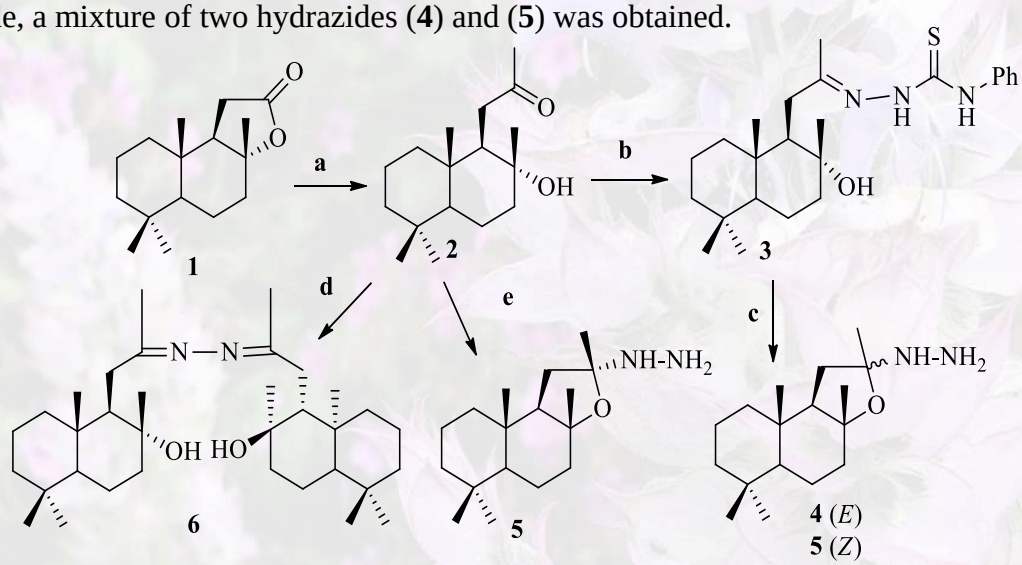
The starting material for the synthesis of trinorlabdane compounds with hydrazide fragments was used hydroxyketone (**2**) which was obtained from commercially available sclareolide (**1**). Ketone (**2**) was coupled with 4-phenylthiosemicarbazide in ethanol, to afford compound (**3**) (Scheme) [1]. 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%.

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

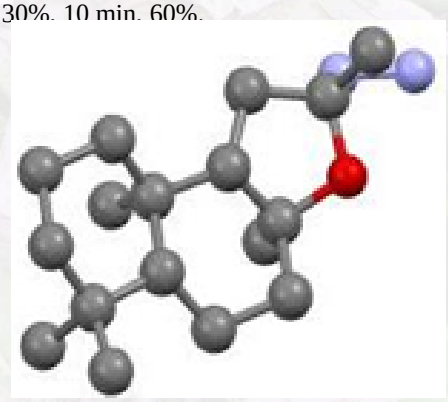


Figure 1. Molecular structure of compound **(4)**.

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

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Background

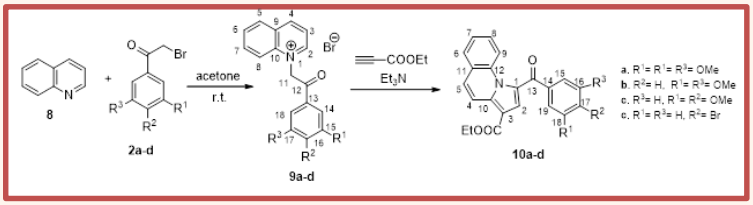
Natural compounds with quinoline and isoquinoline scaffolds have demonstrated numerous biological activities and have found use in both medical research laboratories and clinical practice throughout the world [1]. In particular, semisynthetic pyrroloquinoline derivatives are currently widely accepted 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 chemistry efforts for further improvement of biological activity, including our own group's [3], other heterocycles 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].

Results and discussion

As a continuation of our work in the field of heterocyclic derivatives with anticancer activity, we synthesized novel pyrrolo-fused heterocycles based on quinoline, isoquinoline, benzo[f]quinoline, pyrazine and pyrimidine, in order to see investigate the influence of the heterocyclic core on the biological properties of the new compounds. Our strategy for the generation of pyrroloheterocycles involves the 1,3-dipolar cycloaddition of *N*-ylides generated *in situ* in basic medium from the corresponding monoquaternary salts to ethyl propiolate (Scheme 1).

Table 1. Results of the 5-dose *in vitro* human cancer cell growth inhibition[a] for pyrroloquinoline **10a** and positive control Phenstatin; GI_{50} – the molar concentration of tested compound causing 50% growth inhibition of tumor cells. LC_{50} – the molar concentration of tested compound causing 50% death of tumor cells. [a]Data obtained from NCI's *in vitro* 60 cell 5-dose screening.

Cell type	Compound	10a	10a	Phenstatin	Phenstatin
	Cell line	GI_{50} (μM)	LC_{50} (μM)	GI_{50} (μM)	LC_{50} (μM)
Leukemia	K-562	0.0701	>100	<0.010	>100
	SR	0.0704	>100	<0.010	>100
Colon Cancer	HCT-15	0.197	>100	<0.010	>100
	SW-620	0.256	>100	<0.010	>100
	KM12	0.172	>100	<0.010	>100
	HCT-116	0.335	>100	0.038	>100
CNS Cancer	SF-295	0.258	>100	0.367	>100
	SF-539	0.223	>100	0.011	>100
	SNB-75	0.0351	>100	<0.010	>100
	U251	0.428	>100	0.043	>100
Melanoma	M14	0.202	>100	<0.010	>100
	MDA-MB-435	0.0367	20.4	<0.010	>100
	UACC-62	0.141	>100	0.448	>100
Ovarian Cancer	OVCAR-3	0.151	>100	0.021	>100
	NCI/ADR-RES	0.252	>100	0.012	>100
Renal Cancer	786-0	0.658	>100	0.905	>100
	A498	0.0485	>100	2.28	>100
	RXF 393	0.234	>100	0.016	>100
Breast cancer	MCF7	0.134	>100	0.033	>100
	HS 578T	0.272	>100	0.031	>100
	BT-549	0.172	>100	0.034	>100
	MDA-MB-468	0.396	>100	2.71	>100
Prostate cancer	PC-3	0.332	>100	0.045	>100
	DU-145	0.422	>100	0.039	>100



Scheme 1. General strategy for the generation of pyrrole-fused heterocycles, exemplified for quinolines **10a-d**

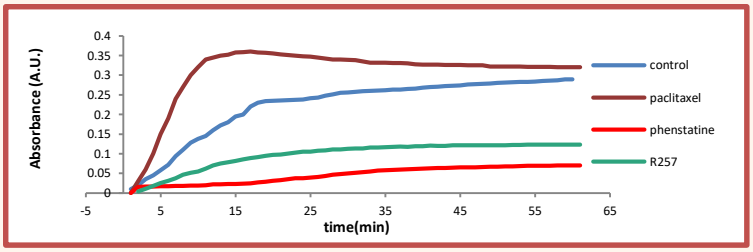


Figure 1. Effects of compound **10a (R257)** (10^{-5} M) on microtubule dynamics. As controls, paclitaxel is used as microtubule stabilizing agent and Phenstatin as microtubule destabilizing agent (10^{-5} M).

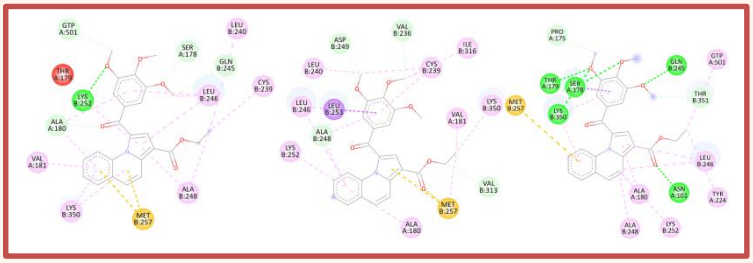


Figure 2. Interactions of the three lowest-scoring poses of **10a** at the colchicine binding site of tubulin

From all newly-synthesized compounds, twenty-five were selected for screening against a panel of 60 human tumor cell lines at the National Cancer Institute in a single-dose assay. Showing the most significant growth inhibition in the first evaluation step, pyrroloquinoline **10a** was selected for evaluation against the same cell panel at five concentrations (Table 1), where it exhibited submicromolar activity in most cell lines. In order to confirm if the observed anticancer effect of compound **10a** is conferred by a microtubule-targeting mechanism, we evaluated the effect of the active compound **10a** on the assembly of tubulin and showed that this compound has a similar tendency as phenstatin, a microtubule-destabilizing agent (Figure 1). Since phenstatin is known to exert its effect through binding to the colchicine binding site of the α,β-tubulin heterodimer, we hypothesize that compound **10a** also prefers to bind to this site. However, as tubulin is known to possess several binding sites for microtubule inhibitors, we investigated the relative preference of compound **10a** to other binding sites present at the surface of tubulin through global molecular docking experiments. The most energetically favorable poses for **10a**, as revealed by global docking experiments, were positioned in the colchicine binding site of tubulin. We then performed local docking on this site in order to investigate the molecular nature of these preferential conformations, which revealed three low scoring clusters of comparable energy (-8.95, -8.77 and -8.69 kcal/mol – Figure 2), which could be used for further conformational optimization.

Conclusions. Compound **10a** exhibits submicromolar GI_{50} inhibitory activity against several cancer cell lines. Excellent activity is noted on A498 renal cancer cell line (48.5 nM), 47-fold more potent that phenstatin, and SNB-75 CNS cancer cell line (35.1 nM). Compound **10a** exerts its anticancer activity by destabilizing microtubules through binding to the colchicine binding site of tubulin. This compound could serve as a useful lead for further structural optimization in the development of novel anticancer agents.

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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 after performing the MTT test, was noticed that 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.

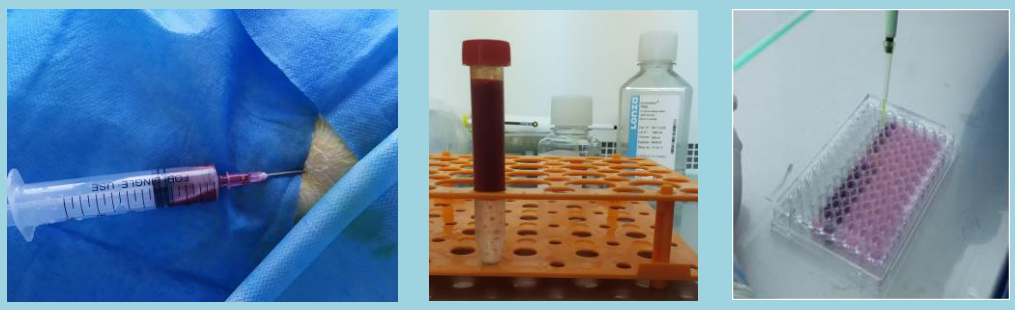

Figure 1. Steps in obtaining of mesenchymal stem cells and performing MTT

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Chemical composition of essential oil of Dill (*Anethum graveolens* L.) growing in Republic of Moldova

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Introduction

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].

Method and Instrumentation

Analysis were carried out on an Agilent Technologies 7890A system with 5975C Mass-Selective Detector (GC-MSD) equipped with split-splitless injector (split, 250°C, split ratio 1:50, 1 mL) and HP-5 ms capillary calibrated column (30 m x 0.25 mm x 0.25 mm); 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, solvent delay 3 min 40 sec.

Conclusions 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.

Results

Phytochemical composition of *Dill* essential oil of Moldovan origin.

No.	RT* (min)	Component	%	No.	RT* (min)	Component	%
1	4.290	*α*-Thujene	0.16	14	10.731	E-Dihydrocarvone	1.00
2	4.438	*α*-Pinene	0.86	15	10.943	Z-Dihydrocarvone	1.93
3	4.737	Camphene	0.08	16	11.255	Z-Dihydrocarveol	0.10
4	5.208	Sabinene	0.26	17	11.400	Z-Carveol	0.05
5	5.294	*β*-Pinene	0.06	18	11.664	Dihydro-izo-carveol	0.20
6	5.525	*β*-Myrcene	0.45	19	11.785	E-Carveol	0.08
7	5.935	*α*-Phellandrene	21.47	20	12.175	S-(+)-Carvone	31.72
8	6.345	*p*-Cymene	0.93	21	12.246	Linalyl acetate	0.38
9	6.521	D-Limonene	26.86	22	13.069	Bornyl acetate	0.08
10	7.136	L-Limonene	0.03	23	15.752	*β*-Cubebene	0.06
11	7.869	*α*-Terpinene	0.12	24	16.514	*β*-Caryophyllene	0.07
12	8.141	Linalool	0.10	25	18.025	D-Germacrene	0.13
13	10.480	Dill ether	12.16	26	19.017	*β*-Cadinene	0.06

**RT - retention time.*

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%).

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