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DIRECTED SYNTHESIS AND STUDY OF ANTIMICROBIAL ACTIVITY OF POLYFUNCTIONALIZED NORLABDANE COMPOUNDS

143.04-Bioorganic chemistry, chemistry of natural and physiologically active compounds

Summary of the PhD thesis in chemical sciences

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The thesis has been elaborated in the Doctoral School of Biological, Geonomic, Chemical and Technological Sciences, of the State University of Moldova and the Institute of Chemistry

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The public defence of the thesis will take place on **May 5, 2022**, **14:00** in the session of the Doctoral Committee within the Doctoral School of Biological, Geonomic, Chemical and Technological Sciences, Senate Hall of the Moldova State University, study block A, 3/2, Academiei Street, Chisinau *(http://www.usm.md)*

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CONCEPTUAL FRAMEWORK OF THE INVESTIGATION

Timeliness and importance of the research

Fungal and bacterial infectious have spread rapidly in recent years, becoming one of the most important concerns in countries around the world. Therefore, it is necessary to design new molecular structures with antimicrobial properties, which could lead to new and effective medicinal preparations for the treatment of fungal and bacterial infections. Natural products are an important source of new biologically active compounds. Their natural origin implies biocompatibility, selective biological activity and low toxicity. Terpenoids are compounds that can be isolated from natural sources or obtained synthetically, and are widely used in medicine, pharmaceuticals, cosmetics and agriculture. Particular attention is paid to terpene compounds that possess anticancer, antimicrobial, antifungal, antimalarial, antidiabetic activity, etc.

On the other hand, it is known that most bioactive pharmaceuticals contain heterocycles and such fragments are invaluable materials for medicine, pharmaceuticals and agriculture, possessing a wide spectrum of activity, including antifungal, antiviral, antituberculosis, anti-HIV, anticancer, etc.

Recently, the synthesis of molecules with a hybrid skeleton has emerged as a powerful tool in the design of drugs and especially preparations with promising biological activity. This approach is based on the combination of several pharmacophores, which produce compounds with a combined backbone and have a higher bioactivity than known drugs.

During the last years in the Laboratory "Chemistry of Natural and Biologically Active Compounds" of the Institute of Chemistry were developed several methods of synthesis of compounds with combined skeleton, containing terpenic and heterocyclic fragments.

In addition to heterocyclic compounds, products with 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments are also used, which are very important for modeling new drugs, solvents, plasticizers or cosmetics. It is also known that some 1,3-thiazoles, 1,3,4-thiadiazoles and benzothiazoles have anticonvulsant, antimicrobial, anti-inflammatory, antitumor and other important biological effects.

It has also been established that thiosemicarbazones are a privileged pharmacophore, which is frequently found in compounds with anticancer, antimicrobial and antiviral properties. At the same time, the imine bond (-N=CH-) in the structure of these compounds is useful in organic synthesis, especially for obtaining heterocyclic fragments.

Thus, the compounds containing in their structure the thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments have been of interest for years due to the wide range of biological activities they possess.

Therefore, in this thesis, the emphasis will be on the synthesis of new terpenoids with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments that have a promising therapeutic potential.

Labdane diterpenoid (-)-sclareol was used as a starting material for this research, which was isolated from renewable resources following the production of volatile sage oil (*Salvia sclarea* L.).

The aim of the thesis

Development of efficient methods for the synthesis of new optically active norlabdane compounds with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments, based on the natural labdane diterpenoid sclareol; elucidation of the possible mechanisms of synthesis reactions of polyfunctionalized compounds with promising biological activity.

The research objectives

- Synthesis of bicyclohomofarnesenic methyl esters from commercially available sclareolide, using non-conventional methods: microwave irradiation, electrooxidation and sensitized photooxidation.
- Synthesis of di- and trinorlabdane compounds with thiosemicarbazone fragment starting from the intermediate ketones, their heterocyclization into di- and trinorlabdane compounds with 1,3-thiazole structural units.
- Obtaining tetra- and pentanorlabdane compounds with thiosemicarbazone and 1,3-thiazole structural units using the methyl ester of 13,14,15,16-tetranorlabd-8(9)-en-7-oxo-12-oic acid and drim-8(9)-en-7-one as a starting products.
- Synthesis of chiral coordination compounds using norlabdane compounds functionalized with thiosemicarbazone structural unit as ligands.
- Synthesis of tetranorlabdane compounds with thiosemicarbazone, 1,3-thiazole and 1,3,4-thiadiazole structural units, starting from 13,14,15,16-tetranorlabd-6(7),8(9)-dien-12-oic acid.
- Obtaining tetranorlabdane compounds with benzothiazole structural units from terpenic acids as substrate, using amides and thioamides as intermediate compounds.

  Determination of the structure of the new compounds by applying physico-chemical methods of analysis such as: IR; ^{1}H, ^{13}C, ^{15}N NMR spectroscopy; mass spectrometry and X-ray diffraction.
- Testing of new obtained compounds for antimicrobial activity on fungal strains and bacterial species.

The research hypothesis involves the directed synthesis of di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole structural units, based on the labdane diterpenoid sclareol. The mentioned compounds are important for the modeling of new drugs, solvents, plasticizers, cosmetics, etc.

The outlook of the research methodology and justification of the research methods

The research methodology includes classic and non-trivial methods, such as microwave irradiation, electrooxidation and sensitized photooxidation. All planned steps are aimed at developing efficient methods for obtaining polyfunctionalized norlabdane compounds.

The antimicrobial activity of the newly synthesized compounds was tested *in vitro* on five fungal strains (*Aspergillus niger, Fusarium solani, Penicillium chrysogenum, Penicillium frequentans, Alternaria alternata*) and two species of bacteria, Gram-negative (*Pseudomonas aeruginosa)* and Gram-positive (*Bacillus sp*.) by the method of consecutive dilutions in the agar medium.

The scientific novelty and originality of the results obtained consists in (i) the application of non-conventional methods (microwave irradiation, anodic oxidation and sensitized photooxidation), based on non-polluting, non-aggressive and cheaper technologies, which have allowed the optimization of known syntheses and obtaining of a series of new polyfunctionalized norlabdane compounds from the mixture of bicyclohomofarnesenic methyl esters; (ii) the development of original methods for the synthesis of a new optically active norlabdanic compounds with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments with promising therapeutic potential; (iii) functionalization of norlabdanic compounds, both in the side chain and in the cycle B, after which it was obtained potential biological activity derivatives with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments; (iv) for the first time, were obtained chiral complex compounds using norlabdane compounds functionalized with thiosemicarbazone fragment as ligands.

The applicative value of the research

The antimicrobial activity of fifty new chiral compounds on five fungal strains and two bacterial species was tested. Four of the reported compounds showed promising antimicrobial activity. These developments may be of interest to pharmaceutical companies, using norlabdane derivatives instead of biologically active chiral compounds.

The implementation of scientific results

The methods of synthesis and activity of two new tri- and tetranorlabdane compounds with thiosemicarbazone and 1,3,4-thiadiazole fragments were patented. These compounds may further become the subject of detailed research, with a view to their implementation in practice in

the treatment of fungal diseases.

The publications related to the thesis

There were published on the topic: 3 articles in peer-reviewed journals (one in an international journal with an impact factor and two in national journals of category A); 4 articles in national collections and 6 abstracts at national and international scientific conferences; 2 patents were obtained.

Thesis overview

The thesis contains 148 pages of the main text, 72 figures and 5 tables. The thesis is divided into 3 chapters, introduction, list of abbreviations, literature review, 2 main chapters, general conclusions and recommendations, 197 references, declaration on the assumption of responsibility and author's CV.

Thesis content:

1. METHODS OF SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME COMPOUNDS WITH THIOSEMICARBAZONE, 1,3-THIAZOLE, 1,3,4-THIADIAZOLE AND BENZOTHIAZOLE FRAGMENTS

This chapter presents a literature review. Methods for the synthesis of organic compounds, including terpenic compounds with various fragments, such as thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole, and the use of thiosemicarbazone moiety derivatives as ligands are reviewed.

2. SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DI-, TRI-, TETRA- AND PENTANORLABDANE COMPOUNDS WITH THIOSEMICARBAZONE FRAGMENT

2.1. Synthesis of di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazone fragment

In recent years, special attention has been paid to the synthesis of biologically active compounds with a combined backbone, especially those containing terpenic and heterocyclic fragments. Compounds with thiosemicarbazone fragment also possess broad spectra of biological activities, including antitumor, antifungal, antibacterial, antiviral, antimalarial, etc. There are publications in the scientific literature about the synthesis of terpenic compounds with thiosemicarbazone fragment and the biological evaluation of these compounds. This led us to realize syntheses of polyfunctionalized norlabdane compounds, especially with thiosemicarbazone structural units.

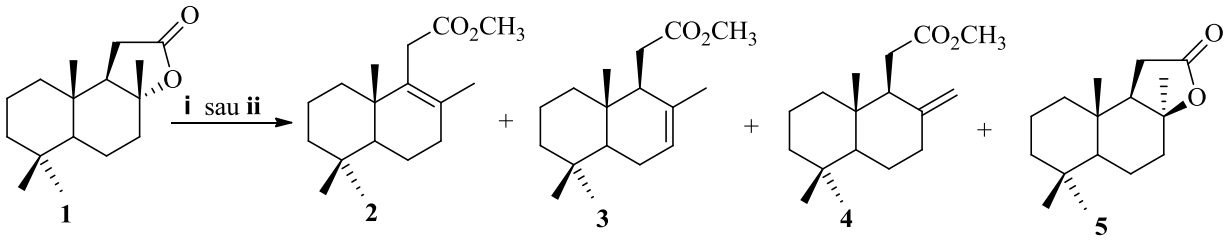
2.1.1. The use of non-conventional methods in the synthesis of bicyclohomofarnesenic methyl esters - valuable intermediates for the synthesis of norlabdane compounds

The non-conventional methods such as: microwave and ultrasonic irradiation,

electrochemical and photochemical transformations belong to green chemistry and offer many advantages. These methods often lead to desired results through non-specific mechanisms, increase yields, reduces costs and excludes the use of reagents or the formation of toxic reaction products. Some examples of successful use of non-conventional methods in the synthesis of new compounds from various classes have been described in the literature [1].

This subchapter describes an efficient method for the synthesis of bicyclohomofarnesenic methyl esters **2-4** from sclareolide **1**, by microwave irradiation, and its comparative analysis with the classical transesterification-dehydration reaction, known as Stoll and Hinder method.

The transesterification-dehydration reaction, proposed for the first time by the mentioned authors, consists in treatment of (+)-sclareolide **1** with sulphuric acid in methanol which led to mixture of isomeric bicyclohomofarnesenic methyl esters **2** and **3** [2]. Later it was found that during isomerization of lactone **1**, a mixture of three methyl esters **2-4** was obtained in 96% yield and 6:3:1 ratio (according to GC-MS and NMR data, together with a small amount of isolactone **5** (Fig. 2.1) [1].



Reagents and conditions: **i**. H_2SO_4, MeOH, Δ, 96 h, 96%; **ii**. H_2SO_4, MeOH, MW, 30 min, 93%.

Fig. 2.1. Synthesis of bicyclohomofarnesenic methyl esters 2-4 from (+)-sclareolide 1

Another procedure for the synthesis of esters **2-4** from lactone **1** was using ion-exchange resins (*Amberlite 15*) [3]. For the same purpose, was used the sulphocationite-catalysed (*KU-23*) in the transesterification reaction of (+)-sclareolide **1** in methanol, which after 7 hours led to bicyclohomofarnesenic methyl esters **2-4** in a 12:6:1 ratio. The same reaction performed in methanol/heptane mixture gave a different ration of isomers 2:1:7 [4].

The main disadvantage of obtaining methyl esters using reaction Stoll and Hinder is multi-hours reflux of lactone **1**. According to this, the transesterification-dehydration reaction of (+)-sclareolide **1** into compounds **2-4** was performed in just 30 minutes using microwave irradiation, with a 95% yield and co-ratio of isomers (Table 2.1).

In this study, the dynamics of esters **2-4** formation was analyzed using GC-MS method during their preparation by the Stoll and Hinder method and compared the data with those of microwave-assisted method (Table 2.1) [5].

Table 2.1. The results of GC-MS analysis of bicyclohomofarnesenic methyl esters 2-4 mixture

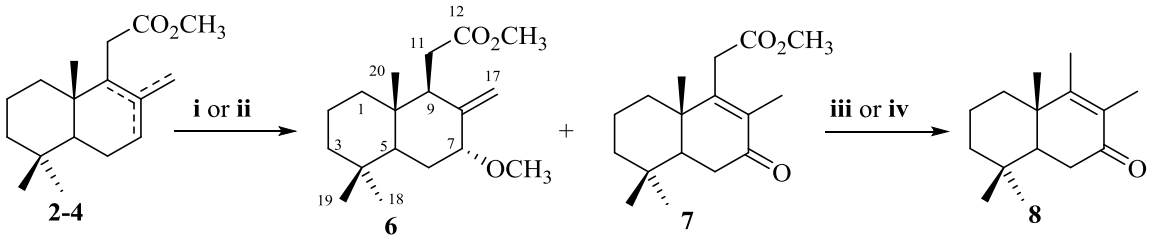
Time, (h), Stoll & Hinder	Compounds, ratio (%)			Time, (h), (min) MW	Compounds, ratio (%)		
	2	**3**	**4**		**2**	**3**	**4**
8	36.43	51.49	7.10	10	14.45	56.69	24.49
24	56.92	40.97	2.11	20	14.05	52.73	26.85
48	60.03	38.87	1.09	30	14.78	55.79	24.32
72	70.17	28.20	1.63	40	Decomposition		
96	73.67	24.39	1.53				

It must be noted, at the beginning of transesterification-dehydration reaction of (+)-sclareolide **1** by Stoll and Hinder procedure the formation of trisubstituted isomer **3** is favored. The tetrasubstituted **2** and exocyclic **4** isomers are obtained in lower yields. Then, in the course of the reaction their ratio changes to 15:5:3, the yield of isomer **2** increases and that of isomer **3** decreases more than twice. The isomer **4** is a minor product of the reaction and its yield varies from 7.10% to 1.53%. In this case only trace amounts of isolactone **5** were detected.

In the case of microwave-assisted transesterification of (+)-sclareolide **1** the ratio of the mixture of methyl esters **2-4** is 3:11:5, quite different from the previously reported. According to GC-MS analysis, in 30 minutes the major isomer is trisubstituted **3** (55.79%), followed by exocyclic **4** (24.32%) and tetrasubstituted **2** (14.78%) ends the series. After this time the decomposition of the reaction products starts [5].

The authors [6] performed the synthesis of 7-oxo-13,14,15,16-tetranorlabd-8(9)-en-12-oic **7** methyl ester with a 38% yield, by oxidizing the ester mixture **2-4** with potassium dichromate with subsequent decarboxylation thereof into drim-8(9)-en-7-one **8**.

Later, another method of synthesis of ketoester **7** was suggested, namely the anodic electrooxidation of the mixture of methyl esters **2-4** with lithium perchlorate in methanol using graphite electrodes. Following this transformation, ketoester **7** was obtained in 63% yield, and methoxyester **6** as a minor compound (6%) (Fig. 2.2). Traditionally, both compounds **7** and **8** are prepared synthetically, because ketoester **7** has not been identified in natural sources, and drimenone **8** in very small amounts [7].

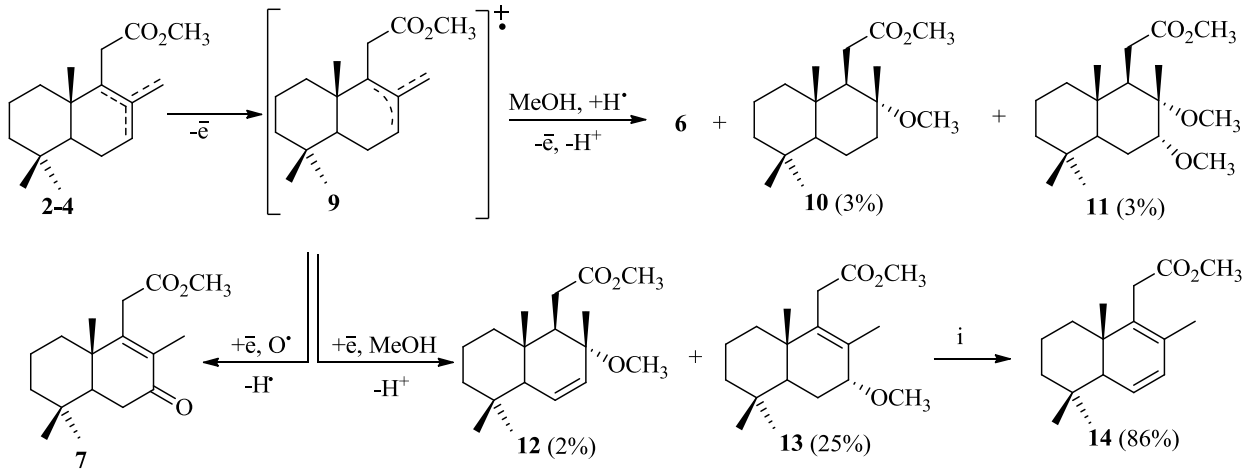


Reagents and conditions: **i**. $K_2Cr_2O_7$, MeOH, Δ, 12 h; **ii**. $LiClO_4$, MeOH, ē, 3 h; **iii**. KOH, EtOH, Δ, 3 h; **iv**. KOH, EtOH, MW, 1.5 h.

Fig.2.2. Synthesis of ketoester 7 and drimenone 8

The compounds **7** and **8** are key intermediates in the synthesis of new polyfunctionalized norlabdane derivatives. The use of microwave irradiation allowed improving the preparation method of drimenone **8** in 92% overall yield, by faster decarboxylation of ketoester **7** (Fig 2.2) [8].

Chromatographic analysis (analytical TLC and GC-MS) of the electrooxidation reaction product of methyl esters **2-4** showed a complex mixture of compounds. For this reason, it was decided to realize an exhaustive study of its chemical composition. As result, additionally to previously reported compounds **6** and **7** a series of minor compounds **10-13** were isolated and characterized (Fig. 2.3) [5].



Reagents and conditions: **i**. H_2SO_4, THF, r.t., 24 h.

Fig. 2.3. Synthesis of the minor compounds 10-13 from the mixture 2-4

It is well known that the anodic oxidation of olefins, including terpenes, occurs by cation radical intermediate generated by anodic one electron elimination from the olefinic π-electron system [9,10]. The olefins bearing at least one allylic hydrogen undergo an allylic substitution reaction in which the solvent is a nucleophile.

In this study, at the first step mixture of methyl esters **2-4** loses an electron and generates cation radical **9** as a reactive species. Next, its interaction with methanol as a nucleophile is accompanied by a series of electrons, radicals or ions additions/eliminations and leads to the allylic substitution products **10-13**, which were isolated and characterized.

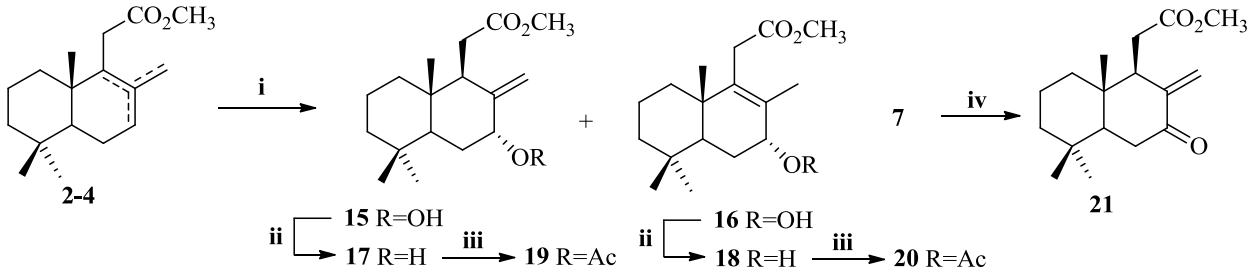
With reference to the ketoester **7**, it can be assumed that this is a product of allylic oxidation of isomer **2**. Lithium perchlorate is a strong oxidizing agent and, in these conditions, its reduction takes place according to equation 2.1 with the formation of atomic oxygen.

$$LiClO_4 \xrightarrow[-\bar{e}]{} LiCl + 4O^{\bullet} \qquad (2.1)$$

The lifetime of this highly reactive species is enough to attack the allylic position of cation radical **9** and to cause its oxidation through several intermediate states (Fig. 2.3) [5].

Due to the high content of metoxyester **13** it was decided to employ it for the synthesis of dienester **14**, an important intermediate used before for the synthesis of polyfunctional homodrimanic compounds [8]. The compound **14** was successful obtained in 86% yield by the reaction with H_2SO_4 concentrate in THF, and its spectral data are described in the paper [11].

The sensitized photooxidation of methyl esters **2-4** with *meso*-tetraphenylporphyrin in dichloromethane leads to new isomeric hydroperoxides **15** and **16** in 77% and 9% yield (Fig 2.4) [5].



Reagents and conditions: **i**. O_2, TPP, hν, CCl_4, r.t.; **ii**. Thiourea, MeOH, 0°C to r.t.; **iii**. Py, Ac_2O, r.t.; **iv**. PCC, CH_2Cl_2, AcOH (gl.), molecular sieves 3Å, r.t.

Fig.2.4. The sensitized photooxidation reaction of the methyl esters 2-4

Further, the hydroperoxides **15** and **16** were converted into alcohols **17** and **18** (96 and 94%) using thiourea in methanol, and their acetylation with acetic anhydride in anhydrous pyridine leads to acetates **19** and **20** in 98% and 97% yields. The oxidation of alcohols **17** and **18** by pyridinium chlorochromate (PCC), molecular sieves 3Å and glacial acetic acid in dichloromethane led to known ketoesters **7** and **21**, both with the same 98% yield [5].

Thus, the utility of the three non-conventional methods was demonstrated: microwave irradiation, electrooxidation and sensitized photooxidation in the syntheses of polyfunctionalized norlabdane compounds. These methods belong to green chemistry and have been used successfully in the synthesis of polyfunctionalized norlabdane compounds and in establishing the mechanism of formation of these products.

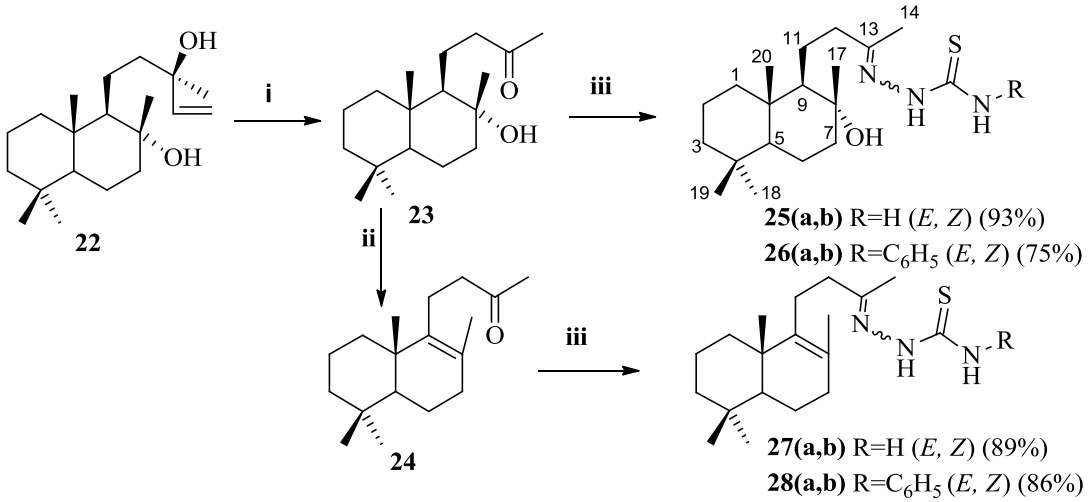
2.1.2. Synthesis of di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazone fragment derived from ketones

Compounds containing a thiosemicarbazone fragment exhibit broad spectra of pharmacological properties including antitumor, antifungal, antibacterial, antiviral, antimalarial, etc. [12, 13]. The ketones and acids can be used as starting material for obtaining norlabdane

compounds with thiosemicarbazone fragment by coupling reaction.

The available labdane diterpenoid (-)-sclareol **22** was used as a starting material for getting dinorlabdane compounds with thiosemicarbazone fragment. First, compound **22** was subjected to oxidative degradation with potassium permanganate in acetone, producing 8α-hydroxy-15,16-dinorlabd-13-one **23** in 90% yield. Then, hydroxyketone **23** was treated with trimethylsilylmethanesulphonate ($MeSO_3SiMe_3$) in acetonitrile and led to 15,16-dinorlabd-8(9)-en-13-one **24** in 80% yield (Fig. 2.5).

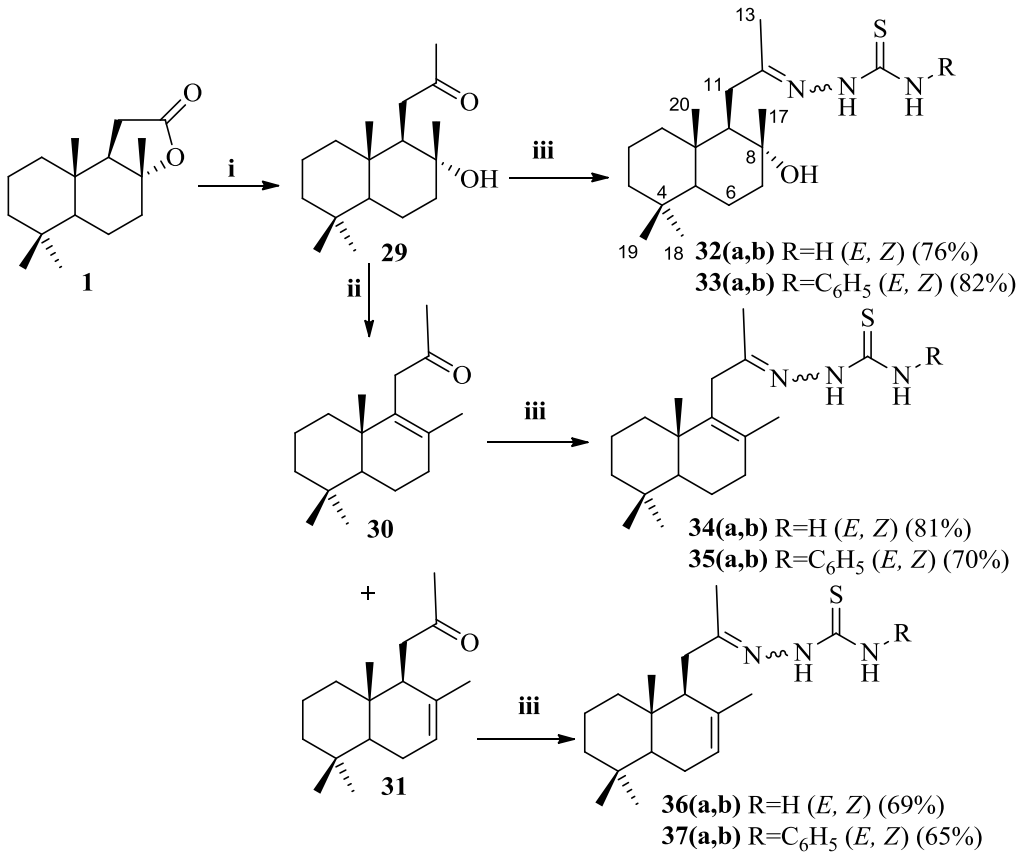
Further, the coupling reactions of hydroxyketone **23** and unsaturated ketone **24** with thiosemicarbazide and 4-phenylthiosemicarbazide (1:1.1 mole ratio) lead to dinorlabdane isomers **25a,b**-**28a,b** [14-16].



Reagents and conditions: **i**. $KMnO_4$, acetone, r.t., 4 h, 90%; **ii**. $MeSO_3SiMe_3$, MeCN, r.t., 15 min, 80%; **iii.** $NH_2NHCSNH_2$ or $NH_2NHCSNHC_6H_5$, EtOH, 8-24 h, 60-80°C.

Fig. 2.5. Synthesis of dinorlabdane compounds with thiosemicarbazone fragment 25a,b-28a,b

Trinorlabdane compounds with thiosemicarbazone fragment were synthesized starting from commercially available sclareolide **1**. The lactone **1** was treated with CH_3Li in ether in molar ratio 1:2, gave 8α-hidroxi-14,15,16-trinorlabd-12-one **29**. After, hydroxyketone **29** was partially dehydrated with trimethylsilylmethanesulphonate in MeCN produced 14,15,16-trinorlabd-8(9)-en-13-one **30** and 14,15,16-trinorlabd-7(8)-en-13-one **31** (4:1 ratio) in 91% overall yield. All the compounds were separated using column chromatography (Fig. 2.6).

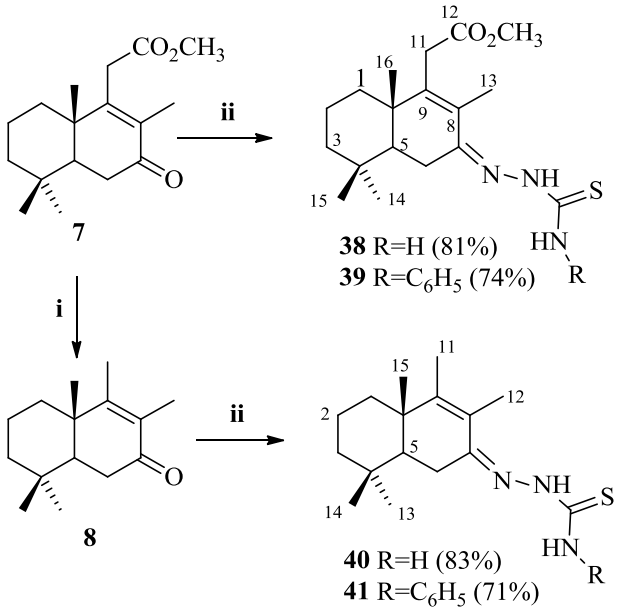


Reagents and conditions: **i**. CH_3Li, Et_2O, r.t., 15 min, 65%; **ii**. $MeSO_3SiMe_3$, MeCN, r.t., 15 min, 91%; **iii**. $NH_2NHCSNH_2$ or $NH_2NHCSNHC_6H_5$, EtOH, 8-24 h, 60-80°C.

Fig. 2.6. Synthesis of trinorlabdane compounds with thiosemicarbazone fragment 32a,b-37a,b

The coupling reaction of hydroxyketone **29** and unsaturated ketones **30**, **31** with thiosemicarbazide and 4-phenylthiosemicarbazide in ethanol led to trinorlabdane compounds with thiosemicarbazone fragment **32a,b**-**37a,b**. Each of these thiosemicarbazone compounds represents mixtures of two inseparable isomers [14, 16-19].

As previously mentioned, ketoester **7** was obtained from (+)-sclareolide **1** in two steps, using non-conventional methods: microwave irradiation and electrooxidation (Fig. 2.2) [5]. Drim-8(9)-en-7-one **8** was obtained by the saponification-decarboxylation reaction of ketoester **7** with potassium hydroxide in ethanol. The coupling of acid **7** and lactone **8** with thiosemicarbazide and 4-phenylthiosemicarbazide in ethanol led to tetra- and pentanorlabdane compounds with thiosemicarbazone fragment **38-41** (Fig. 2.7) [14, 16].



Reagents and conditions: **i**. KOH, EtOH, Δ, 3 h, 98%; **ii**. $NH_2NHCSNH_2$ or $NH_2NHCSNHC_6H_5$, EtOH, 24 h, 60-80°C.

Fig. 2.7. Synthesis of tetra- and pentanorlabdane compounds with thiosemicarbazone fragment 30-41

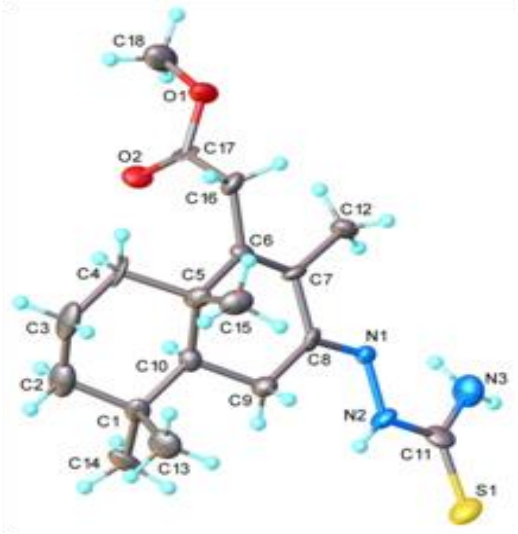
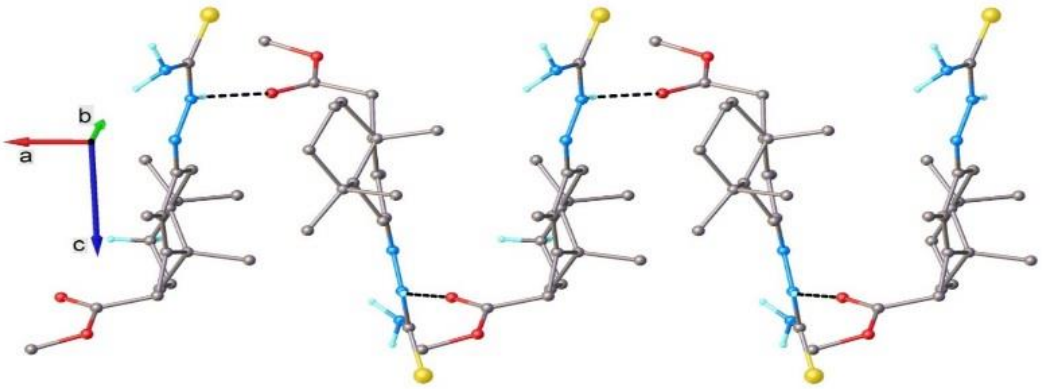


Fig. 2.8. Molecular structure of thiosemicarbazone tetranorlabdane 38. Thermal ellipsoids are represented at 40% probability

The structure and stereochemistry of compound **38** was confirmed by the X-ray diffraction method. The compound crystallizes in the Sohnke orthorhombic space group $P2_12_12_1$ and has a molecular structure. The asymmetric part of the elementary cell consists of a neutral molecule in enantiomerically pure form as shown in Figs. 2.8. In the crystal, molecules are associated due to hydrogen bonds with the participation of -NH_2 groups as donors and the oxygen atom in the ester groups as proton acceptors. These interactions lead to the formation of 1D type supramolecular arrangements, as shown in Fig. 2.9.



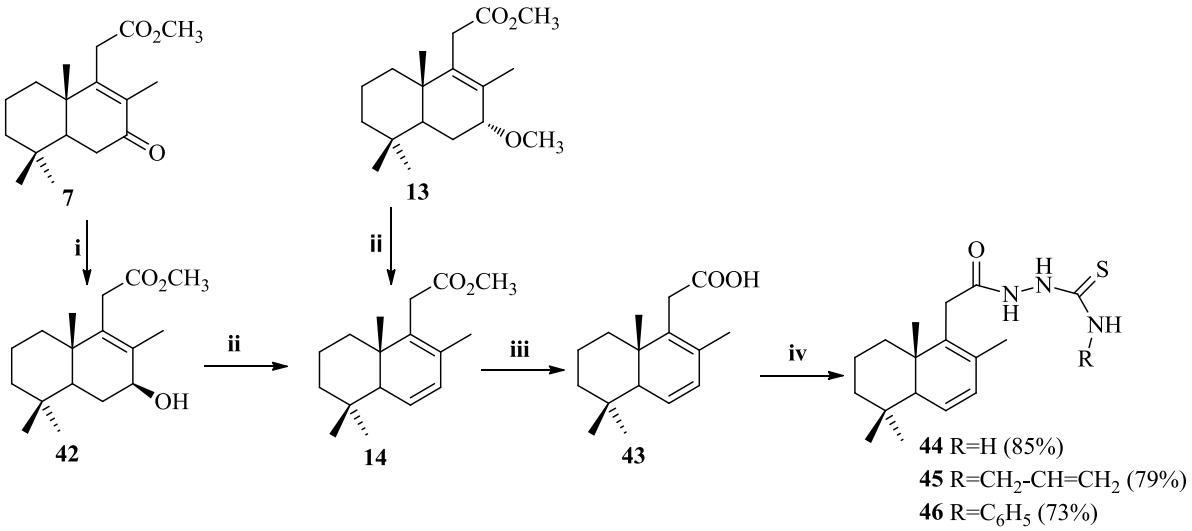
H-bond parametrs: N2H···O2 (Å,°) [N2-H 0.86, H···O2 2.39, N2···O2(x – 0.5, -y – 0.5, -z – 1) 3.183(10), ∠ N2HO2 153.2]

Fig. 2.9. The role of hydrogen bonds in the formation of supramolecular (1D) chains in the crystal structure of compound 38

2.1.3. Synthesis of tetranorlabdane compounds with thiosemicarbazone unit derived from acids

There are two classical methods of obtaining dien ester **14**. The first way is to reduce methyl ester **7** with sodium borohydride ($NaBH_4$) in the presence of cerium chloride (III) heptahydrate ($CeCl_3 \cdot 7H_2O$) in methanol, obtaining hydroxyester **42** in 97% yield. The dehydration reaction of hydroxyester **42** with H_2SO_4 (conc.) in tetrahydrofuran gave methyl ester **14** in 89% yield. The second way includes direct treatment of methoxyester **13** with H_2SO_4 (conc.) in tetrahydrofuran, whereby the yield of diene **14** is 86%. Further, 13,14,15,16-tetranorlabd-6(7),8(9)-dien-12-oic acid **43** was obtained by saponification of ester **14** with KOH in ethanol, the yield being 96%.

Dienoic acid **43** was coupled with thiosemicarbazide, 4-allylthiosemicarbazide and 4-phenylthiosemicarbazide in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) in methylene chloride to give three compounds with combined tetranorlabdane and thiosemicarbazone skeleton **44-46** (Fig. 2.10).



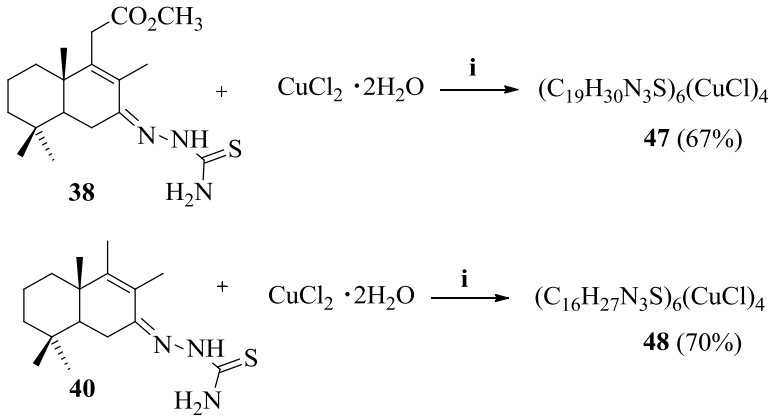
Reagents and conditions: **i**. $CeCl_3 \cdot 7H_2O$, MeOH, $NaBH_4$, r.t., 0.5 h, 97%; **ii**. THF, H_2SO_4 conc., r.t., 24 h, 86%, 89%; **iii**. EtOH, KOH, 50°C, 3 h, 96%. **iv**. $NH_2NHCSNH_2$, $NH_2NHCSNHCH_2$-CH=CH_2 or $NH_2NHCSNHC_6H_5$, EDCI, CH_2Cl_2, r.t., 24 h.

Fig. 2.10 Synthesis of tetranorlabdane compounds with thiosemicarzone fragment 44-46

2.2. The use of norlabdane compounds with thiosemicarbazone fragment as ligands

Biologically active compounds, used as ligands, considerably increase the efficiency of the corresponding metal complexes. In this case, thiosemicarbazones can serve as complexes with transition metals, these being among the most studied compounds due to their numerous therapeutic properties: antimicrobial, antitumor, antifungal or antibacterial [20, 21]. The

complexation reaction of thiosemicarbazones **38** with $CuCl_2 \cdot 2H_2O$ (molar ratio 2:1) in methanol, with stirring at 50°C for one hour, gave complexes $(C_{19}H_{30}N_3S)_6(CuCl)_4$ **47** and $(C_{16}H_{27}N_3S)_6(CuCl)$ **48** with 67% and 70% yields (Fig. 2.11).



Reagents and conditions: **i**. $CuCl_2 \cdot 2H_2O$, MeOH, 50°C, 1 h, **47** and **48**.

Fig. 2.11. The complexation of tetra- and pentanorlabdane bearing thiosemicarbazone fragment with $CuCl_2 \cdot 2H_2O$ salt

The structure and stereochemistry of complex **48** was confirmed by the X-ray diffraction method (Fig. 2.12). The compound crystallizes in the Sohnke triclinic space group *P*1. The crystal has a molecular structure consisting of two entities (A and B), chemically identical but crystallographically independent of complex tetranuclear molecules with the composition $[Cu_4Cl_4(HL)_6]$, where HL is the ligand **40**. The asymmetric part of the elementary cell also contains three molecules of DMF and three molecules of water, therefore the chemical composition is: $[Cu_4Cl_4(HL)_6] \cdot 3DMF \cdot 3H_2O$. The molecular structure of the complex compound $[Cu_4Cl4(HL)_6]$ is shown in Fig. 2.12.

The complex molecule consists of a tetranuclear nucleus $[Cu_4Cl_4S_6]$ (Fig. 2.13), where each copper atom (I) is surrounded by ClS_3 with a slightly distorted tetrahedral geometry. The four copper atoms are linked by six sulphur atoms as bidentate-bridge type donor atoms derived from six HL neutral ligands [22]. Cu-Cu distances vary in the range 3,722 (7) - 3,924 (7) Å. It should be mentioned that the molecular structure of the complex is stabilized by a series of intramolecular hydrogen bonds of N-H ⋯ Cl type (Fig.2.12).

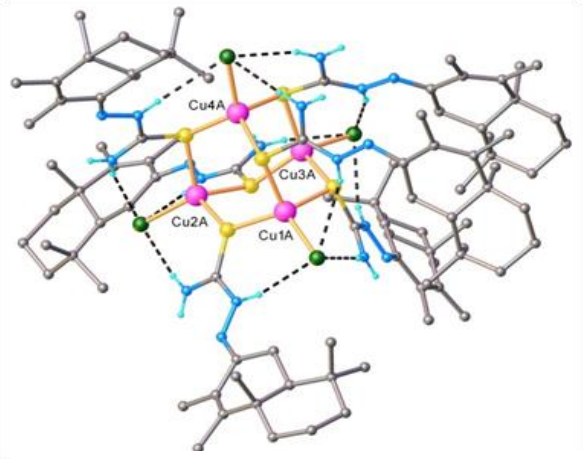


Fig. 2.12. Molecular structure of complex 48 $[Cu_4Cl_4(HL)_6]$ (asymmetric molecule A). H atoms bonded to C atoms are omitted for clarity

In the research described above, tetra- and pentanorlabdane compounds with the thiosemicarbazone fragment in position C_7 of cycle B, as a ligand were used. Then, the trinorlabdane compound **32a,b** with the thiosemicarbazone fragment located in the side chain was studied. It has been established in this case that the complexation with $CuCl_2 \cdot 2H_2O$, under the same conditions, proceeds differently than in the case of ligands with thiosemicarbazone moiety located in C_7 position of cycle B. The complexations of compound **32a,b** with other transition metal salts, such as: $Cu(CH_3COO)_2$ and $Ni(CH_3COO)_2$, were attempted to confirm the formation of complexes **49-51**.

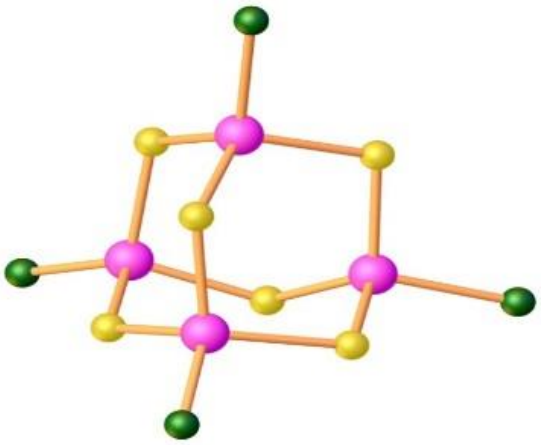
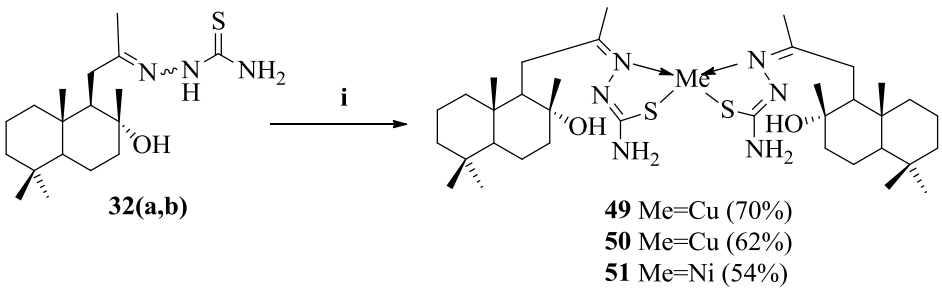


Fig. 2.13. The structure of the tetranuclear fragment $[Cu_4Cl_4S_6]$



Reagents and conditions: **i**. $CuCl_2 \cdot 2H_2O$; $Cu(CH_3COO)_2$ or $Ni(CH_3COO)_2$, MeOH, 50°C, 1 h.

Fig. 2.14. The complexation reaction of norlabdane compounds bearing thiosemicarbazone with transition metal salts

Table 2.2. Elemental analysis of complexes 49-51

Metal salts	Compound	Molecular formula	Elemental analysis: found (calculated)		
			C (%)	H (%)	N (%)
-	Thiosemicarbazone **32a,b** (TSC)	$C_{18}H_{33}N_3OS$	63.41 (63.67)	9.65 (9.0)	12.25 (12.38)
$CuCl_2 \cdot 2H_2O$	**49** $[Cu(TSC)_2]$	$C_{36}H_{66}N_6O_2S_2Cu$	58.05 (58.22)	8.90 (8.96)	11.05 (11.32)
$Cu(CH_3COO)_2$	**50** $[Cu(TSC)_2]$	$C_{36}H_{66}N_6O_2S_2Cu$	58.40 (58.22)	8.76 (8.96)	10.98 (11.32)
$Ni(CH_3COO)_2$	**51** $[Ni(TSC)_2]$	$C_{36}H_{66}N_6O_2S_2Ni$	58.87 (58.61)	9.07 (9.02)	11.20 (11.39)

Table 2.3. IR spectra (cm^{-1}) of coordinating compounds 49-51

Compound	*v* (NH_2)	*v* (C=S)	*v* (C=N)	*v* (N-N)	*v* (C-OH) (H_2O)	*v* (M-N)
Tiosemicarbazone **32a**,**b** (TSC)	3430, 3265	798	1594	937	3677	-
49 [Cu $(TSC)_2$]	3243, 3162	778	1527, 1600	937	3412	-
50 [$Cu(TSC)_2$]	3310, 3205	780	1530, 1625	935	3450	540
51 [$Ni(TSC)_2$]	3301, 3196	766	1527, 1628	943	3387	559

According to the elemental analysis data (Table 2.2) and IR spectra (Table 2.3) of the complexes, it was assumed that the reaction is carried out as shown in the scheme (Fig. 2.14). In complexes **49-51** ligands manifest as mono-deprotonated bases in thioenol form. Copper (II) ions possess a square plane configuration with two bidentate thiosemicarbazones linked by azomethine nitrogen and thioenolic sulphur atoms.

2.3. Methods for the synthesis of di-, tri-, tetra- and pentanorlabdane with thiosemicarbazone fragment

It includes the description of working techniques and experimental procedures. The structures of all newly synthesized compounds were confirmed using spectral data (^1H, ^{13}C, ^{15}N NMR, IR), mass spectrometry and X-ray analysis.

2.4. Antimicrobial activities of the di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazone fragment

The di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazone fragment were tested for antimicrobial activity. Compounds **26a,b** and **27a,b** possessed antifungal activity with minimal inhibitory activities (MIC=0.25 μg/mL), comparable to the antifungal drug Caspofungin (MIC=0.25 μg/mL) and also showed antibacterial activity (MIC=4.0 μg/mL), comparable to the antibiotic Kanamycin (MIC=4.0 μg/mL).

Thiosemicarbazone **32a,b** has antifungal activity with minimal inhibitory concentration (MIC=0.19 μg/mL), comparable to the antifungal drug Caspofungin (MIC=0.25 μg/mL) and also has antibacterial activity (MIC=3 μg/mL), comparable to the antibiotic Kanamycin (MIC=4.0 μg/mL) [23]. According to patent no. 4780 granted by the State Agency for Intellectual Property [19] compound **32a,b** can be used as an antifungal remedy.

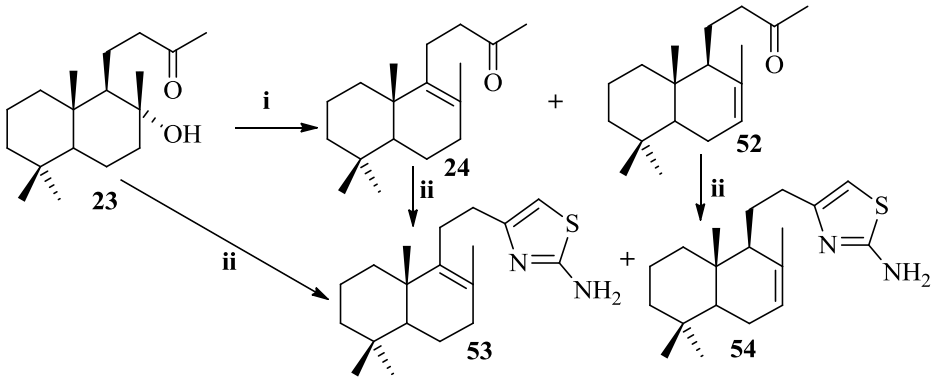
Compound **40** possessed moderate antifungal activity with minimal inhibitory concentration (MIC=1.5 μg/mL) compared to the activity of the antifungal agent Caspofungin (MIC=0.2 μg/mL) and also has significant antibacterial activity (MIC=0.125 μg/mL), that is, it is twenty-four times more active than the known antibiotic Kanamycin (MIC=3.0 μg/mL).

3. SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DI-, TRI-, TETRA- AND PENTANORLABDANE COMPOUNDS WITH 1,3-THIAZOLE, 1,3,4-THIADIAZOLE AND BENZOTHIAZOLE FRAGMENTS

3.1. Synthesis of di-, tri-, tetra- and pentanorlabdane compounds with 1,3-thiazole fragment

1,3-Thiazole fragment is a very important structural unit for the design of new drugs. It is also known that compounds with thiazole fragment possess antiviral, antioxidant, antimicrobial, anti-inflammatory, antitumor and other important biological activities. For the first time, di- and trinorlabdanic compounds with 1,3-thiazole fragment were obtained starting from the corresponding ketones. As a starting material, hydroxyketone **23**, unsaturated ketones **24** and **52** were used for the synthesis of the mentioned compounds, which were subjected to the condensation-cyclization reaction with thiourea and iodine in ethanol, with the formation of 2-amino-4-(15,16-dinorlabd-8(9)-en)-1,3-thiazole **53** and 2-amino-4-(15,16-dinorlabd-7(8)-en)-1,3-thiazole **54** (Fig. 3.1) [24].

Hydroxyketone **23** forms a mixture of two compounds with 2-amino-1,3-thiazole fragment **53** and **54** (1.5:1 ratio) in 87% yield, under the described conditions. The formation of this mixture can be explained as follows: the presence of molecular iodine favors the elimination of hydroxy group in the initial compound and leads to thiazoles **53** and **54**, obtained in 52% and 35% yields. The unsaturated ketones **24** and **52**, under the same conditions, gave only the mentioned 2-amino-4-(15,16-dinolabd-8(9)-en)-1,3-thiazole **53** and 2-amino-4-(15,16-dinorlabd-7(8)-en)-1,3-thiazole **54** with 85% and 80% overall yields [24].

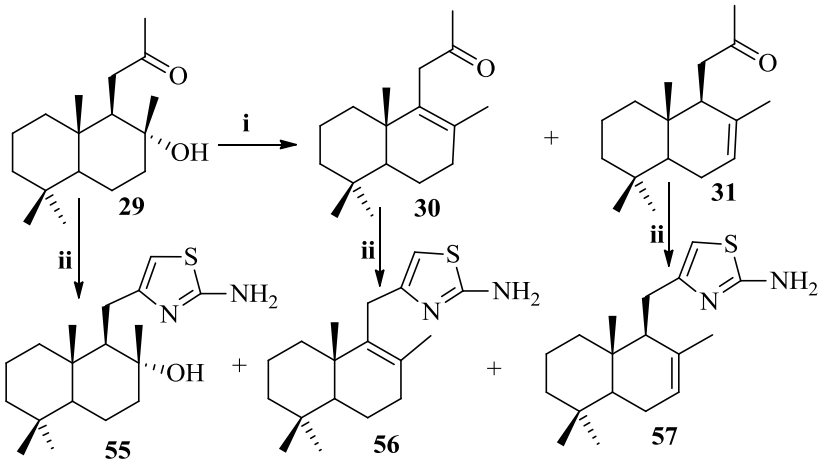


Reagents and conditions: **i**. $MeSO_3SiMe_3$, MeCN, r.t., 15 min, **24** (80%), **52** (15%);
ii. $SC(NH_2)_2$, I_2, EtOH, 12 h, Δ, **53** (52% and 85%), **54** (35% and 80%).

Fig. 3.1. Synthesis of dinorlabdane compounds with 2-amino-1,3-thiazole fragment 53 from ketones

Trinorlabdane compounds with 2-amino-1,3-thiazole fragment **55-57** were obtained by treating ketones **29-31** with thiourea and iodine in ethanol. But in the case of hydroxyketone **29**,

a mixture of thiazoles **55-57** was obtained with 85% overall yield in 1:1.5:2.5 ratio. The formation of this mixture can be explained analogically as in the case of hydroxyketone **23**, with the difference that hydroxyketone **29** undergoes partial dehydration, which led to 2-amino-4-(14,15,16-trinorlabd-8(9)-en)-1,3-thiazole **56** and 2-amino-4-(14,15,16-trinorlabd-7(8)-en)-1,3-thiazole **57**, in 25% and 43% yields. This fact is confirmed by the formation of minor hydroxylated 2-amino-4-(8*α*-hidroxy-14,15,16-trinorlabd)-1,3-thiazole **55**, isolated from the reaction mixture in 17% yield. The condensation-cyclization reaction of unsaturated ketones **30** and **31**, under the same conditions, led to tetrasubstituted **56** and trisubstituted **57** thiazoles, with 82% and 80% yields (Fig.3.2) [24, 25].



Reagents and conditions: **i**. $MeSO_3SiMe_3$, MeCN, r.t., 15 min, **30** (73%), **31** (18%);
ii. $SC(NH_2)_2$, I_2, EtOH, 12 h, Δ, **55** (17%), **56** (25% and 82%), **57** (43% and 80%).

Fig. 3.2. Synthesis of trinorlabdane compounds 55-57 with 2-amino-1,3-thiazole fragment

A proposed mechanism for the synthesis of di- and trinorlabdane compounds with 2-amino-1,3-thiazole fragment is given in Fig.3.3. Initially, this involves formation of iodine derivative **58**, then next nucleophilic substitution of the iodine atom affords intermediate **60**, which by intramolecular addition of the nitrogen to the carbonyl group gives intermediate **61**, and its dehydration generates the desired compound with 2-amino-1,3-thiazole fragment.

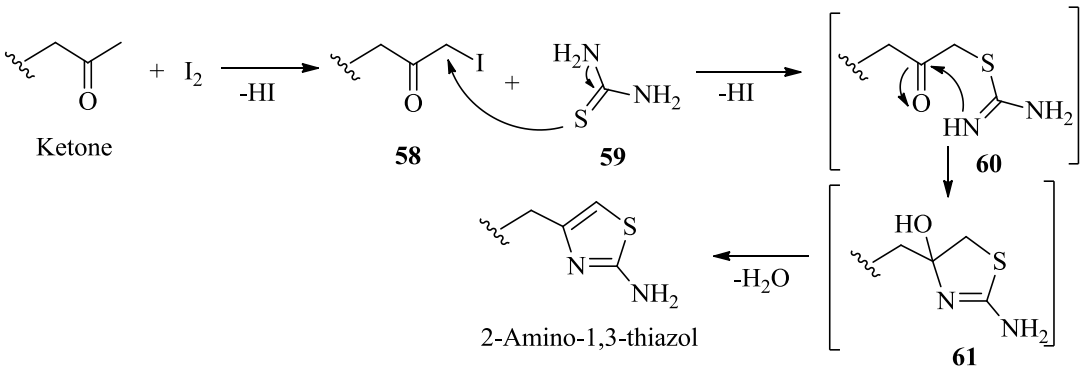
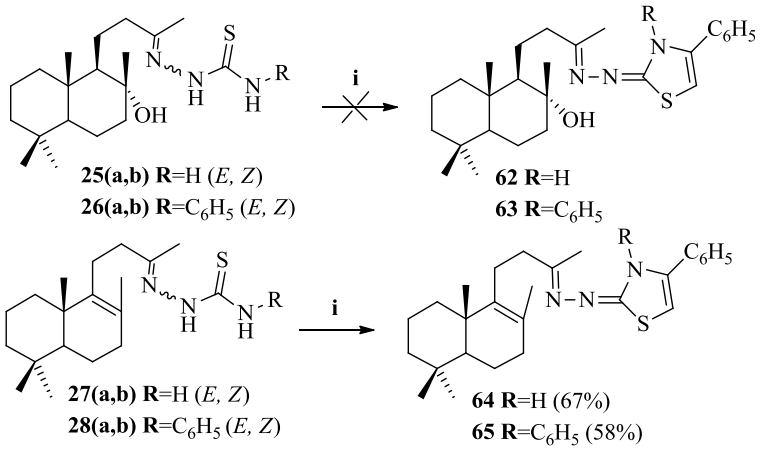


Fig. 3.3. Proposed mechanism for the synthesis of 2-amino-1,3-thiazole fragment

In the continuation of the research on the synthesis of di-, tri, tetra- and pentanorlabdanic compounds with 1,3-thiazole structural units, the synthesis of mentioned compounds was performed from their thiosemicarbazones. For this reason, dinorlabdanic thiosemicarbazones **25a,b**-**28a,b** were subjected to the heterocyclic reaction with bromoacetophenone, in a molar ratio of 1:1 in ethanol. Unfortunately, attempts to obtain compounds **62** and **63** via heterocyclization of thiosemicarbazones **25a,b** and **26a,b** were unsuccessful (Fig. 3.4).

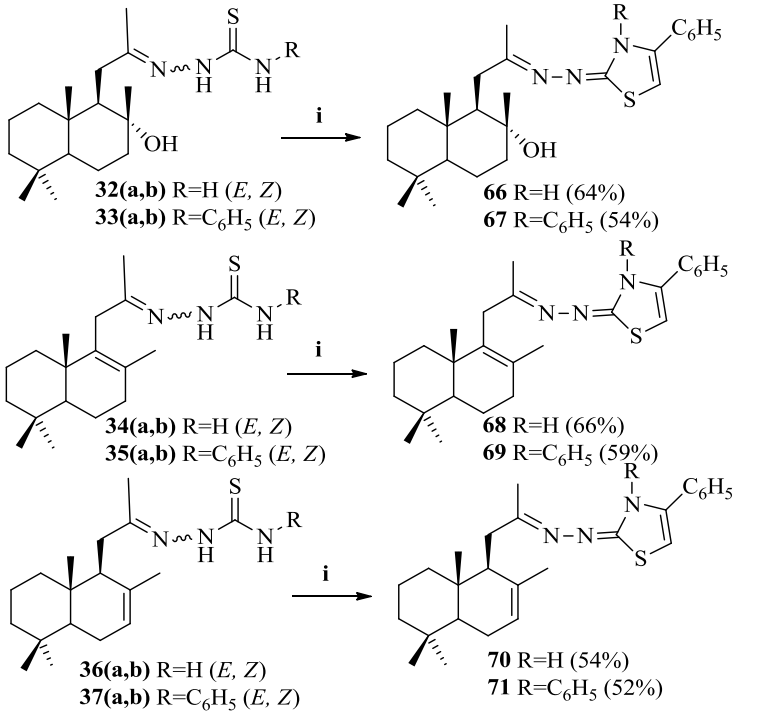


Reagents and conditions: **i**. $C_6H_5COCH_2Br$, EtOH, r.t., 8-14 h.

Fig. 3.4. Synthesis of dinorlabdane compounds with 1,3-thiazole fragment 64 and 65 from thiosemicarbazones

Reaction of thiosemicarbazones **27a,b** and **28a,b** with 2-bromoacetophenone in ethanol (1:1 mole ratio) formed dinorlabdane compounds with 1,3-thiazole fragment **64** (67% yield) and **65** (58% yield) [14-16].

Likewise, isomeric trinorlabdane thiosemicarbazones **32a,b**-**37a,b** that were described in subchapter 2.1.2 (Fig.2.6) were



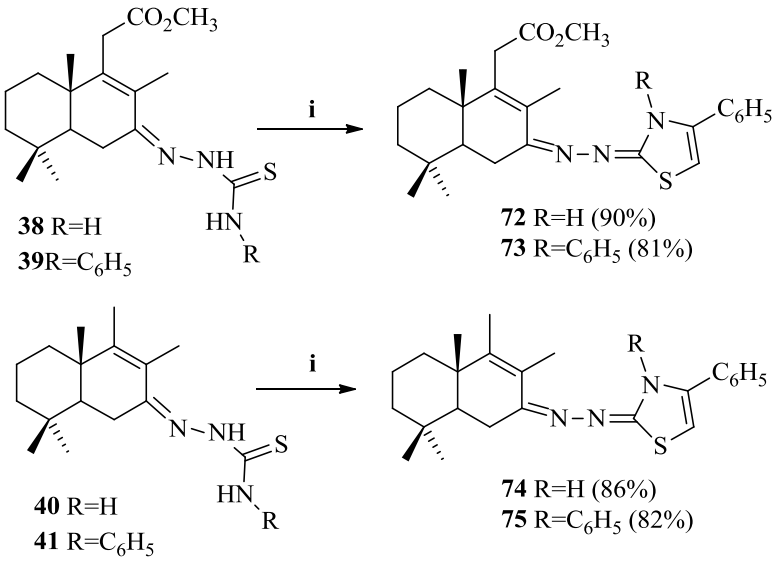
Reagents and conditions: **i**. $C_6H_5COCH_2Br$, EtOH, r.t., 8-24 h.

Fig. 3.5. Synthesis of trinorlabdane compounds 66-71 with 1,3-thiazole fragment

treated with 2-bromoacetophenone in alcohol (1:1) led to the formation of six trinorlabdane compounds **66**-**71** (52-66% yield) with a 1,3-thiazole fragment [14, 16, 17].

In the continuation of our research on the synthesis of new compounds containing the terpenic and 1,3-thiazole fragments, the synthesis of pentanorlabdanic compounds bearing 1,3-thiazole structural unit **72-75** was performed.

Tetra- and pentanorlabdanic thiosemicarbazones **38-41** were subjected to the heterocyclization reaction with 2-bromoacetophenone, with the formation of the above-mentioned compounds (Fig. 3.6) [14, 26]. Therefore, from the di-, tri-, tetra- and pentanorlabdanic thiosemicarbazones a series of norlabdanic compounds with 1,3-thiazole structural unit were obtained.

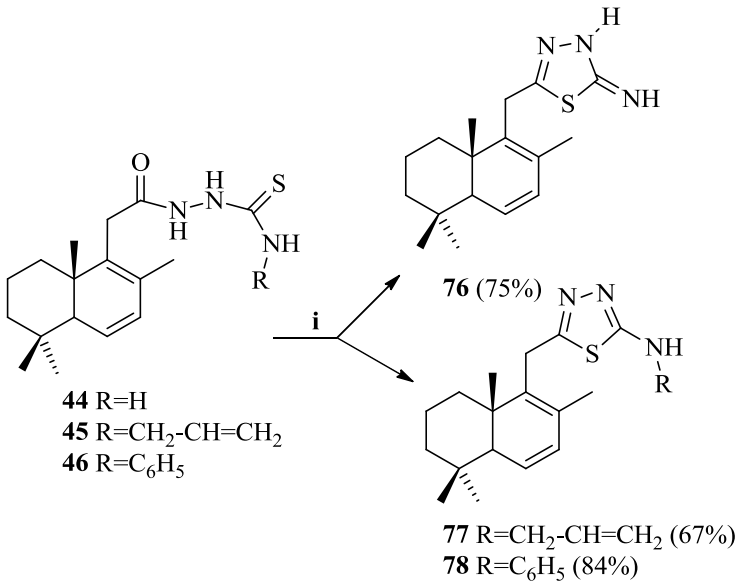


Reagents and conditions: **i**. $C_6H_5COCH_2Br$, EtOH, r.t., 4-6 h.

Fig. 3.6. Synthesis of tetra- and pentanorlabdane compounds with 1,3-thiazole fragment 72-75 from thiosemicarbazones

3.2. Synthesis of tetranorlabdane compounds with 1,3,4-thiadiazole fragment

Thiadiazoles are a class of heterocyclic compounds that are widely used in medical chemistry due to their broad spectra of pharmaceutical and biological activities, such as anti-inflammatory, anticonvulsant, antibacterial, antimitotic and muscle relaxation. This fact determined us to choose as a research objective the synthesis of tetranorlabdane compounds with 1,3,4-thiadiazole fragment. The tetranorlabdane thiosemicarbazones **44-46** obtained from 13,14,15,16-tetranorlabd-6(7),8(9)-dien-12-oic acid **43**, described in subchapter 2.1.3 (Fig.2.10), were used for the synthesis of compounds with 1,3,4-thiadiazole fragment. The cyclization of thiosemicarbazones **44-46** in the presence of triethylamine (Et_3N) in aqueous medium led to the formation of 2-aminothiadiazoles **76-78**, with 67-84% yields (Fig. 3.7) [27].



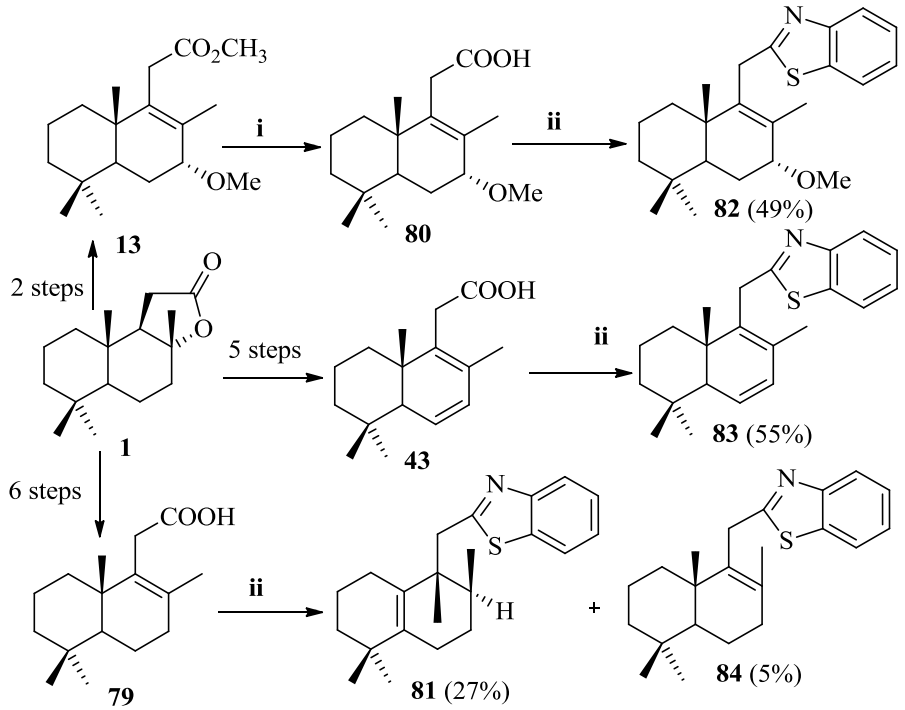
Reagents and conditions: **i**. Et_3N, H_2O, Δ, 18 h.

Fig. 3.7. Synthesis of tetranorlabdane compounds 76-78 with 1,3,4-thiadiazole fragment from tiosemicarbazones

3.3. Synthesis of tetranorlabdane compounds with benzothiazole fragment

Further, the aim of the research was to obtain new biologically active terpeno-heterocyclic hybrid compounds with benzothiazole fragment.

As a starting material, for the synthesis of the compounds with benzothiazole fragment, was used commercially available (+)-sclareolide **1**, which was converted into methoxy ester **13** in two steps, with a 25% overall yield. Then the acid **80** was obtained by the saponification reaction of ester **13** in 89% yield, and acids **43** and **79** were also obtained from (+)-sclareolide **1** in 5 and 6 steps in 81% and 62% yields, respectively. The intramolecular cyclization of acids **43**, **79** and **80** with 2-aminothiophenol in the presence of triethylamine and triphenylphosphine in CCl_4, provided compounds **81**-**84**.



Reagents and conditions: **i**. KOH, EtOH, r.t., 3 h, 89%; **ii**. Ph_3P, Et_3N, CCl_4, 2-aminothiophenol, Δ, 4 h.

Fig. 3.8. Synthesis of trinorlabdane compounds with 1,3-benzothiazole fragment 81-84 from acids

The formation of benzothiazole **81** with rearranged skeleton can be explained by the following reaction mechanism (Fig. 3.9). The nucleophilic substitution caused by 2-aminothiophenol in the carboxyl group of $\Delta^{8,9}$–bicyclohomopharnesic acid **79**, leads to the formation of intermediate amide **85**, which due to the sulphur donor atom forms the unstable cyclic intermediate **86**. Subsequently, the elimination reaction forms compound **81**, which leads to the desired 2-homodrimenyl 1,3-benzothiazole **84**, followed by protonation to form the carbocation **87**. This carbocation undergoes a rearranged carbon skeleton, with the migration of

the methyl group from carbon C_{10} to C_9, followed by the deprotonation of the C_5 carbon atom and the formation of the double bond.

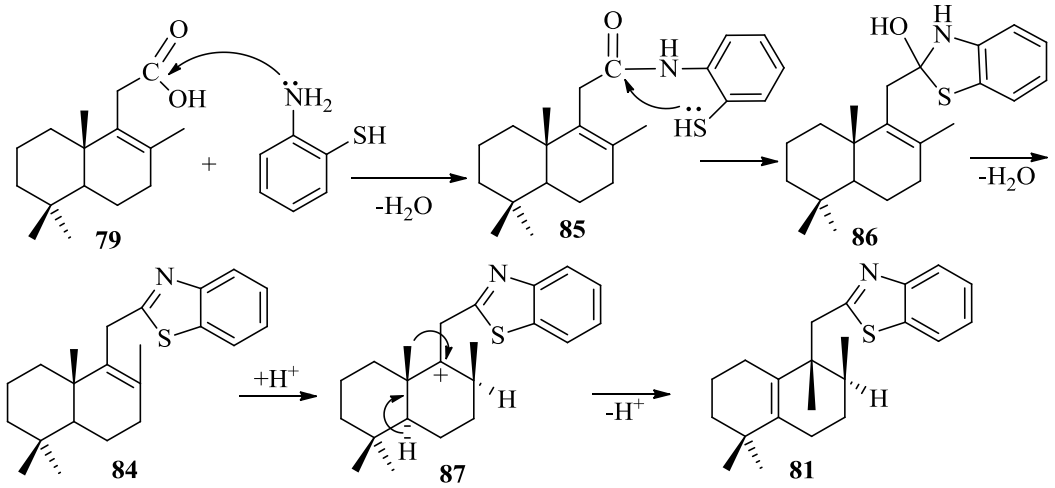
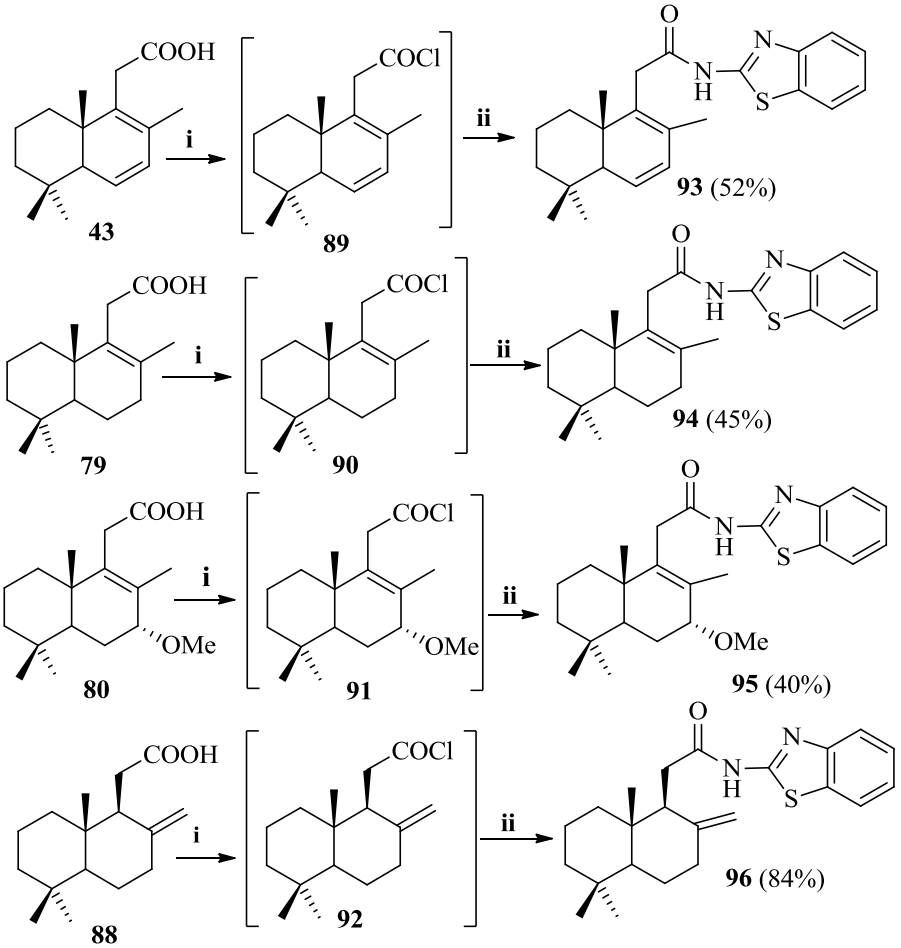


Fig. 3.9. The proposed mechanism for the formation of the benzothiazole 81



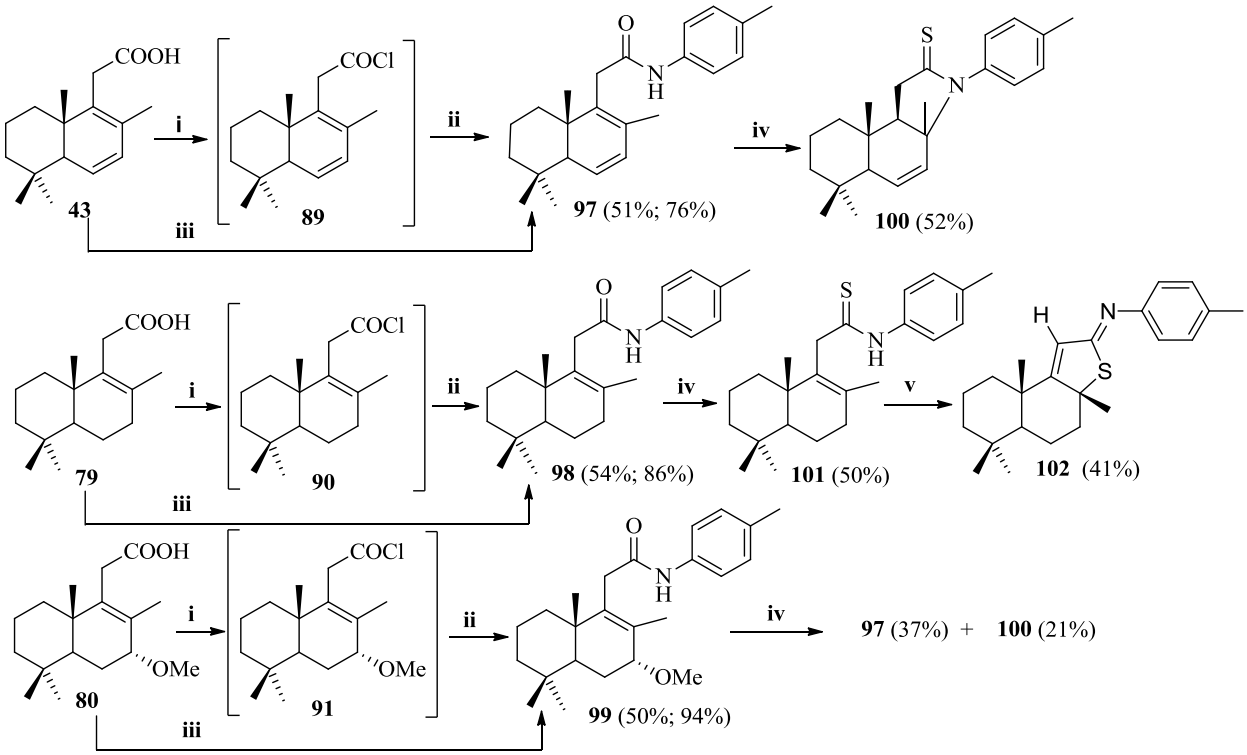
Reagents and conditions: **i**. $(COCl)_2$, C_6H_6, r.t., 1 h; **ii**. 2-Aminobenzothiazole, CH_2Cl_2, Δ, 4 h.

Fig. 3.10. Synthesis of tetranorlabdane compounds with 1,3-benzothiazole fragment 93-96

Another method of synthesizing tetranorlabdane compounds with 1,3-benzothiazole fragment has been proposed, namely condensation of the benzothiazole fragment with

tetranorlabdane compounds. $\Delta^{8,13}$–Bicyclohomopharnesic acid **88** was obtained from (+)-sclareolide **1** in 6 steps, in 60% overall yield. Acid chlorides **89**-**92** generated *in situ* by treating acids **43**, **79**, **80** and **88** with oxalyl chloride in anhydrous benzene were coupled with 2-aminobenzothiazole in methylene chloride on stirring to give benzothiazoles **93**-**96** (Fig. 3.10) [28].

The second method of synthesis of tetranorlabdane compounds with 1,3-benzothiazole fragment involves the formation of amides from carboxylic acids in two ways. The first pathway includes the coupling reaction of acid chlorides **89**-**91** obtained *in situ* with *p*-toluidine in methylene chloride, with the formation of amides **97**-**99**, the yields of the final products varying from 50% to 54% (Fig. 3.11). The second pathway involves the direct coupling reaction of terpenic acids **43**, **79** and **80** with *p*-toluidine in the presence of *N*,*N*'-bicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (4-DMAP), in methylene chloride, providing the amides **97**-**99**. It is noteworthy mentioning that the second method is more efficient because the yields have increased considerably to 76%-94% [29].



Reagents and conditions: **i**. $(COCl)_2$, C_6H_6, r.t., 1 h, Δ, 1 h; **ii**. *p*-Toluidine, CH_2Cl_2, r.t., 5 h, Δ, 10-12 h; **iii**. *p*-Toluidine, DCC, 4-DMAP, CH_2Cl_2, r.t., 10 h; **iv**. Toluene, Lawesson reagent, Δ, 48-50 h, **v**. $K_3[Fe(CN)_6]$, H_2O, 30% NaOH, EtOH, 85ºC, 5 h.

Fig. 3.11. Synthesis of thioamide 100 and 101 in two pathways

Subsequently, tetranorlabdane amides **97**-**99** were subjected to the thionation reaction using the Lawesson reagent in refluxing toluene. In the case of amide **98**, the reaction led to the

formation of thioamide **101**. Whereas, the reaction of amide **97** under the same conditions proceeded in a unique way, resulting in cyclic thioamide **100** with an unexpected structure. The thionation reaction of amide **99** leads to the same thioamides **97** and **100** which have been isolated and characterized. Several attempts to obtain target hybrid 1,3-benzothiazole by cyclization of carbothioamide **101** with potassium ferricyanide in a basic medium were unsuccessful, providing unexpectedly compound **102**.

The formation of thioamide **100** can be explained by a sequence of transformations described in Figs. 3.12. First at all, the elimination of methoxy group from the C_7 position of amide **99**, led to the formation of amide **97**. The thionation of amide **97** with Lawesson reagent forms the intermediate **103** which further forms the cyclic amide **100** due to the donor nitrogen atom.

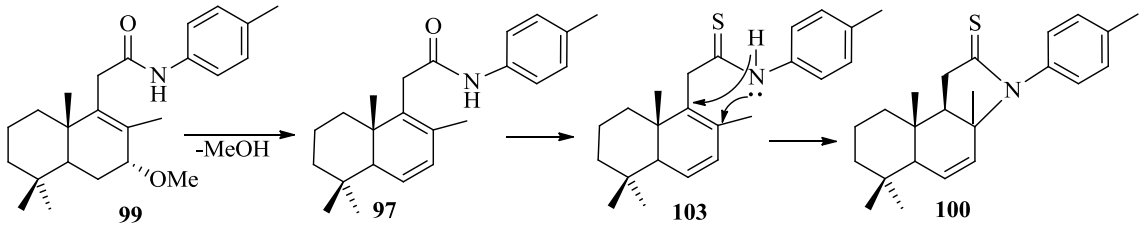


Fig. 3.12. Proposed mechanism for the formation of amide 100

As a result, eight tetranorlabdanic compounds with a 1,3-benzothiazole structural unit were synthesized using terpenic acids **43**, **79**, **80** and **88** as a substrate, and two new methods of synthesis were developed.

3.4. Methods for the synthesis of di-, tri-, tetra- and pentanorlabdane compounds with 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments

It includes the description of working techniques and experimental procedures. The structures of all newly synthesized compounds were confirmed using spectral data (^{1}H, ^{13}C, ^{15}N NMR, IR).

3.5. Antimicrobial activity of di-, tri-, tetra- and pentanorlabdanic compounds with 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole structural units

The 33 di-, tri-, tetra- and pentanorlabdane compounds with 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments were tested for antimicrobial activity.

2-Amino-thiadiazole **76**, obtained for the first time, demonstrated the highest antimicrobial activity and was patented as a compound possessing promising antifungal properties [27]. The benzothiazoles **83** and **100** possess good antifungal activity with MIC values equal to 1 and 2 μg/mL, comparable to the Caspofungin (1.5 μg/mL), and compound **93**

demonstrated good antifungal activity with MIC values equal to 0.25 μg/mL, comparable to the reference Caspofungin (0.25 μg/mL), and good antibacterial activity with MIC values equal to 3 μg/mL, comparable to the reference compound Kanamycin (3 μg/mL).

CONCLUSIONS AND RECOMMENDATIONS

1. The usefulness of the three non-conventional (microwave irradiation, electrooxidation and sensitized photooxidation) green chemistry-related methods, has been demonstrated in the synthesis of polyfunctionalized norlabdane compounds and a new method has been developed for the synthesis of bicyclohomofarnesic methyl esters from sclareolide by microwave irradiation, which leads to the acceleration of the process, increases yields, reducing the amount of solvents and energy used. At the same time, this reaction has a favorable impact on the environment.
2. The anodic oxidation reaction of the methyl ester mixture was studied in detail, the reaction products were isolated and characterized, and a mechanism for the formation of allyl substitution products was proposed, demonstrating the importance of this reaction in the synthesis of tetranorlabdane compounds. The efficacy of the sensitized photooxidation of the methyl esters mixture in the synthesis of norlabdane compounds has also been demonstrated.
3. Coupling reactions of di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazide, 4-phenylthiosemicarbazide and 4-allylthiosemicarbazide were performed, leading to the formation of 17 new norlabdane compounds with thiosemicarbazone fragment.
4. For the first time, the complexation reaction of tetra- and pentanorlabdane compounds with thiosemicarbazone moiety at the C_7 carbon of cycle B and of trinorlabdane compounds with thiosemicarbazone moiety in the side chain by the interaction with transition metal salts was performed. The structures of the coordinating compounds were confirmed by the elemental analysis, IR spectroscopy and in the case of complex $(C_{16}H_{27}N_3S)_6(CuCl)_4$ by X-ray diffraction analysis.
5. Due to the condensation-cyclization reaction, for the first time the di- and trinorlabdane compounds with 2-amino-1,3-thiazole fragment were obtained and the reaction mechanism was tentatively suggested.
6. Starting from important intermediate 13,14,15,16-tetranorlabd-6(7),8(9)-dien-12-oic acid, corresponding thiosemicarbazones were obtained, from which three tetranorlabdane compounds with 1,3,4- thiadiazole fragment were synthesized.
7. New methods have been developed for the synthesis of tetranorlabdane compounds with 1,3-benzothiazole moiety, using norlabdane acids as a substrate. The first method involves the

formation of the benzothiazole ring by intramolecular cyclization of acids with 2-aminothiophenol. In the case of $\Delta^{8,9}$–bicyclohomopharnesic acid, a compound with a rearranged backbone was isolated as the major product and its mechanism was established. The second method involves the condensation of the benzothiazole fragment with tetranorlabdane acids or their chloroanhydrides.

8. The use of *p*-toluidine and Lawesson's reagent for the preparation of tetranorlabdane compounds with 1,3-benzothiazole fragment led to the corresponding carboamides and thioamides, insted of benzothiazoles. The thionation reaction of amide has gone in a unique way, obtaining cyclic thioamide with unexpected structure. And as a result of the cyclization of the synthesized carboamide on a selected substrate, a product with a structure different from the benzothiazole one was obtained.
9. The antimicrobial activity of a series including fifty norlabdane compounds was tested. Biological tests were performed *in vitro* on five fungal strains (*Aspergillus niger, Fusarium solani, Penicillium chrysogenum, Penicillium frequentans, Alternaria alternata*) and two species of Gram-positive and Gram-negative bacteria (*Bacillus sp.* and *Pseudomonas aeruginosa*). Four of the reported compounds showed promising antimicrobial activity.

Based on the presented conclusions, the following are recommended:

- *5- (Homodrim-6,8-dien-11-yl)-1,3,4-thiadiazol-2(3H)-imine and (Z/E)-2-(1-((1R,2R,8αS)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)propan-2-ylidene)hydrazincarbothioamide* was for the first time, tested and patented as a compound possessing antifungal properties which can be widely used in the pharmaceutical industry.
- New di-, tri-, tetra- and pentanorlabdane compounds with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments, which showed promising antimicrobial activity, may be the subject of more detailed research, with the aim of implementing in practice the treatment of fungal and bacterial infections.

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ADNOTARE

BLAJA Svetlana, „Sinteza dirijată şi studiul activităţii antimicrobiene a unor compuși norlabdanici polifuncţionalizaţi”, teză de doctor în științe chimice, mun. Chișinău, Republica Moldova, 2022

Structura tezei. Teza a fost elaborată în cadrul Institutului de Chimie, laboratorul Chimia Compușilor Naturali și Biologic Activi. Teza este scrisă în limba română și constă din introducere, trei capitole, concluzii generale și recomandări, 197 referințe bibliografice, 121 pagini cu text de bază, 72 figuri, 5 tabele. Rezultatele obținute sunt publicate în 15 lucrări științifice.

Cuvinte-cheie: sinteză, heterociclizare, (+)-sclareolidă, compus norlabdanic, tiosemicarbazidă, 1,3-tiazol, 1,3,4-tiadiazol, benzotiazol, activitate antimicrobiană.

Scopul și obiectivele lucrării constau în elaborarea metodelor eficiente de sinteză dirijată a compușilor norlabdanici optic activi noi cu fragmente tiosemicarbazonice, 1,3-tiazolice, 1,3,4-tiadiazolice și benzotiazolice, în baza diterpenoidei labdanice naturale sclareol; elucidarea mecanismelor posibile ale reacțiilor de sinteză a compușilor polifuncționalizați care sunt înzestrați cu activitate biologică promițătoare.

Noutatea și originalitatea științifică rezidă în elaborarea unor metode noi, eficiente și originale de sinteză dirijată a unei serii de compuși norlabdanici optic activi noi cu unități structurale tiosemicarbazonice și heterociclice, care manifestă un potențial terapeutic promițător; obținerea în premieră a compușilor complecși chirali cu utilizarea în calitate de liganzi a compușilor norlabdanici funcționalizați cu unitate structurală tiosemicarbazonică.

Problema științifică importantă soluționată constă în sinteza dirijată a compușilor norlabdanici optic activi noi cu schelet hibrid în baza diterpenoidei labdanice naturale sclareol - o concepție nouă în sinteza organică fină. Acești compuși reprezintă sintoni chirali importanți pentru obținerea substanțelor biologic active de interes sporit pentru aplicații în industria farmaceutică.

Semnificația teoretică. Rezultatele cercetării contribuie la lărgirea informației științifice privind studiul legităților structurale și sterice în reacțiile de sinteză a compușilor norlabdanici chirali noi cu fragmente tiosemicarbazonice și heterociclice, care manifestă potențial sporit de activitate biologică.

Valoarea aplicativă: A fost testată activitatea antimicrobiană a cincizeci de compuși chirali noi pe cinci tulpini de fungi și două specii de bacterii. Patru dintre compușii raportați au prezentat o activitate antimicrobiană pronunțată. De aceste elaborări pot fi interesate firmele farmaceutice, care produc medicamente ce conţin compuşi biologic activi chirali, locul cărora îl pot ocupa derivaţii norlabdanici. Impactul pozitiv asupra mediului este legat de utilizarea metodelor neconvenționale (microunde, electrooxidare, fotooxidare sensibilizată), care stau la baza tehnologiilor non-poluante, non-agresive şi mai ieftine.

Implementarea rezultatelor științifice: Au fost brevetate metodele de sinteză și activitatea a doi compuși noi tri- și tetranorlabdanici cu fragment tiosemicarbazonic și 1,3,4-tiadiazolic, care pot deveni în continuare obiectul cercetărilor mai detaliate, în scopul implementării în practică la tratarea bolilor provocate de fungi.

SUMMARY

BLAJA Svetlana, „Directed synthesis and study of antimicrobial activity of polyfunctionalized norlabdane compounds", the thesis for the degree of Doctor in chemical sciences, Chisinau, Republic of Moldova, 2022

Dissertation contents. The thesis was developed in the Institute of Chemistry, Laboratory of Chemistry of Natural and Biologically Active Compounds. The thesis was written in Romanian and consists of the introduction, three chapters, general conclusions and recomandations, bibliography of 197 references, 121 basic text pages, 72 figures and 5 tables. The obtained results were presented in 15 scientific publications.

Key words: synthesis, heterocyclization, (+)-sclareolide, norlabdane compound, thiosemicarbazide, 1,3-thiazole, 1,3,4-thiadiazole, benzothiazole, antimicrobial activity.

The purpose and objectives of the study is devoted to the elaboration of the efficient methods for the directed synthesis of new optically active norlabdane compounds with thiosemicarbazone, 1,3-thiazole, 1,3,4-thiadiazole and benzothiazole fragments, based on the natural labdane diterpenoid sclareol; elucidation of the possible mechanisms of synthesis reactions of polyfunctionalized compounds that are endowed with promising biological activity.

Novelty and scientific originality consists in the elaboration of new, efficient and original methods of directed synthesis of a series of new optically active norlabdane compounds with thiosemicarbazone and heterocyclic structural units, which show a promising therapeutic potential; obtaining for the first time the chiral complex compounds with the use as ligands of the norlabdanic compounds functionalized with thiosemicarbazone structural unit.

The important scientific problem solved is the directed synthesis of new optically active norlabdanic compounds with hybrid skeleton based on the natural labdanic diterpenoid sclareol - a new concept in fine organic synthesis. These chiral compounds are important syntons for obtaining biologically active substances of high interest for applications in the pharmaceutical industry.

Theoretical significance. The research results contribute to the expansion of scientific knowledge on the study of structural and steric laws in the synthesis reactions of new chiral norlabdanic compounds with thiosemicarbazone and heterocyclic fragments, which show increased potential for biological activity.

Applicative value of the study: The antimicrobial activity of fifty new chiral compounds on five fungal strains and two bacterial species was tested. Four of the reported compounds showed pronounced antimicrobial activity. These developments may be of interest to pharmaceutical companies, which produce drugs containing chiral biologically active compounds, which may be replaced by norlabdane derivatives. The diminished impact on the environment is related to the use of unconventional methods (microwave, electrooxidation, sensitized photooxidation), which are the basis of non-polluting, non-aggressive and cheaper technologies.

Implementation of scientific results: The methods of synthesis and activity of two new tri- and tetranorlabdane compounds with thiosemicarbazone and 1,3,4-thiadiazole fragment have been patented, which may continue to be the subject of more detailed research, in order to be implemented in practice in the treatment of diseases caused by fungi.

АННОТАЦИЯ

БЛАЖА Светлана, „Направленный синтез и исследование антимикробной активности полифункциональных норлабдановых соединений”, диссертация на соискание ученой степени доктора химических наук, Кишинёв, Республика Молдова, 2022

Структура диссертации: Диссертация разработана в Лаборатории Химия Природных и Биологически Активных Соединений Института Химии. Диссертация написана на румынском языке и состоит из введения, трех глав, общих выводов и рекомендаций, библиографии из 197 наименований, 121 страниц основного текста, включая 72 рисунков и 5 таблиц. Полученные результаты опубликованы в 15 научных работах.

Ключевые слова: синтез, гетероциклизация, (+)-склареолид, норлабдановое соединение, тиосемикарбазид, 1,3-тиазол, 1,3,4-тиадиазол, бензотиазол, антимикробная активность.

Цель и задачи диссертации заключаются в разработке эффективных методов направленного синтеза ряда новых оптически активных норлабдановых соединений с тиосемикарбазоновыми, 1,3-тиазольными, 1,3,4-тиадиазольными и бензотиазольными фрагментами на основе природного лабданового дитерпеноида склареола; установление возможных механизмов реакций синтеза полифункционализированных соединений, наделенных многообещающей биологической активностью.

Научная новизна и оригинальность заключается в разработке новых эффективных и оригинальных методов направленного синтеза ряда новых оптически активных норлабдановых соединений с тиосемикарбазоновыми и гетероциклическими структурными единицами, которые обладают многообещающим терапевтическим потенциалом; впервые получены комплексные хиральные соединения с использованием в качестве лигандов норлабдановых соединений, функционализированных тиосемикарбазоновой структурной единицей.

Решение важной научной задачи заключается в направленном синтезе новых оптически активных норлабдановых соединений с гибридным скелетом на основе природного лабданового дитерпеноида склареола - новой концепции в тонком органическом синтезе. Эти соединения являются хиральными синтонами которые важны для получения биологически активных веществ, представляющих большой интерес для применения в фармацевтической промышленности.

Теоретическое значение. Результаты исследований способствуют расширению научной информации по изучению структурных и стерических закономерностей в реакциях синтеза новых хиральных норлабдановых соединений с тиосемикарбазоновыми и гетероциклическими фрагментами, которые проявляют повышенный потенциал биологической активности.

Практическая ценность. Была протестирована антимикробная активность пятидесяти новых хиральных соединений на пяти штаммах грибков и двух видах бактерий. Четыре из описанных соединений показали выраженную антимикробную активность. Данные разработки могут заинтересовать фармацевтические компании, производящие препараты, содержащие хиральные биологически активные соединения, которые могут быть заменены производными норлабдана. Положительное воздействие на окружающую среду связано с использованием нетрадиционных методов (микроволновое излучение, электроокисление, сенсибилизированное фотоокисление), которые являются основой экологически чистых, неагрессивных и более дешевых технологий.

Внедрение научных результатов: Запатентованы методы синтеза и активность двух новых три- и тетранорлабдановых соединений с тиосемикарбазоновым и 1,3,4-тиадиазоловым фрагментом, которые в дальнейшем могут стать предметом более детальных исследований с целью реализации на практике лечения грибковых заболеваний.

BLAJA SVETLANA

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