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**SYNTHESIS AND EVALUATION OF  
ANTIMICROBIAL ACTIVITY OF  
TETRANORLABDANE COMPOUNDS BEARING  
1,3,4-THIADIAZOLE UNITS**

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## SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF TETRANORLABDANE COMPOUNDS BEARING 1,3,4-THIADIAZOLE UNITS

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**Abstract.** Synthesis of novel tetranorlabdane compounds bearing 1,3,4-thiadiazole units and intermediary tetranorlabdane compounds with thiosemicarbazone fragment has been reported. The structures of the new synthesized compounds were confirmed using IR and <sup>1</sup>H, <sup>13</sup>C, and <sup>15</sup>N NMR spectroscopy. The *in vitro* antifungal and antibacterial activities of the mentioned compounds have been evaluated. Results of this study have shown that the 1,3,4-thiadiazole-2-imine has excellent activity against tested strains of fungi and species of bacteria at minimum inhibitory concentration values of 0.125 and 2.5 µg/mL, respectively.

**Keywords:** (+)-sclareolide, tetranorlabdane compound, 1,3,4-thiadiazole, thiosemicarbazone, antimicrobial activity.

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### Introduction

From the diversity of terpenic compounds, labdane diterpenoids, which contain the bicyclic *trans*-decalin system, are of particular interest, many of them being natural or synthetic products of practical importance [1]. The labdane type diterpenes have been described to have broad spectrum of biological activities [2-4].

Compounds that contain heterocyclic fragments in their molecules often exhibit pronounced biological activities. Thiadiazoles are a very important class of heterocyclic compounds. During recent years remarkable progress has been made in the development of new thiadiazole compounds, many of which possess interesting biological activities such as anticancer, antituberculous, antimicrobial, anti-inflammatory, analgesic and anticonvulsant, *etc.* [5,6].

A wide variety of methods and reagents which lead to 1,3,4-thiadiazole are known. One of the most used methods of their synthesis employs the cyclocondensation of acid hydrazides with triethyl orthoalkanoates [7], isothiocyanates or dithiocarbamates [8]. Frequently, the synthesis of mentioned heterocycles involves the formation of intermediary thiosemicarbazones by the interaction of the thiosemicarbazide and acids [9] or aldehydes [10], followed by their subsequent heterocyclization.

The synthesis of novel hybrid compounds containing both terpenic and heterocyclic units is a promising direction of research in organic chemistry. Series of compounds containing both terpene and diazine [11,12], azaheterocyclic [13,14], 1,2,4-triazole and carbazole [15,16], hydrazinecarbothioamide and 1,2,4-triazole [17], thiosemicarbazone and 1,3-thiazole [18], 1,3,4-oxadiazole and 1,3,4-thiadiazole [19] units were reported, many of synthesized compounds exhibit excellent antifungal and/or antibacterial activity.

The aim of this study was to synthesize the novel tetranorlabdane compounds bearing 1,3,4-thiadiazole units *via* some important intermediary tetranorlabdane compounds comprising the thiosemicarbazone fragment. The structures of the synthesized compounds have been fully confirmed by spectral analyses (IR, <sup>1</sup>H, <sup>13</sup>C, and <sup>15</sup>N NMR). Their antifungal and antibacterial activity was tested against several fungi and bacteria taxons.

### Experimental

#### Generalities

The following reagents and solvents were used in the research: thiosemicarbazide, allylthiosemicarbazide, phenylthiosemicarbazide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

(EDCI), triethylamine (Et<sub>3</sub>N), dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), methanol (MeOH) and deuterated chloroform (CDCl<sub>3</sub>). Reagents and solvents were purchased from Sigma-Aldrich and used without further purification.

*Optical rotations* were determined on a Jasco DIP 370 polarimeter with a 1-dm microcell, in CHCl<sub>3</sub>. *Melting point values* were recorded on a Boetius hot stage apparatus. *IR spectra* were recorded on a Spectrum 100 FT-IR spectrometer using ATR technique. <sup>1</sup>H, <sup>13</sup>C, and <sup>15</sup>N NMR (400, 100, and 40 MHz, respectively) and COSY, <sup>1</sup>H-<sup>13</sup>C HSQC, <sup>1</sup>H-<sup>13</sup>C HMBC, and DEPT spectra were acquired on a Bruker Advance DRX 400 spectrometer. Chemical shifts are given in ppm in the δ scale and referred to CDCl<sub>3</sub> (δ<sub>H</sub> at 7.26 ppm) and to CDCl<sub>3</sub> (δ<sub>C</sub> at 77.00 ppm). The coupling constants (*J*) are reported in Hertz (Hz). Progress of reactions and purity of products were examined by the *analytical thin-layer chromatography* on Merck silica gel 60 plates, gradient elution from 2 to 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Visualization was achieved by treatment with concentrated H<sub>2</sub>SO<sub>4</sub> and heating at 80°C or using a UV lamp (254 or 365 nm).

#### **General method of synthesis of tetranorlabdane compounds with thiosemicarbazone fragment 3-5**

A solution of acid **2** (248 mg, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was treated with thiosemicarbazide (109 mg, 1.2 mmol), allylthiosemicarbazide (157 mg, 1.2 mmol) or phenylthiosemicarbazide (200 mg, 1.2 mmol) and EDCI (232 mg, 1.5 mmol) [20]. The resulting mixture was stirred at room temperature for 24 h, after that was concentrated under reduced pressure and the crude reaction product was purified by column chromatography (SiO<sub>2</sub>, gradient elution from 2 to 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>).

*2-(2-((8aS)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetyl)hydrazine carbothioamide (3)* (273 mg, 85%), m.p. 134-135°C, [α]<sub>D</sub><sup>26</sup> = -89.2° (c 0.6, CHCl<sub>3</sub>). IR (ν, cm<sup>-1</sup>): 3368, 3282, 3181, 2926, 1653, 1608, 1583, 1472, 1398, 1156, 729. <sup>1</sup>H NMR: δ 9.69, 9.25 (s, NH); 7.88, 7.36 (s, NH<sub>2</sub>); 5.86 (1H, dd, *J* = 9.6, 2.8, 7-CH); 5.76 (1H, dd, *J* = 9.6, 2.2, 6-CH); 3.07 (1H, d, *J* = 16.0) and 2.89 (1H, d, *J* = 15.6, 11-CH<sub>2</sub>); 1.65 (3H, s, 17-CH<sub>3</sub>); 0.92 (3H, s, 19-CH<sub>3</sub>); 0.89 (3H, s, 18-CH<sub>3</sub>); 0.74 (3H, s, 20-CH<sub>3</sub>). <sup>13</sup>C NMR: δ 182.3 (C=S); 170.7 (C-12); 137.8 (C-9); 129.8 (C-7); 129.7 (C-8); 127.7 (C-6); 52.3 (C-5); 40.7 (C-3); 38.6 (C-10); 34.7 (C-1); 31.8 (C-11); 32.7 (C-19); 23.0 (C-18); 18.8 (C-2); 18.6 (C-17); 15.3 (C-20). <sup>15</sup>N NMR: δ 134;

123 and 107.

*N-Allyl-2-(2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetyl)hydrazinecarbothioamide (4)* (285 mg, 79%), m.p. 120-121°C, [α]<sub>D</sub><sup>26</sup> = -97.2° (c 0.1, CHCl<sub>3</sub>). IR (ν, cm<sup>-1</sup>): 3169, 3034, 2926, 1693, 1644, 1545, 1458, 1369, 1172, 960, 917. <sup>1</sup>H NMR: δ 10.02, 9.49, 7.28 (s, NH); 5.94-5.84 (3H, m, 6-CH, 7-CH and 2'-CH); 5.25 (1H, d, *J* = 17.0) and 5.17 (1H, d, *J* = 10.5, 3'-CH<sub>2</sub>); 4.25-4.14 (2H, m, 1'-CH<sub>2</sub>); 3.24 (1H, d, *J* = 17.3) and 2.99 (1H, d, *J* = 17.3, 11-CH<sub>2</sub>); 1.79 (3H, s, 17-CH<sub>3</sub>); 0.97 (6H, s, 18-CH<sub>3</sub>, 19-CH<sub>3</sub>); 0.84 (3H, s, 20-CH<sub>3</sub>). <sup>13</sup>C NMR: δ 179.9 (C=S); 167.3 (C-12); 135.2 (C-9); 133.4 (C-2'); 130.6 (C-8); 129.4 (C-7); 128.7 (C-6); 116.8 (C-3'); 52.5 (C-5); 46.8 (C-1'); 40.5 (C-3); 38.8 (C-10); 33.2 (C-11); 34.5 (C-1); 32.3 (C-19); 22.7 (C-18); 18.8 (C-2); 18.5 (C-17); 15.2 (C-20). <sup>15</sup>N NMR: δ 179, 145 and 109.

*N-Phenyl-2-(2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetyl)hydrazinecarbothioamide (5)* (290 mg, 73%), m.p. 106-107°C, [α]<sub>D</sub><sup>26</sup> = -108.07° (c 1.4, CHCl<sub>3</sub>). IR (ν, cm<sup>-1</sup>): 3185, 3035, 2925, 1676, 1598, 1540, 1497, 1447, 1351, 1167, 1030, 974, 744, 691. <sup>1</sup>H NMR: δ 10.13, 9.73, 8.94 (s, NH); 7.49 (2H, d, *J* = 7.4, 2'-CH and 6'-CH); 7.38 (2H, t, *J* = 7.8, 3'-CH and 5'-CH); 7.22 (1H, t, *J* = 7.4, 4'-CH); 5.89-5.87 (2H, m, 6-CH and 7-CH); 3.30 (1H, d, *J* = 17.4) and 3.06 (1H, d, *J* = 17.4, 11-CH<sub>2</sub>); 1.81 (3H, s, 17-CH<sub>3</sub>); 0.97 (3H, s, 19-CH<sub>3</sub>); 0.95 (3H, s, 18-CH<sub>3</sub>); 0.86 (3H, s, 20-CH<sub>3</sub>). <sup>13</sup>C NMR: δ 177.2 (C=S); 167.1 (C-12); 137.6 (C-1'); 135.0 (C-9); 130.8 (C-8); 129.5 (C-7); 129.2 (C-3' and C-5'); 128.7 (C-6); 126.1 (C-4'); 124.0 (C-2' and C-6'); 52.5 (C-5); 40.5 (C-3); 38.8 (C-10); 33.3 (C-11); 34.5 (C-1); 32.3 (C-19); 22.7 (C-18); 18.8 (C-2); 18.5 (C-17); 15.2 (C-20). <sup>15</sup>N NMR: δ 177, 131 and 124.

#### **General method of synthesis of tetranorlabdane compounds with 1,3,4-thiadiazole fragment 6-8**

To a solution of one of thiosemicarbazones **3** (321 mg, 1 mmol), **4** (361 mg, 1 mmol) or **5** (397 mg, 1 mmol) in H<sub>2</sub>O (6 mL) was added Et<sub>3</sub>N (0.5 mL, 4 mmol) and the resulting mixture was refluxed with stirring for 18 h [8]. Afterwards, the cooled reaction mixture was diluted with H<sub>2</sub>O (15 mL), then the extraction was proceeded with CH<sub>2</sub>Cl<sub>2</sub> (3×20 mL). Further, the combined organic layers were dried up, filtered and withdrawn under reduced pressure. The crude reaction product was purified by column chromatography (SiO<sub>2</sub>, gradient elution from 2 to 3% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

5-(((8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)methyl)-1,3,4-thiadiazol-2(3*H*)-imine (**6**) (227 mg, 75%), m.p. 210-211°C,  $[\alpha]_D^{26} = -5.99^\circ$  (*c* 2.2, CHCl<sub>3</sub>). IR (ν, cm<sup>-1</sup>): 3083, 3033, 2915, 1578, 1498, 1451, 1385, 1208, 1090, 994, 759. <sup>1</sup>H NMR: δ 13.20, 13.08 (s, NH); 5.89 (1H, dd, *J* = 9.6, 2.9, 7-CH); 5.80 (1H, dd, *J* = 9.6, 2.3, 6-CH); 3.36 (1H, d, *J* = 16.2) and 3.25 (1H, d, *J* = 16.6, 11-CH<sub>2</sub>); 1.95 (1H, t, *J* = 2.70, 5-CH); 1.69 (3H, s, 17-CH<sub>3</sub>); 0.89 (3H, s, 19-CH<sub>3</sub>); 0.91 (3H, s, 18-CH<sub>3</sub>); 0.74 (3H, s, 20-CH<sub>3</sub>). <sup>13</sup>C NMR: δ 166.2 (C-2 thiadiazole); 152.2 (C-5 thiadiazole); 137.1 (C-9); 129.7 (C-7); 128.4 (C-8); 128.1 (C-6); 52.6 (C-5); 40.9 (C-3); 38.7 (C-10); 34.9 (C-1); 33.1 (C-4); 32.6 (C-19); 23.5 (C-11); 23.2 (C-18); 18.5 (C-17); 18.8 (C-2); 15.4 (C-20). <sup>15</sup>N NMR: δ 277, 208 and 177.

*N*-Allyl-5-(((8a*S*)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)methyl)-1,3,4-thiadiazol-2-amine (**7**) (260 mg, 76%), m.p. 106-107°C,  $[\alpha]_D^{26} = -53.78^\circ$  (*c* 0.1, CHCl<sub>3</sub>). IR (ν, cm<sup>-1</sup>): 3094, 2997, 1644, 1571, 1501, 1436, 1365, 1273, 1138, 935, 714. <sup>1</sup>H NMR: δ 11.46 (s, NH); 5.98-5.82 (3H, m, 6-CH, 7-CH and 2'-CH); 5.33 (1H, d, *J* = 9.6) and 5.17 (1H, d, *J* = 17.6, 3'-CH); 4.79-4.66 (2H, m, 1'-CH); 5.88 (1H, dd, *J* = 9.7, 2.9, 6-CH); 5.84 (1H, dd, *J* = 9.4, 2.5, 7-CH); 3.40 (1H, d, *J* = 16.8) and 3.24 (1H, d, *J* = 16.8, 11-CH<sub>2</sub>); 1.67 (3H, s, 17-CH<sub>3</sub>); 0.96 (3H, s, 19-CH<sub>3</sub>); 0.94 (3H, s, 18-CH<sub>3</sub>); 0.85 (3H, s, 20-CH<sub>3</sub>). <sup>13</sup>C NMR: δ 167.6 (C-2 thiadiazole); 151.8 (C-5 thiadiazole); 134.6 (C-9); 128.9 (C-2'); 129.4 (C-8); 130.4 (C-7); 128.6 (C-6); 118.4 (C-3'); 52.3 (C-5); 45.9 (C-1'); 40.6 (C-3); 38.7 (C-10); 34.7 (C-1); 32.3 (C-19); 23.7 (C-11); 22.7 (C-18); 18.8 (C-2); 18.3 (C-17); 15.6 (C-20). <sup>15</sup>N NMR: δ 275 and 198.

*N*-Phenyl-5-(((8a*S*)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)methyl)-1,3,4-thiadiazol-2-amine (**8**) (220 mg, 84%), m.p. 78-79°C,  $[\alpha]_D^{26} = -41.08^\circ$  (*c* 0.4, CHCl<sub>3</sub>). IR (ν, cm<sup>-1</sup>): 3253, 2927, 1627, 1565, 1499, 1451, 1407, 1370, 1249, 1178, 976, 748. <sup>1</sup>H NMR: δ 8.82 (s, NH); 7.46 (2H, d, *J* = 7.8, 2'-CH and 6'-CH); 7.34 (2H, t, *J* = 8.3, 3'-CH and 5'-CH); 7.05 (1H, t, *J* = 7.4, 4'-CH); 5.91 (1H, dd, *J* = 9.4, 3.0, 6-CH); 5.85 (1H, dd, *J* = 9.7, 2.8, 7-CH); 3.66 (1H, d, *J* = 16.6) and 3.56 (1H, d, *J* = 15.4, 11-CH<sub>2</sub>); 1.87 (3H, s, 17-CH<sub>3</sub>); 0.97 (3H, s, 19-CH<sub>3</sub>); 0.94 (3H, s, 18-CH<sub>3</sub>); 0.81 (3H, s, 20-CH<sub>3</sub>). <sup>13</sup>C NMR: δ 159.8 (C-2 thiadiazole); 156.9 (C-5 thiadiazole); 138.1 (C-1'); 135.7 (C-9); 128.7 (C-8); 129.2 (C-7); 129.3 (C-3' and C-5'); 128.7 (C-6); 122.7 (C-4'); 117.4 (C-2' and C-6'); 52.6 (C-5); 40.7 (C-3); 38.9 (C-10); 35.8 (C-1);

33.9 (C-11); 32.4 (C-19); 22.8 (C-18); 18.8 (C-2); 18.3 (C-17); 15.3 (C-20). <sup>15</sup>N NMR: δ 295 and 183.

#### Antifungal and antibacterial activity assay

Pure cultures of fungus strains *Alternaria alternata* (ATCC 8741), *Aspergillus niger* (ATCC 53346), *Penicillium chrysogenum* (ATCC 20044), *P. frequentans* (ATCC 10110) and *Fusarium solani* (ATCC 20327), Gram-positive and Gram-negative bacteria: *Bacillus polymyxa* (ATCC 15970) and *Pseudomonas aeruginosa* (ATCC 27813) were purchased from the American Type Culture Collection (ATCC). The successive double dilution procedure and direct colony method were used for testing. For suspensions of microorganisms was used DMSO [21]. The final concentration of the stock inoculum was 1·10<sup>-4</sup> µg/mL. Antibacterial and antifungal activity assay was achieved by applying a mixture of microorganism suspension and solution of the target compound in a ratio of 1:1 to Petri dishes. Merck Sabouraud agar or agar-agar was used as a solid medium. DMSO did not register an inhibitory effect on the tested microorganisms.

## Results and discussion

### Synthesis and characterization

As starting material for the synthesis of novel tetranorlabdane compounds with thiosemicarbazone or 1,3,4-thiadiazole fragments, the 13,14,15,16-tetranorlabd-6(7),8(9)-dien-12-oic acid (**2**) obtained from commercially available (+)-sclareolide (**1**) in 5 steps, with an overall yield 47%, was used [16]. Further, the coupling reaction between acid **2** and one of thiosemicarbazide, allylthiosemicarbazide, or phenylthiosemicarbazide (molar ratio 1:1.2) was performed in dichloromethane in the presence of EDCI and afforded the tetranorlabdane compounds with thiosemicarbazone fragment **3-5** in 73-85% yield (Scheme 1).

The structures of intermediary compounds **3-5** were confirmed by <sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N and 2D NMR, as well as IR spectroscopy. The formation of desired hybrid compound **3** was proved, first of all by the presence of broad singlet signals attributed to the aminic protons at 7.88 and 7.36 ppm, as well as to amidic and thioamides protons at 9.69 and 9.25 ppm. The singlet signals of the same protons from the molecules of hybrids **4** and **5** are in a range of 10.13-7.28 ppm. In the case of compound **4**, the doublets and multiplets at 5.25 and 5.17 ppm, 4.25 and 4.14 ppm confirm the presence of the methylene groups from the allyl fragment. The presence of aromatic protons

in the molecule of compound **5**, is proved by doublets and triplets in a range of 7.49-7.22 ppm show. The most important signals of the common tetranorlabdane unit of compounds **3-5** are doublets and multiplets of C<sub>6</sub>-H and C<sub>7</sub>-H at ~5.9-5.8 ppm, as well as singlets of C<sub>17</sub> methyl group at 1.8-1.6 ppm. The <sup>13</sup>C NMR spectra provide additional information confirming the structures of compounds **3-5**, by signals at 182-177 ppm (>C=S) and 170-167 ppm (C<sub>12</sub>).

The IR spectra of synthesized compounds **3-5** contain absorption bands at 3185-3169 cm<sup>-1</sup>, which are characteristic to the molecular vibration of N-H bonds. The IR spectra of compound **3**, additionally, contains two absorption bands at 3368 and 3282 cm<sup>-1</sup>, which are attributed to the molecular vibration of NH<sub>2</sub>. The strong bands presented at 1693-1653 cm<sup>-1</sup> and 1167-1151 cm<sup>-1</sup> confirm the presence of >C=O and >C=S in thiosemicarbazones **3-5**, and are similar to those reported in the literature [22].

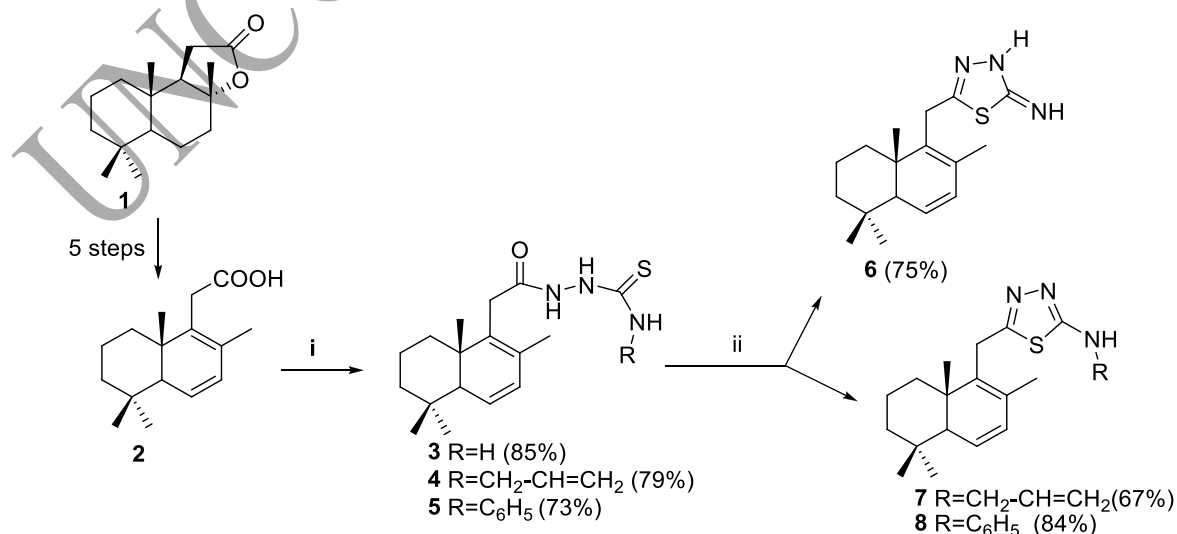
In continuation, the heterocyclization reaction of thiosemicarbazones **3-5** was carried out in the presence of Et<sub>3</sub>N and H<sub>2</sub>O, giving the tetranorlabdane compounds with 1,3,4-thiosemicarbazone fragment **6-8** in 67-84% yields (Scheme 1).

The structures of target compounds **6-8** were confirmed by <sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N, 2D NMR, and IR spectroscopy. The <sup>1</sup>H NMR spectrum of compound **6** includes the singlets at the 13.20 and 13.08 ppm belonging to the =N-H and >N-H protons. The same singlet signals for the compounds **7** and **8** are visible at the 11.46 and 8.82 ppm. In the case of compound **7**, the doublets

at 5.33 and 5.17 ppm prove the presence of the methylene group from the allyl fragment. The doublet and triplet signals of the aromatic protons from the molecule of compound **8** are visible in a range of 7.46-7.05 ppm and confirm their presence. The formation of thiadiazole ring is confirmed by carbon spectra. The signals of C<sub>2</sub> atoms are localized at 159-167 ppm and those of C<sub>5</sub> atoms at 156-151 ppm. The IR spectra of mentioned compounds include the absorption bands in the range of 3094-3036 cm<sup>-1</sup>, which are characteristic to the vibration of >N-H bonds. Also, there are present the absorption bands characteristic to the vibration of >C=N bonds in the range of 1578-1565 cm<sup>-1</sup>. Absence of absorption bands belonging to >C=O and >C=S from thiosemicarbazone units confirms their cyclization into heterocyclic ring [23]. In the case of compounds **7** and **8** are present the absorption bands at 1644 cm<sup>-1</sup>, which are characteristic for the vibration of double bond of the allylic group and those of the aromatic rings presented by the absorption bands at 1053 cm<sup>-1</sup>.

#### Antimicrobial activity

The results of *in vitro* preliminary screening of antifungal and antibacterial activities of novel tetranorlabdane compounds with thiosemicarbazone or 1,3,4-thiadiazole moiety **3-8** against five pure cultures of fungi and two gram-positive and gram-negative bacteria strains are presented in Table 1 [24]. According to these values, 1,3,4-thiadiazole-2-imine **6** possess pronounced antifungal activity at MIC= 0.125 µg/mL and to a lesser extent antibacterial activity at MIC= 2.5 µg/mL [25].



Reagents and conditions: i. NH<sub>2</sub>NHCSNH-R, EDCI, CH<sub>2</sub>Cl<sub>2</sub>, 20°C, 24 h; ii. Et<sub>3</sub>N, H<sub>2</sub>O, reflux, 18 h.

Scheme 1. Synthesis of tetranorlabdane compounds with thiosemicarbazone or 1,3,4-thiadiazole fragment.

**In vitro antimicrobial activity of compounds 3-8.**

Compound	MIC ( $\mu\text{g/mL}$ )						
	<i>Aspergillus niger</i>	<i>Fusarium solani</i>	<i>Penicillium chrysogenum</i>	<i>Penicillium frequentans</i>	<i>Alternaria alternata</i>	<i>Bacillus polymyxa</i>	<i>Pseudomonas aeruginosa</i>
<b>3</b>	>32	>32	>32	>32	>32	>256	>256
<b>4</b>	>32	>32	>32	>32	>32	>256	>256
<b>5</b>	>32	>32	>32	>32	>32	>256	>256
<b>6</b>	<b>0.125</b> ( $\pm 0.001$ )	<b>0.125</b> ( $\pm 0.001$ )	<b>0.125</b> ( $\pm 0.001$ )	<b>0.125</b> ( $\pm 0.001$ )	<b>0.125</b> ( $\pm 0.001$ )	<b>2.5</b> ( $\pm 0.002$ )	<b>2.5</b> ( $\pm 0.002$ )
<b>7</b>	>32	>32	>32	>32	>32	>256	>256
<b>8</b>	>32	>32	>32	>32	>32	>256	>256
<b>Caspofungin</b>	0.25	0.25	0.25	0.25	0.25	-	-
<b>Kanamycin</b>	-	-	-	-	-	4	4

Other compounds of this series, **3-5**, **7** and **8**, are biologically inactive (Table 1). This fact leads to the conclusions that the thiosemicarbazone fragment does not determine the activity of compounds **3-5**, as well as 5-substituted 1,3,4-thiadiazole fragment the activity of compounds **7** and **8**. The activity of compound **6**, whose structure differs from that of compounds **7** and **8**, is determined by the amine-imine fragment (-NH-C=NH) from the 5-substituted 1,3,4-thiadiazole ring.

### Conclusions

Starting from the (+)-sclareolide a series of 6 novel hybrid terpeno-heterocyclic compounds containing tetranorlabdane and 1,3,4-thiadiazole or thiosemicarbazone units were synthesized. The structures of novel compounds were proved using IR and  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  NMR spectroscopy.

The *in vitro* antifungal and antibacterial activities of the tetranorlabdane compounds with thiosemicarbazone or 1,3,4-thiadiazole units have been assessed. The 1,3,4-thiadiazole-2-imine possesses excellent activity against strains of fungi and species of bacteria at MIC values of 0.125 and 2.5  $\mu\text{g/mL}$ , respectively, in comparison to the reference drugs Caspofungin (MIC= 0.25  $\mu\text{g/mL}$ ) and Kanamycin (MIC= 4  $\mu\text{g/mL}$ ).

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