THE USE OF ALIPHATIC ALDEHYDES IN THE SYNTHESIS OF NEW PYRAN ANNULATED DERIVATIVES OF 1H-2,1-BENZOTHIAZIN-4-ONE 2,2-DIOXIDE VIA DOMINO-TYPE INTERACTIONS.

THE ANTIMICROBIAL ACTIVITY OF THE COMPOUNDS SYNTHESIZED

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Key words: 2,1-benzothiazine 2,2-dioxide; aliphatic aldehydes; malononitrile; pyran, domino reaction; antimicrobial activity

Domino-type Knoevenagel-Michael-hetero-Thorpe-Ziegler and Knoevenagel-hetero-Diels-Alder interactions using 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide and aliphatic aldehydes as initial compounds have been studied. These reactions have led to 2-amino-3-cyano-4H-pyran and 2H-3,4-dihydropyran derivatives, respectively. It has been shown that the three-component one-pot interaction of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide with saturated aliphatic aldehydes and malononitrile proceeds under rather mild conditions and results in formation of 2-amino-6-ethyl-4-alkyl-4,6-dihydropyran[3,2-c][2,1]benzothiazin-3-carbonitrile 5,5-dioxides with moderate and high yields. At the same time, the yields of target products decrease with the increase of the length of the aliphatic aldehyde carbon chain. In this regard, the use of citronellal allowed us to obtain the product of the three-component interaction with a low yield. To date, there is no information in the literature about the possible application of aliphatic dialdehydes in such three-component interactions. It has been found that the use of glutaric aldehyde results in the synthesis of a new class of bis-derivatives of 2-amino-4H-pyran, in which two fragments are linked by the polymethylene bridge. The use of α,β-unsaturated aldehydes in the three-component interaction with 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide and malononitrile was accompanied by decrease in the process efficiency compared to saturated aliphatic aldehydes. The target fused 2-amino-3-cyano-4H-pyran was obtained only when α-methylcinnamic aldehyde was used in the reaction.

A two-component interaction of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide with citronellal has been also studied. It has been shown that this reaction is stereospecific. It proceeds through domino Knoevenagel-hetero-Diels-Alder sequence resulting in a new heterocyclic system – 2,2a,3,4,5,6,6a,8-octahydroisochromeno[4,3-c][2,1]benzothiazine 7,7-dioxide. The study of the antimicrobial activity of the compounds synthesized has allowed finding compounds with a moderate activity against P. aeruginosa і C. albicans.
ИСПОЛЬЗОВАНИЕ АЛИФАТИЧЕСКИХ АЛЬДЕГИДОВ В СИНТЕЗЕ НОВЫХ 1H-2,1-БЕНЗОТИАЗИН-4-ОН 2,2-ДИОКСИДОВ, КОНДЕНСИРОВАННЫХ С ПИРАНОВЫМ ЯДРОМ С ПОМОЩЬЮ ДОМИНО-РЕАКЦИЙ. АНТИМИКРОБНАЯ АКТИВНОСТЬ СИНТЕЗИРОВАННЫХ СОЕДИНЕНИЙ

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Ключевые слова: 2,1-бензотиазин 2,2-диоксид; алифатические альдегиды; малонодинитрил; тиран; домино-реакции; антимикробная активность

Изучены домино-взаимодействия Кневенагеля-Михаэля-Торпа-Циглера и Кневенагеля-гетеро-Дильса-Альдера с участием 1-этил-2,1-бензотиазин-4(3Н)-он 2,2-диоксида и алифатических альдегидов, приводящих соответственно к образованию производных 2-амино-3-циано-4Н-пирана и 2Н-3,4-диацидирипира. Показано, что трехкомпонентное одностадийное взаимодействие 1-этил-2,1-бензотиазин-4(3Н)-он 2,2-диоксида с насыщенными алифатическими альдегидами и малонодинитрилом протекает в очень мягких условиях и приводит к образованию 2-амино-6-этил-4-алкил-4,6-диацидирипира [3,2-c][1]бензотиазин-3-карбонитрил 5,5-диоксидов с высокими и умеренными выходами. В то же время увеличение длины углеродной цепи алифатических альдегидов приводит к уменьшению выхода целевых продуктов. Так, при использовании цитронеллаля продукт трехкомпонентного взаимодействия удалось получить только с невысоким выходом. Алифатические диальдегиды не были ранее использованы в данных взаимодействиях; показано, что применение ароматического альдегида приводит к новому классу бис-производных 2-амино-4Н-пирана, в котором фрагменты соединены полиметиленовым мостиком. Использование α,β-ненасыщенных альдегидов в трехкомпонентном взаимодействии с 1-этил-2,1-бензотиазин-4(3Н)-он 2,2-диоксидом и малонодинитрилом сопровождалось уменьшением эффективности процесса по сравнению с насыщенными алифатическими альдегидами. Целевой продукт взаимодействия конденсированный 2-амино-3-циано-4Н-пиран был получен только в случае применения а-метилкоричного альдегида. Изучено взаимодействие между 1-этил-2,1-бензотиазин-4(3Н)-он 2,2-диоксидом и цитронеллалем; показано, что данная реакция протекает исключительно как стереоспецифичное домино-взаимодействие Кневенагеля-гетеро-Дильса-Альдера и приводит к образованию новой гетероциклической системы – 2,2а,3,4,5,6,6а,8-октагидроизохромено[4,3-c][2,1]бензотиазин 7,7-диоксида. Изучение антимикробной активности синтезированных соединений позволило обнаружить производные, проявляющие умеренную активность против P. aeruginosa и C. albicans.

Природа пиранов широка и включает в себя широкий спектр биологических и фармацевтических активных свойств, в том числе противовирусную [8], антивирусную [9], антиверепирическую [10], антибактериальную [11] и другие. Некоторые из них были изучены в работах, где описана антибактериальная активность на P. aeruginosa и C. albicans.

**Fig. 1. Some of the natural and synthetic bioactive pyrans.**

**Until recently the common approach for construction of an organic compound was consistent formation of an individual bond using a “step-by-step” format. Unlike this, “domino-reactions” represent one-pot processes allowing to construct two or more bonds in a one step and to obtain a complex compound without isolation of intermediates. So, it is not surprising that such type of reactions becomes more popular among the synthetic community. The main advantages of a domino reaction are a bond-forming efficiency – formation of a number of bonds in one sequence, the structure economy, increase in the structural complexity, and their suitability for general application [1]. Domino-reactions have been successfully applied for the synthesis of a skeleton of many natural compounds in one step based on more simple precursors, e.g. progesterone [2], daphnilactone A [3], sophoradiol [4], some alkaloids etc. [5].**

Pyrans are ubiquitous in many important naturally occurring and available compounds; they have shown a wide range of biological and pharmacological activities that include anticancer [6], cytotoxic [7], anti-HIV [8], anti-inflammatory [9], antimalarial [10], antimicrobial [11] and others. Some of the natural and synthetic bioactive pyrans exhibiting a diverse kind of pharmaceutical properties are presented in Fig. 1.

In our previous works we reported on the synthesis of 2-amino-4H-pyrans via the three-component interaction of 1H-2,1-benzothiazin-4(3H)-one 2,2-di oxide with active methylene nitriles and carbonyl compounds (isatins [17], arylcarbaldehydes [18], heteryl carbaldehydes [19]) proceeding as a domino Knoevenagel/Michael/hetero-Thorpe-Ziegler sequence (Scheme 1).

Such straightforward domino approach turned out to be a powerful method for the synthesis of new
4,6-dihydropyrano[3,2-c][2,1]benzothiazine 5,5-dioxides in a single operation using simple experimental procedures. In its turn, in recent years derivatives of 1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide have become important due to their reported biological activities such as a potent antibacterial effect [20] and their bioisosteric relationships with 2,3-dihydro-4H-1,2-benzothiazin-4-one 1,1-dioxide core, which is a structural motif of the well-known analgesic and anti-inflammatory drugs (Piroxicam®, Droxicam® and Meloxicam®) [21]. The incorporation of two structural features (2,1-benzothiazine and 4H-pyran) into the interesting motif may also have some significance to the design of new therapeutic agents.

Encouraged by our previous successful efforts for obtaining the 4,6-dihydropyrano[3,2-c][2,1]benzothiazine 5,5-dioxide heterocyclic system and aimed to demonstrate the efficiency and generality of the three-component domino approach for their synthesis, here we report the use of aliphatic aldehydes in the synthesis of 2-amino-4H-pyran fused with the 1H-2,1-benzothiazine 2,2-dioxide core. This study becomes important since such reactions involving aliphatic aldehydes have been studied poorly and rarely occurred in the literature [22-24]. The one-pot multicomponent format is a cornerstone for the interaction because of inability to apply a stepwise approach [25] in this case. Such limitation is caused by the reported instability and easy cyclodimerization of intermediate Knoevenagel products – alkylidene-malononitriles with formation of 2-aminoisophthalonitrile (Scheme 2A) [26]. We also failed in our attempts to obtain another potentional Knoevenagel intermediate in the synthesis of the target fused 2-amino-4H-pyran (Scheme 2).

Therefore, previously we aimed to find out the most suitable reaction conditions for a model three-component interaction of 1-ethyl-1H-2,1-benzothiazin-4 (3H)-one 2,2-dioxide (1) with malononitrile (2) and propionaldehyde (3c) (Tab. 1). In general, such three-component interactions of enolnucleophiles with active methylene nitriles and aldehydes are easily conducted when heating in ethanol with basic catalysts (among which triethylamine, piperidine and morpholine are the most common) and result in formation of 2-amino-4H-pyran in good to excellent yields. The model reaction was carried out for 1 h using different solvents, as well as the temperature modes in the presence or in the absence of triethylamine as a catalyst. As one can see (Tab. 1), the reaction proceeded in different conditions and, interestingly enough, that product 4c was also formed in the catalyst-free approach. At the same time the best result was achieved using ethanol as a solvent with the catalytic amount of Et3N at room temperature. Therefore, the following reaction conditions were used as common in our experiments.

To demonstrate the general applicability of the above-mentioned conditions we introduced other aliphatic aldehydes into the reaction studied. As it was
found, the three-component interaction of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide (1) and malononitrile (2), the interaction resulted in formation of bis-derivative 4h. In general, for the reactions described the yields slightly decrease when the carbon chain length in the aldehyde molecule increases.

The simple performance and high yields of the reactions given above encouraged us to introduce α,β-unsaturated aliphatic aldehydes in the interaction studied. To the best of our knowledge, only cinnamic aldehyde was successfully applied in the synthesis of 2-amino-4H-pyran using the multicomponent format [27]. Thus, we had the opportunity to expand the data about these interactions. As it was found when α,β-unsaturated aldehydes were reacted under the conditions mentioned above, a significant decrease in the process efficiency was observed as compared with saturated aldehydes. The target 2-amino-4H-pyran 4i was obtained only in the case of α-methylcinnamaldehyde (3i) with the yield of 79%, whereas when cinnamic (3j) and crotonic (3k) aldehydes were used, we failed in our attempts to obtain the desired derivatives 4 despite of different conditions applied in the reaction (Scheme 4). This fact may indicate the crucial role of α-substituent in the initial unsaturated aldehyde for the synthesis of 2-amino-4H-pyran based on 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide (1).

The same decrease in the process efficiency was observed when citronellal ((R)-3,7-dimethyloct-6-enal) (3l) was introduced in the three-component interaction studied (Scheme 5). We succeeded to synthesize 4l in the yield of 23% by heating of the reaction mixture at 30-35°C in BuOH in the presence of the catalytic amount of Et3N for 20 h with the subsequent recrystallisation of the crude product from n-hexane.

Another domino-type interaction toward condensed pyrans, which allows to construct 3,4-dihydro-2H-pyran core, is domino Knoevenagel-hetero-Diels-Alder reaction. It can be performed as a two-component reaction putting together 1,3-dicarbonyl compound I and aldehyde containing the dienophile moiety II (Scheme 6) [1, 28]. The first stage of such interac-

### Table 1

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Et3N</th>
<th>Temp. mode</th>
<th>Yield of 4c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol</td>
<td>equimolar</td>
<td>reflux</td>
<td>not isolated</td>
</tr>
<tr>
<td>ethanol</td>
<td>catalytic</td>
<td>reflux</td>
<td>60</td>
</tr>
<tr>
<td>ethanol</td>
<td>catalytic</td>
<td>room temp.</td>
<td>75</td>
</tr>
<tr>
<td>ethanol</td>
<td>none</td>
<td>reflux</td>
<td>31</td>
</tr>
<tr>
<td>acetonitrile</td>
<td>equimolar</td>
<td>room temp.</td>
<td>not isolated</td>
</tr>
<tr>
<td>ethanol</td>
<td>catalytic</td>
<td>35-40°C</td>
<td>73</td>
</tr>
<tr>
<td>ethanol</td>
<td>none</td>
<td>room temp.</td>
<td>traces</td>
</tr>
</tbody>
</table>

Scheme 3. The use of aliphatic saturated aldehydes in the three-component reaction.
tion is formation of $\alpha,\beta$-unsaturated carbonyl compound III, which comprises the 1-oxa-1,3-butadiene moiety as diene and a double bond as dienophile. The subsequent intramolecular hetero-Diels-Alder interaction with an inverse electron demand leads to fused 3,4-dihydro-$2H$-pyran IV.

Different carbocyclic and heterocyclic 1,3-dicarbonyl compounds (1,3-cyclohexanediones, indandiones, dimethylbarbituric acid), as well as acyclic 1,3-dicarbonyl compounds (acetylacetone, acetoacetic ester) were introduced in this interaction. [1, 28, 29].

The common aldehydes applied in such interactions were O-substituted salicylic aldehydes and aliphatic aldehydes containing a double bond in the side chain. The domino Knoevenagel-hetero-Diels-Alder reaction was used for the synthesis of natural products comprising the 3,4-dihydro-$2H$-pyran core, e.g. tetrahydrocannabinol, secologanin, deoxyloganin, strictosidine, etc. [30]. Selected representatives of naturally occurring bioactive fused 3,4-dihydro-$2H$-pyrans are present in Fig. 2.

Since 1-ethyl-$1H$-2,1-benzothiazin-4-$(3H)$-one 2,2-dioxide (1) was similar to 1,3-dicarbonyl compound, and (R)-3,7-dimethyloct-6-enal (31) represented aldehyde containing the dienophile moiety, their interaction was also studied to obtain a new condensed heterocyclic system combining 3,4-dihydro-$2H$-pyran and $1H$-2,1-benzothiazine 2,2-dioxide cores. The literature data indicate that this interaction can lead to three different products, which are the result of three different domino reactions (Scheme 7).

The reaction conditions studied were AcOH/rt/24h, AcOH/Et$_3$N(equimolar)/rt/24h and DMF/100°C/15h. In first two cases only the starting benzothiazinone 1 was recovered after the reaction, whereas when the initial compounds were heated in DMF at 100°C for 15 h, another product was isolated as a light yellow crystalline powder. The $^1$H NMR-spectrum of the latter did not comprise any signals in the region common for protons bonded to aliphatic sp$^2$-carbon (Fig. 3), therefore, the structure 7 was desirable for the product isolated (Scheme 7).
Two stereogenic centres were introduced into the molecule of 7 (Fig. 4A) during the course of the two-component interaction. It is known that the similar domino Knoevenagel-hetero-Diels-Alder reaction in the case of aromatic α,β-unsaturated aldehydes, either exclusively or with high preference, leads to cis-cycloadducts, whereas in the case of aliphatic aldehydes the reaction provides trans-products with a high selectivity [1,30]. Previously, the interaction of 1,3-cyclohexanedione with R-citronellal was reported to form diastereo pure derivative of benzo[c]chromen-1-one with the trans linkage of the rings A and B (Fig. 4) [34].
In this connection, we inspired to determine the configuration of the chiral carbons in this tetracyclic derivative 7.

Based on 1D and 2D (COSY) $^1$H NMR (solvent – CDCl$_3$), as well as the literature $^1$H NMR data for similar citronellal derived products \[34\] we postulated the hydrogen shifts of 7 (Fig. 5).

To confirm the postulated shifts and to determine the configuration of the chiral carbons in 7 the $^1$H NMR NOE experiments were carried out via irradiation of protons, being the characteristic for our task and located at 0.97, 1.48, 1.59, 2.49, 2.73 ppm. Additionally, these experiments may also help to distinguish two CH$_3$-groups bonded to 2-carbon.

Primarily, the protons with 0.97 and 1.59 ppm clearly corresponding to 5-CH$_3$ group and 5-H, respectively, were studied (Fig. 6, 7). The results indicated that proton 6a with the shift of 2.49 ppm was below the plane of the cyclohexane ring because of its response, while proton with 1.59 ppm was irradiated, and there was the absence of the response, while proton with 0.97 ppm was irradiated.

When proton 6a was irradiated at 2.49 ppm (Fig. 8), there was no any response of protons with 1.48 and
1.44 ppm. This clearly proves the trans-configuration of protons 6a and 2a and together with abovementioned experiments indicates that 2-CH$_3$ with the shift of 1.14 ppm is below of the pyran ring, and 2-CH$_3$ with the shift of 1.44 ppm is up of the pyran ring.

Our attempt to confirm the conclusion about configuration of 2a and 6a by irradiation of 2a proton (1.48 ppm) did not succeed. The results of the NOE experiment in this case were complicated (Fig. 9) due to associated resenaion of 2a (1.48 ppm), 2-CH$_3$ (1.44 ppm) and 5-H (1.57-1.67 ppm) protons under irradiation impulse. Nevertheless, owing to this experiment we were able to explain the significant difference in chemical shifts of 2-(CH$_3$)$_2$ methyl groups.
This is most probably due to the unshielded influence of the benzene ring toward the equatorial bonded 2-CH$_3$ group (the NOE effect of 2-CH$_3$ with 13-H).

Finally, the NOE experiment by irradiation of proton with 2.73 ppm was carried out (Fig. 10). It confirmed the results previously obtained and proved attachment of the irradiated proton to 6-H. Thus, this proton is below the cyclohexane ring. Significant downfield shifting of this proton can be explained by a short contact with the oxygen atom of the SO$_2$-group.

Therefore, we can assert that the hetero-Diels-Alder interaction studied represents a stereospecific process allowing to obtain diastereo pure 2H-3,4-dihydropyran 7 with the trans-linked pyran and cyclohexane cores in a nearly quantitative yield (Fig. 11). All NOE experiments are well correlated with the postulated chemical shifts for hydrogen of 7.

Considering the high antimicrobial activity of pyran-annulated compounds previously reported (Fig. 1, 2) in this work the antibacterial activity of compounds 4a-i,l and 7 against Gram positive (S. aureus ATCC 6538 and B. subtilis ATCC 6633) and Gram negative (E. coli ATCC 8739 and P. aeruginosa ATCC 9027) bacterial strains, as well as the antifungal activity against the fungal strain of C. albicans (ATCC 10231) were studied in vitro by the double serial dilution method in the liquid growth medium [35]. Stock solutions of the test compounds were prepared using dimethylsulphoxide (DMSO) as a solvent. Since DMSO possessed a moderate antimicrobial activity [36], it was used as a reference antimicrobial drug. The minimum concentration, at which no growth was observed, was taken as the minimum inhibitory concentration (MIC) value. The comparison of the MICs (µg/mL) of the compounds under research and the reference drug against the strains tested are presented in Tab. 2.

The results showed that most of the compounds tested did not reveal any antimicrobial activity or possess a slight antimicrobial effect. However, formaldehyde, pentanal and isobutyraldehyde derived products showed the antimicrobial activity against the strains of P. aeruginosa and C. albicans. We have received an interesting result for α-methylcinnamic aldehyde 4i and citronellal derived products 4l, 7. These compounds have been proven to be promoters of the microbial growth and can be used as modifiers of the culture medium to improve its properties.

**Experimental Part**

Starting aldehydes and active methylene nitriles were commercially supplied and used without further purification. Starting 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide was obtained according
to the procedure previously described [17]. Dry DMF was prepared in accordance with the standard method. Melting points were determined on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. 1H NMR-spectra were recorded on a Varian Mercury MR-400 instrument using DMSO-d6 (for 4a-i) or CDCl3 (for 4l-7) as solvents and TMS as an internal standard. The 13C NMR experiment for 7 was performed using a Varian Mercury MR-400. Elemental analyses were carried out using a Carlo Erba CHNS-O EA 1108 analyzer.

The general procedure for the synthesis of 2-amino-6-ethyl-4,6-dihydropyran[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide 4a-i

To the solution of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide 1 (0.225 g, 0.001 Mol), malononitrile 2 (0.066g, 0.001 Mol) and appropriate aliphatic aldehyde 3a-g (0.001 Mol) or 3h (0.0005 Mol) in ethanol (5-10 mL) add the catalytic amount of triethylamine. Allow the mixture to stand at room temperature for 1 h until the precipitate of the target 2-amino-4H-pyran derivative is gradually formed. Filter the resulting precipitates 4a-i, wash with cooled ethanol, then dry in the air and recrystallize from ethanol.

Aldehyde 3a is used as 40% aqueous solution (0.075 g of the solution contains 0.001 Mol of aldehyde), and aldehyde 3i is used as 50% aqueous solution (0.11 g of the solution contains 0.0005 Mol of aldehyde).

**Table 2**
The data of the antimicrobial activity for compounds 4a-i, l and 7 under research

<table>
<thead>
<tr>
<th>Compound</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4g</th>
<th>4h</th>
<th>4i</th>
<th>4l</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC (µg/mL)</td>
<td>275</td>
<td>137.5</td>
<td>137.5</td>
<td>275</td>
<td>550</td>
<td></td>
<td></td>
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DMSO* = Concentration for DMSO was calculated based on its density value 1.1 g/mL.

**2-Amino-6-ethyl-4,6-dihydropyran[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide (4a).** Yield – 0.25 g (83%), a light yellow fine crystalline powder. M. p. – 231-233°C (EtOH). 1H NMR-spectrum (400 MHz, DMSO-d6), δ ppm (J, Hz): 1.18 (3H, t, J = 7.02, NCH2CH3); 3.28 (2H, s, CH pyran); 3.98 (2H, q, J = 7.02, NCH2CH3); 7.23 (2H, s, NH2); 7.33 (1H, t, J = 7.63, H-9); 7.49 - 7.55 (1H, m, H-7); 7.58 - 7.65 (1H, m, H-8); 7.81 (1H, d, J = 7.32, H-10). Found, %: C 55.58; H 4.67; N 14.02; S 10.81. C15H13N3O3S. Calculated, %: C 55.43; H 4.32; N 13.85; S 10.57.

**2-Amino-6-ethyl-4-methyl-6-dihydropyran[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide (4b).** Yield – 0.27 g (85%), white needles. M. p. – 205-207°C (EtOH). 1H NMR-spectrum (400 MHz, DMSO-d6), δ ppm (J, Hz): 1.15 (3H, t, J = 7.02, NCH2CH3); 1.36 (3H, d, J = 6.71, CH2CH2N); 3.53 (1H, q, J = 6.61, CH pyran); 3.98 (2H, q, J = 7.02, NCH2CH3); 7.21 (2H, br. s, NH2); 7.31-7.37 (1H, m, H-9); 7.51-7.56 (1H, m, H-7); 7.59-7.64 (1H, m, H-8); 7.83 (1H, dd, J = 8.09, 1.37, H-10). Found, %: C 57.03; H 5.07; N 13.41; S 10.33. C15H13N3O3S. Calculated, %: C 56.77; H 4.76; N 13.24; S 10.10.

**2-Amino-4,6-dimethyl-6-dihydropyran[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide (4c).** Yield – 0.25 g (75%), colourless prisms. M. p. – 190-192°C (EtOH). 1H NMR-spectrum (400 MHz, DMSO-d6), δ ppm (J, Hz): 0.80 (3H, t, J = 7.4, CH2CH3); 1.15 (3H, t, J = 7.0, NCH2CH3); 1.59-1.62 (2H, m, CH2CH2N); 3.62 (1H, t, J = 3.9, CH pyran); 3.99 (2H, q, J = 7.0, NCH2CH3); 7.24 (2H, s, NH2); 7.33 (1H, t, J = 7.6, H-9); 7.53 (1H, d, J = 8.3, H-7); 7.58-7.65 (1H, m, H-8); 7.83 (1H, d, J = 7.9, H-10). Found, %: C 57.73; H 4.95; N 12.89; S 9.35. C15H15N3O3S. Calculated, %: C 57.99; H 5.17; N 12.68; S 9.68.

**2-Amino-6-ethyl-4-propyl-6-dihydropyran[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide (4d).** Yield – 0.18 g (50%), colourless prisms. M. p. – 178-180°C (EtOH). 1H NMR-spectrum (400 MHz, DMSO-d6), δ ppm (J, Hz): 0.80 (3H, t, J = 6.71, CH2CH3); 1.14 (3H, t, J = 7.02, NCH2CH3); 1.18-1.33 (4H, m, CH2CH2CH2CH3); 1.57-1.78 (2H, m, CH2CH2CH2CH3); 2.60 (1H, t, J = 4.43, CH pyran); 3.99 (2H, q, J = 7.02, NCH2CH3); 7.24 (2H, s, NH2) 7.73 (1H, t, J = 7.63,
The procedure for the synthesis of 2-amino-6-ethyl-4-[(2R)-2,6-dimethylhept-5-en-1-yl]-4,6-dihydropyran[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide (4I)

To the solution of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide 1 (0.225 g, 0.001 Mol), malononitrile 2 (0.066 g, 0.001 Mol) and citronellal ((R)-3,7-dimethyloct-6-enal) 3I (0.154 g, 0.001 Mol) in n-butanol (10 mL) add the catalytic amount of triethylamine. Heat the mixture at 30-35°C for 20 h. Dilute the resulting mixture with 50 mL of n-hexane, and wash the oily product formed with 30 mL of n-hexane. The white solid precipitate of 4I is formed under intensive friction of the oily product in n-hexane. Recrystallize the precipitate from n-hexane, then filter, wash with n-hexane and dry in the air to yield the pure product 4I.

Yield – 0.10 g (23%), a white powder. M. p. – 137-139°C. 1H NMR-spectrum (400 MHz, CDCl3), δ ppm (J, Hz): 0.87-1.12 (3H, m); 1.13-1.46 (5H, m); 1.47-1.79 (8H, m); 1.80-2.03 (3H, m); 3.70-3.81 (1H, m, CH pyran); 3.97-4.13 (2H, m, NCH2CH3); 4.98-5.17 (1H, m, =CH2); 7.17-7.28 (2H, m, Ar); 7.47-7.57 (1H, m, Ar); 7.72 (1H, d, J = 6.60, H-10). Found, %: C 64.61; H 6.84; N 9.83; S 7.50. C21H21N3O3S. Calculated, %: C 65.01; H 7.12; N 9.55; S 7.22.

The procedure for the synthesis of (2AR, 5R, 6AR)-8-ethyl-2,2,5-trimethyl-2,2a,3,4,5,6,6a,8-octahydroisochromeno[4,3-c][2,1]benzothiazone 7,7-dioxide (7)

Heat the solution of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide 1 (0.225 g, 0.001 Mol) and citronellal ((R)-3,7-dimethyloct-6-enal) 3I (0.154 g, 0.001 Mol) in DMF at 100°C for 15 h and dilute with water. To the resulting oily dark precipitate add methanol (10 mL), and boil the mixture until dissolution of the precipitate. Allow to stand the solution obtained at room temperature. Filter the crystalline precipitate formed, wash with methanol and dry in the air.

Yield – 0.35 g (97%), a light yellow crystalline powder. M. p. – 133-135°C (MeOH). 1H NMR-spectrum (400 MHz, CDCl3), δ ppm (J, Hz): 0.97 (3H, d, J = 6.60, CH3); 1.05-1.20 (6H, m, C(CH3)2); 1.27-1.57 (18H, m, Ar); 1.67 (1H, m, C(CH3)=N); 2.49 (1H, d, J = 11.07, H-6a); 2.73 (1H, d, J = 12.72, H-6); 3.89-4.06 (2H, m, NCH2CH3); 7.11-7.20 (2H, m, H-9, H-11); 7.36-7.43 (1H, m, H-10); 7.76 (1H, d, J = 7.83, H-12). 13C NMR-spectrum (100 MHz, CDCl3), δ ppm: 13.92, 19.73, 22.25, 27.24, 32.29, 34.65, 34.95, 35.77; 46.39; 69.36; 70.14. C27H27N3O3S. Calculated, %: C 67.13; H 6.56; N 11.15; S 9.07.
References

Nадійшла до редакції 23.04.2016 р.