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THE USE OF ALIPHATIC ALDEHYDES IN THE SYNTHESIS OF NEW PYRAN ANNULATED DERIVATIVES OF 1*H*-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-dihydropyrano[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.

ВИКОРИСТАННЯ АЛІФАТИЧНИХ АЛЬДЕГІДІВ У СИНТЕЗІ НОВИХ 1Н-2,1-БЕНЗОТІАЗИН-4-ОН 2,2-ДІОКСИДІВ, КОНДЕНСОВАНИХ З ПІРАНОВИМ ЯДРОМ ЗА ДОПОМОГОЮ ДОМІНО-ВЗАЄМОДІЙ. АНТИМІКРОБНА АКТИВНІСТЬ СИНТЕЗОВАНИХ СПОЛУК

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***Ключові слова**: 2,1-бензотіазину 2,2-діоксид; аліфатичні альдегіди; малонодинітрил; піран; доміно-реакції; антимікробна активність*

Вивчені доміно-взаємодії Кньовенагеля-Міхаеля-гетеро-Торпа-Ціглера та Кньовенагеля-гетеро-Дільса-Альдера за участю 1-етил-1Н-2,1-бензотіазин-4(3Н)-ону 2,2-діоксиду та аліфатичних альдегідів, що приводять до утворення відповідно похідних 2-аміно-3-ціано-4Н-пірану та 2Н-3,4-дигідропірану. Показано, що трикомпонентна одностадійна взаємодія 1-етил-1Н-2,1-бензотіазин-4(3Н)-ону 2,2-діоксиду з насиченими аліфатичними альдегідами і малонодинітрилом перебігає у дуже м'яких умовах і приводить до утворення 2-аміно-6-етил-4-алкіл-4,6-дигідропірано[3,2-с][2,1]бензотіазин-3-карбонітрил 5,5-діоксидів з високими та помірними виходами. У той же час збільшення довжини вуглецевого ланцюга аліфатичного альдегіду приводить до зменшення виходу цільових продуктів. Так, при використанні цитронелалю продукт трикомпонентної взаємодії вдалося одержати тільки з невисоким виходом. Аліфатичні діальдегіди не були раніше використані у даних взаємодіях; показано, що використання глутарового альдегіду дозволяє отримати новий клас біс-похідних 2-аміно-4Н-пірану, в якому фрагменти з'єднані поліметиленовим містком. Використання α,β-ненасичених альдегідів у трикомпонентній взаємодії з 1-етил-1Н-2,1-бензотіазин-4(3Н)-ону 2,2-діоксидом і малонодинітрилом супроводжувалося зменшенням ефективності процесу в порівнянні з насиченими аліфатичними альдегідами. Цільовий продукт взаємодії конденсований 2-аміно-3-ціано-4Н-піран був отриманий тільки у випадку застосування α-метилкоричного альдегіду. Вивчена взаємодія між 1-етил-1Н-2,1-бензотіазин-4(3Н)-ону 2,2-діоксидом і цитронелалем; показано, що така реакція перебігає винятково як стереоспецифічна доміно-взаємодія Кньовенагеля-гетеро-Дільса-Альдера і приводить до утворення нової гетероциклічної системи – 2,2a,3,4,5,6,6a,8-октагідроізохромено[4,3-с][2,1]бензотіазин 7,7-діоксиду. Вивчення антимікробної активності синтезованих сполук дозволило виявити похідні, що проявляють помірну активність проти P. aeruginosa і C. albicans.

ИСПОЛЬЗОВАНИЕ АЛИФАТИЧЕСКИХ АЛЬДЕГИДОВ В СИНТЕЗЕ НОВЫХ 1Н-2,1-БЕНЗОТИАЗИН-4-ОН 2,2-ДИОКСИДОВ, КОНДЕНСИРОВАННЫХ С ПИРАНОВЫМ ЯДРОМ С ПОМОЩЬЮ ДОМИНО-РЕАКЦИЙ. АНТИМИКРОБНАЯ АКТИВНОСТЬ СИНТЕЗИРОВАННЫХ СОЕДИНЕНИЙ

Д.А.Лега, Н.И.Филимонова, О.Г.Гейдерих, В.П.Черных, Л.А.Шемчук

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

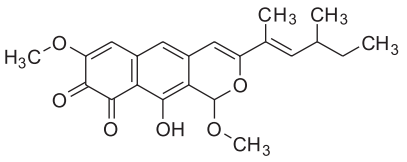
Изучены домино-взаимодействия Кневенагеля-Михаэля-гетеро-Торпа-Циглера и Кневенагеля-гетеро-Дильса-Альдера с участием 1-этил-2,1-бензотиазин-4(3Н)-он 2,2-диоксида и алифатических альдегидов, приводящих соответственно к образованию производных 2-амино-3-циано-4Н-пирана и 2Н-3,4-дигидропирана. Показано, 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-дигидропирано[3,2-c][2,1]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 глутарового 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 α-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 – 2,2a,3,4,5,6,6a,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.

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].

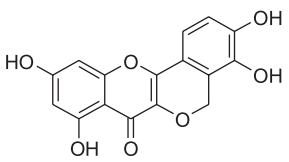
Pyrans are ubiquitous in many important naturally occurring and synthetically available compounds; they have shown a wide range of biological and pharmacological activities that include anticancer [6], cytotoxic [7], anti-HIV [8], anti-inflammatory [9], antimalarial [10], antimicrobial [11] and others. 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-4*H*-pyrans via the three-component interaction of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with active methylene nitriles and carbonyl compounds (isatins [17], arylcarbaldehydes [18], heterylcarbaldehydes [19]) proceeding as a domino Knoevenagel/Michael/*hetero*-Thorpe-Ziegler sequence (Scheme 1).

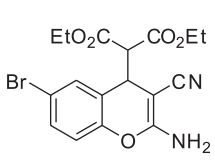
Such straightforward domino approach turned out to be a powerful method for the synthesis of new



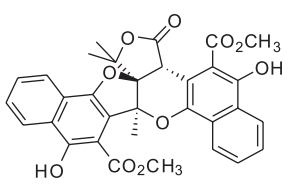
Laccaridione A – *antiprolifirative* [12]



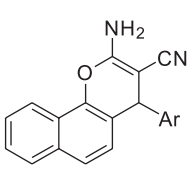
Ophioglonin – *antihepatitis B virus* [13]



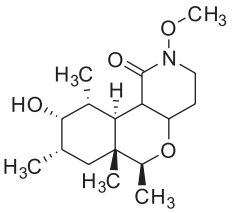
Ophioglonin – *antihepatitis B virus* [14]



Rubioncolin B – *anticancer* [15]

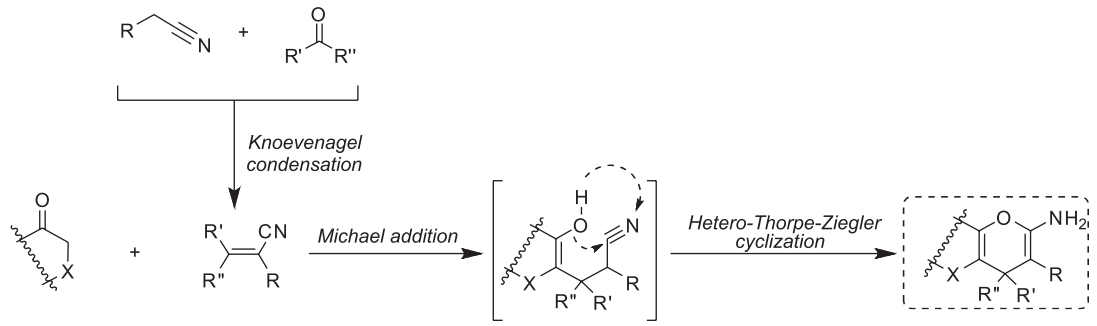


Anti-rheumatic [16]

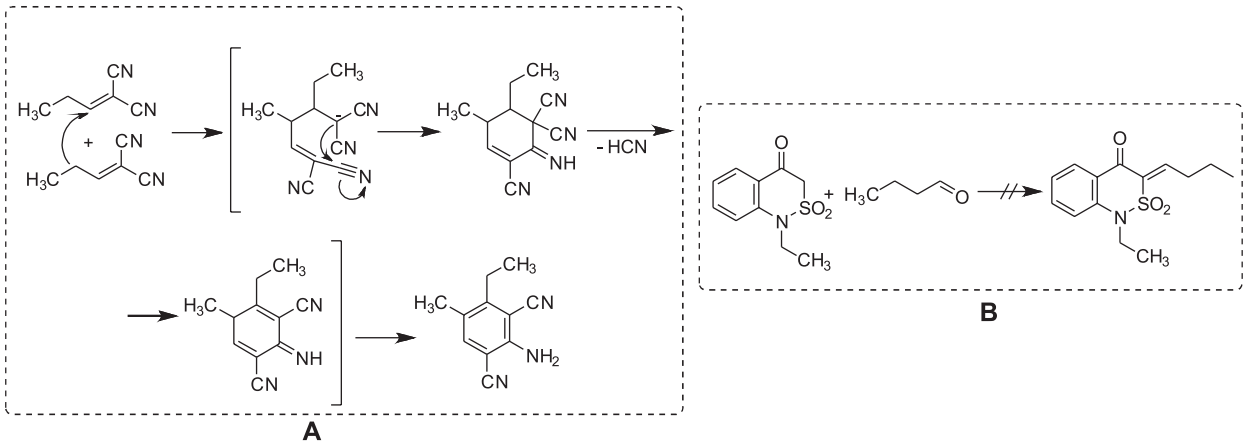


Cordypyridone D – *antimalarial* [10]

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



Scheme 1. The mechanism of 2-amino-4H-pyrans formation via the three-component format.



Scheme 2.

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 1*H*-2,1-benzothiazin-4(3*H*)-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-4*H*-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 4*H*-pyran) into the interesting motif may also have some significance to the design of new therapeutic agents.

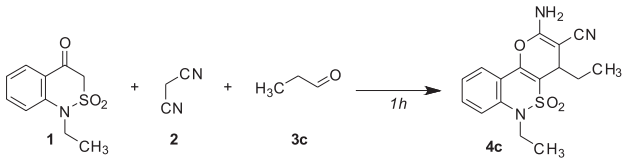
Encouraged by our previous successful efforts for obtaining the 4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide heterocyclic system and aimed to demonstrate the efficiency and generality of the three-component domino approach for their synthesis, here we report the use of aliphatic aldehydes in the synthesis of 2-amino-4-alkyl-3-cyano-4*H*-pyrans fused with the 1*H*-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 – alkylidenemalononitriles 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-4*H*-pyrans (Scheme 2).

Therefore, previously we aimed to find out the most suitable reaction conditions for a model three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-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-4*H*-pyrans 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 Et_3N 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

Table 1

Optimization steps for the model interaction



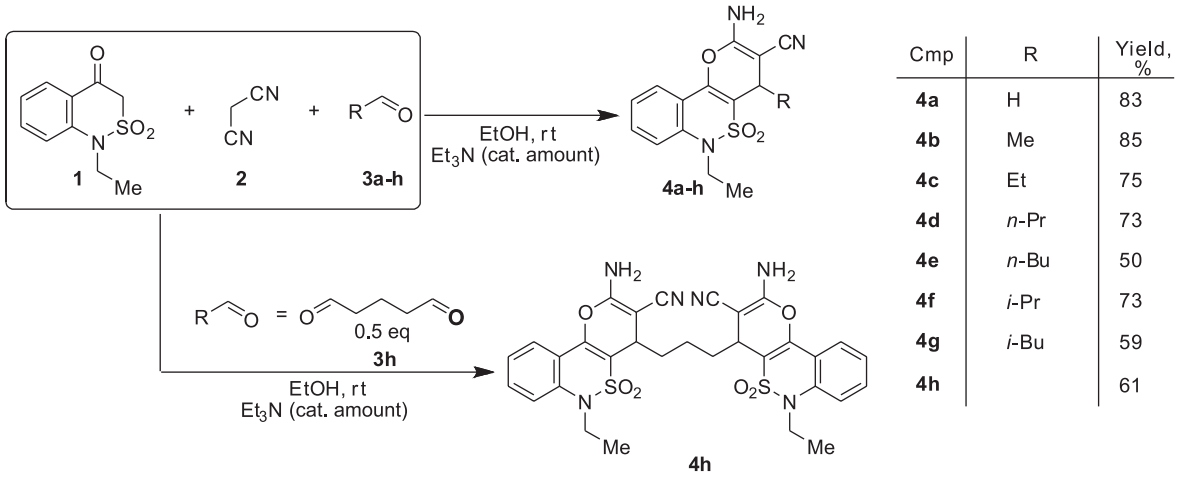
Solvent	Et_3N	Temp. mode	Yield of 4c, %
ethanol	equimolar	reflux	not isolated
ethanol	catalytic amount	reflux	60
ethanol	catalytic amount	room temperature	75
ethanol	none	reflux	31
acetonitrile	equimolar	room temperature	not isolated
ethanol	catalytic amount	35-40°C	73
ethanol	none	room temperature	traces

found, the three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**1**) with malononitrile (**2**) and aldehydes **3b-g** led to the desired 2-amino-3-cyano-4-alkyl-4*H*-pyrans with moderate to high yields (Scheme 3) when aldehydes with normal or branched saturated carbon chain were used. Application of formaldehyde **3a** in this interaction allowed us to obtain 4-unsubstituted 4*H*-pyran derivative **4a** with the yield of 83%. It is also known from the literature that only terephthalic aldehyde was used as representative of dialdehydes in the synthesis of 2-amino-4*H*-pyrans while other classes of dialdehydes were not applied in the interaction studied. In this regard, glutaric aldehyde (**3h**) as a new representative of dialdehydes was used in the current study. When it was used (0.5 equiv) in the reaction with 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-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-4*H*-pyrans 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-4*H*-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-4*H*-pyrans based on 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**1**).

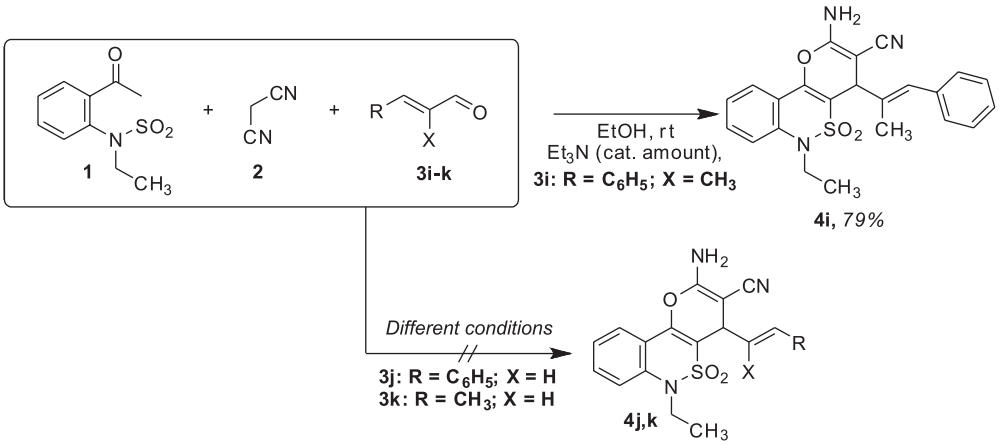
The same decrease in the process efficiency was observed when citronellal ((*R*)-3,7-dimethyloct-6-enal) (**3l**) was introduced in the three-component interaction studied (Scheme 5). We succeeded to synthesize **4l** in the yield of 23% by heating of the reaction mixture at 30-35°C in BuOH in the presence of the catalytic amount of Et_3N 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-2*H*-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-

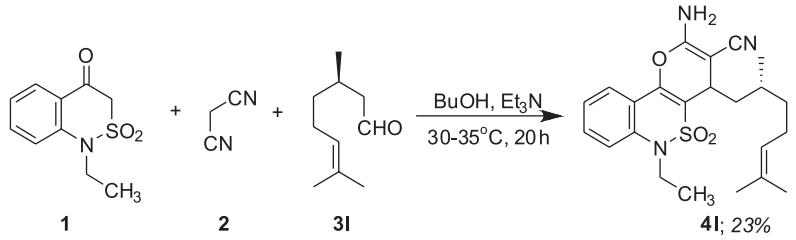


Cmp	R	Yield, %
4a	H	83
4b	Me	85
4c	Et	75
4d	*n*-Pr	73
4e	*n*-Bu	50
4f	*i*-Pr	73
4g	*i*-Bu	59
4h		61

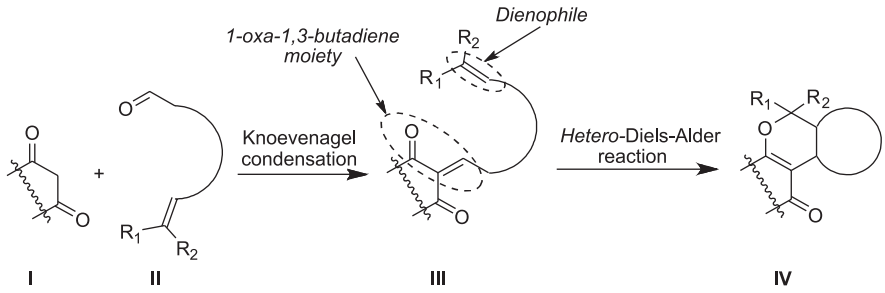
Scheme 3. The use of aliphatic saturated aldehydes in the three-component reaction.



Scheme 4. The use of aliphatic α,β-unsaturated aldehydes in the three-component reaction.



Scheme 5. The use of citronellal in the three-component reaction.



Scheme 6. The mechanism of 3,4-dihydro-2*H*-pyrans formation.

tion is formation of α,β-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-2*H*-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-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**1**) was similar to 1,3-dicarbonyl compound, and (R)-3,7-dimethyloct-6-enal (**3l**) represented aldehyde containing the dienophile moiety, their interaction was also studied to obtain a new condensed heterocyclic system combining 3,4-dihydro-2*H*-pyran and 1*H*-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_3N(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).

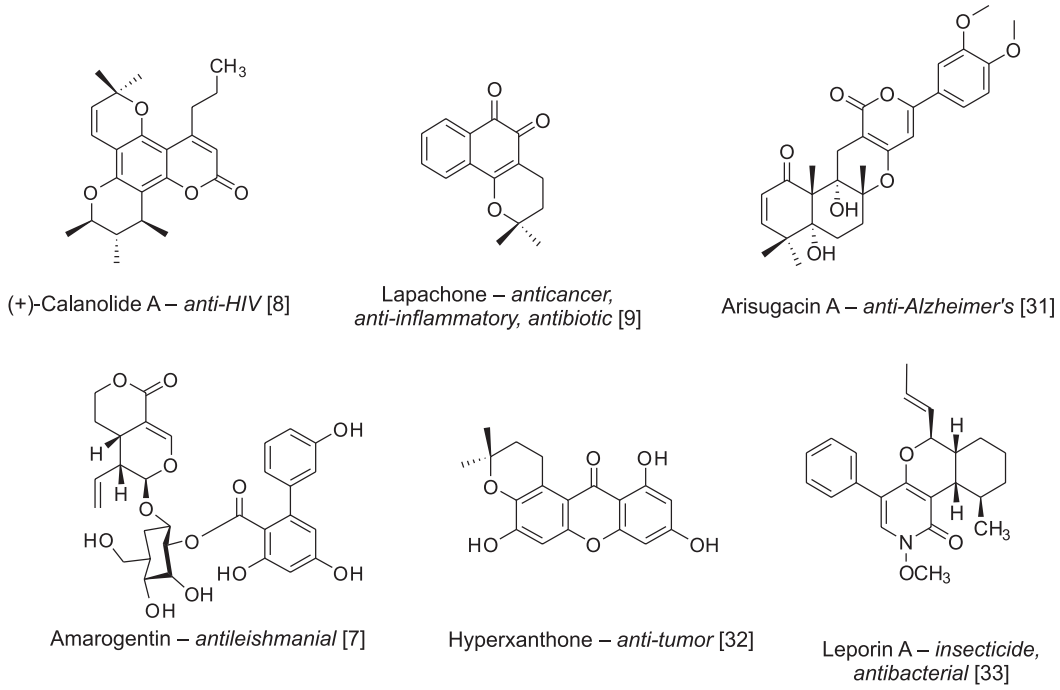
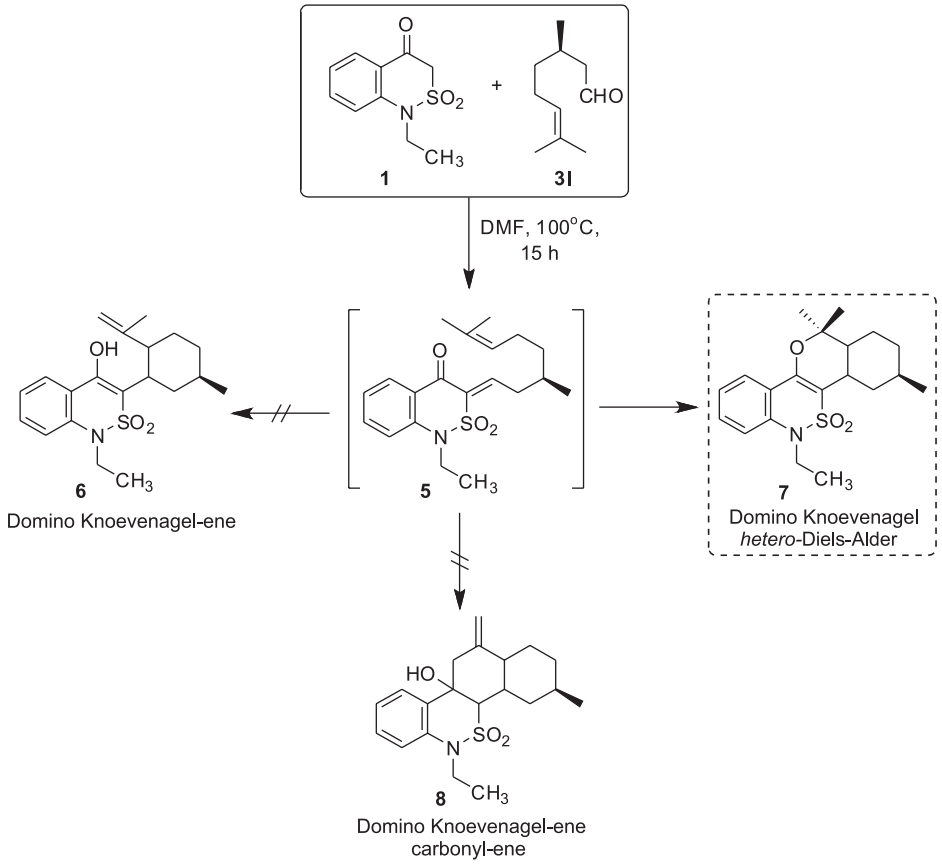


Fig. 2. Some of the naturally occurring bioactive compounds bearing 3,4-dihydro-2*H*-pyran annulated scaffolds.



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*-cyclo-adducts, 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].

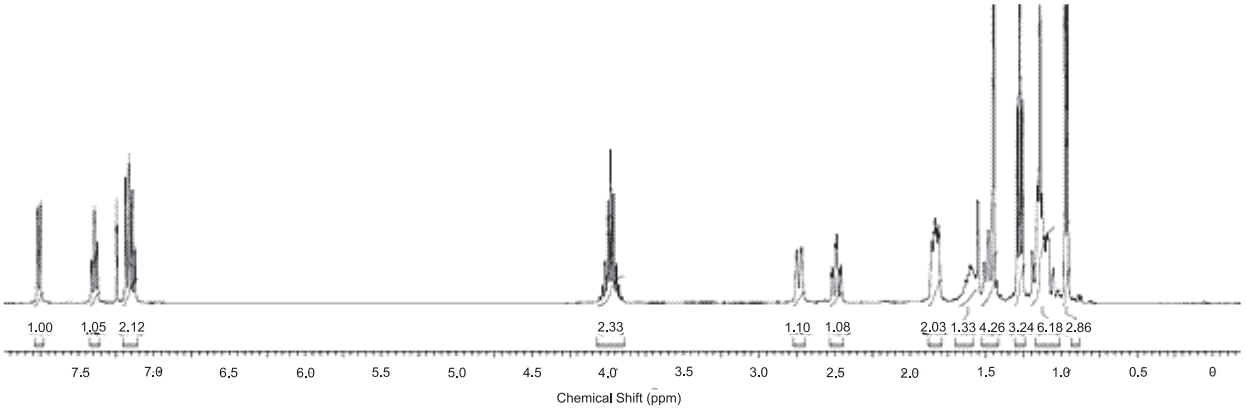


Fig. 3. The ^{1}H NMR-spectrum (solvent – $CDCl_3$) of **7**.

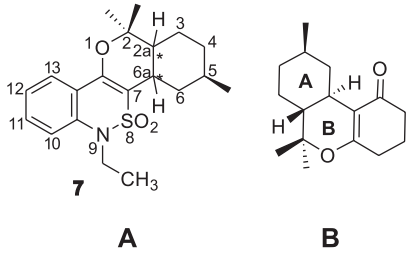


Fig. 4.

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

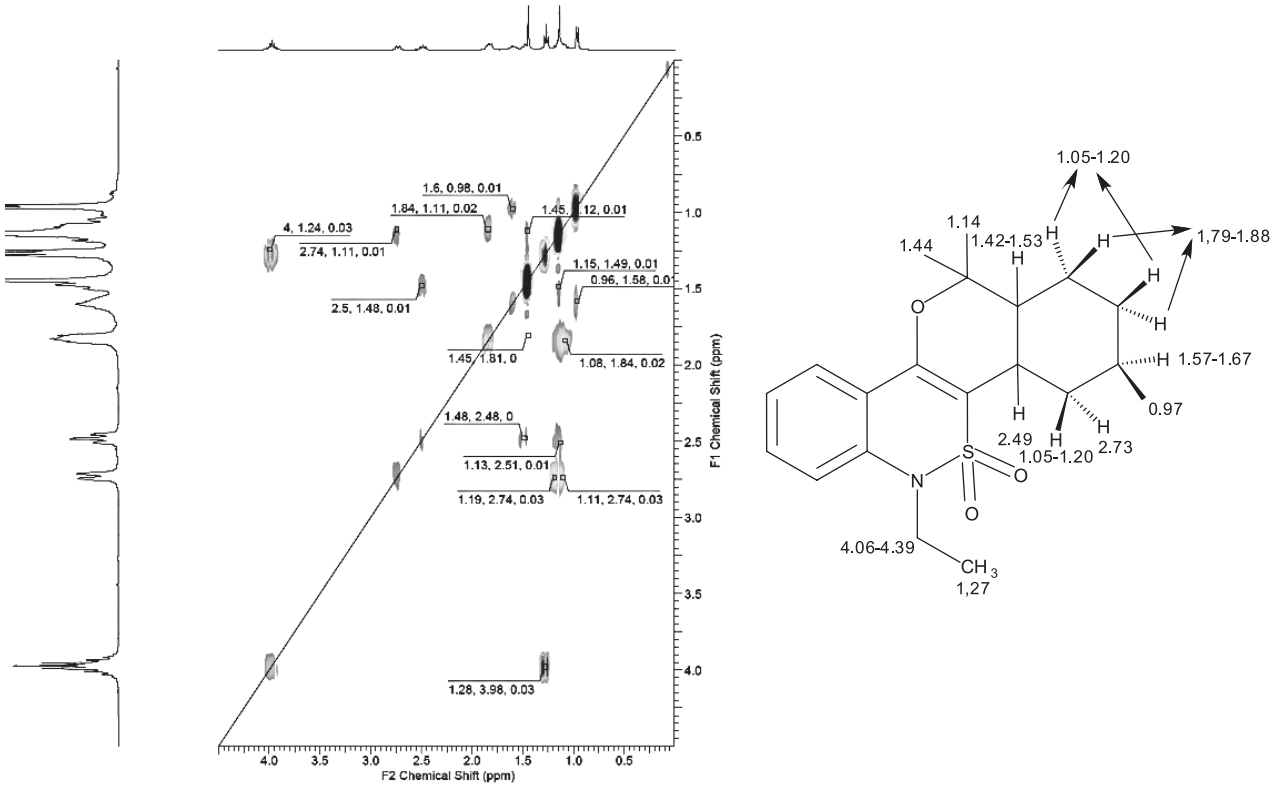


Fig. 5. Two-dimensional ^{1}H NMR (COSY, $CDCl_3$ showed only aliphatic region) and estimated ^{1}H chemical shifts for **7**.

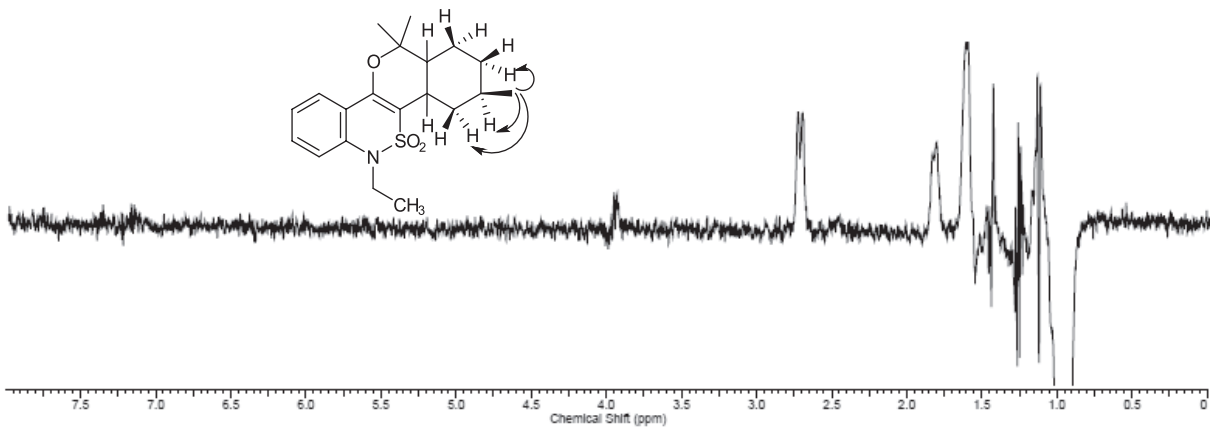


Fig. 6. The ^{1}H NMR NOE experiment – 0.97 ppm.

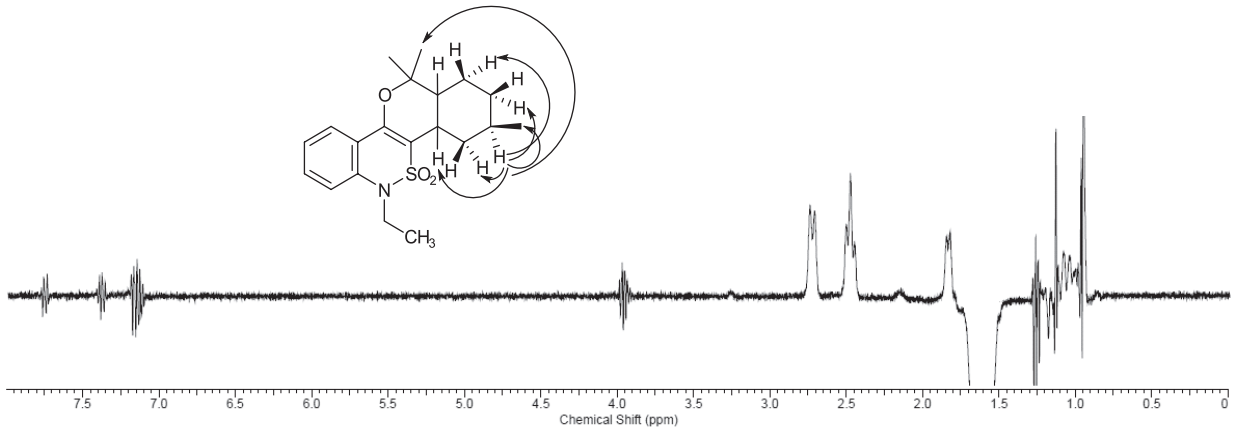


Fig. 7. The ^{1}H NMR NOE experiment – 1.59 ppm.

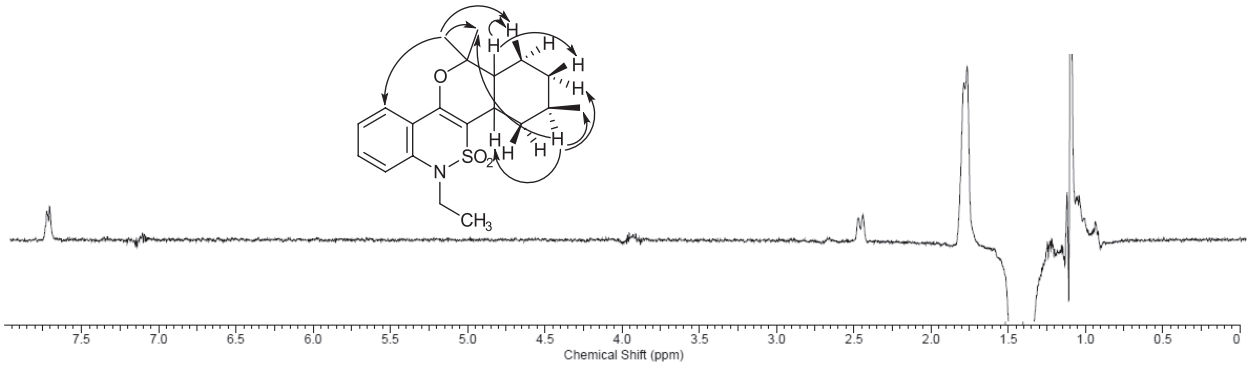


Fig. 8. The ^{1}H NMR NOE experiment – 2.49 ppm.

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 resonation 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.

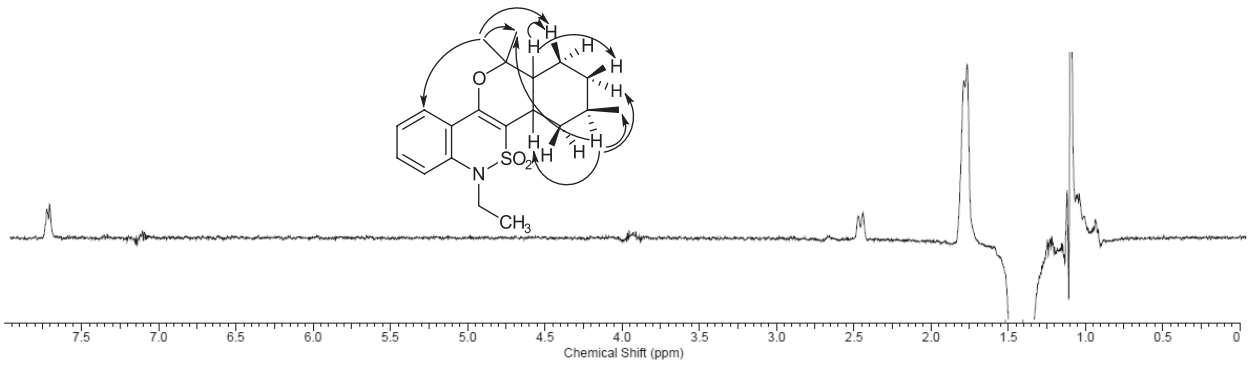


Fig. 9. The ^{1}H NMR NOE experiment – 1.48 ppm.

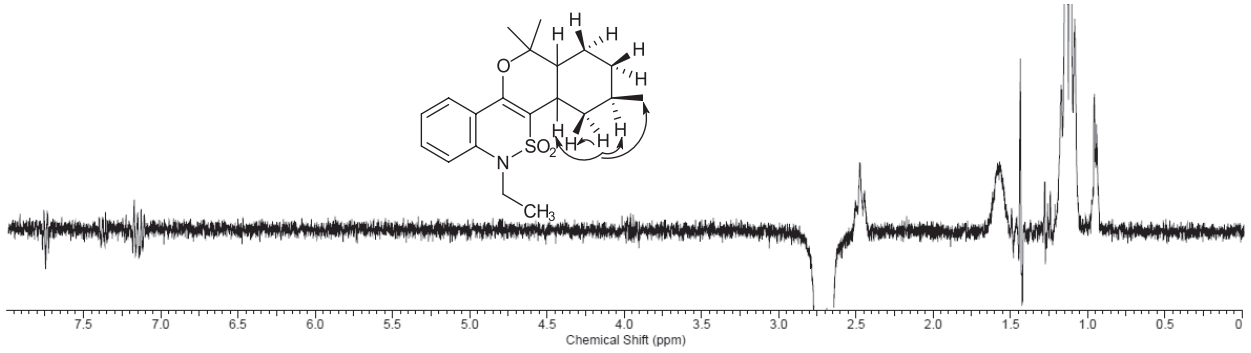


Fig. 10. The ^{1}H NMR NOE experiment – 1.73 ppm.

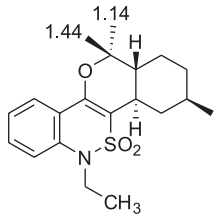


Fig. 11. The confirmed structure of **7**.

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 2*H*-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-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide was obtained according

Table 2

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

Compound	MIC (μg/mL)				
	S. aureus (ATCC 6538)	*E. coli* (ATCC 8739)	*B. subtilis* (ATCC 6633)	*P. aeruginosa* (ATCC 9027)	*C. albicans* (ATCC 10231)
4a	250	125	250	62.5	125
4b	125	125	125	125	125
4c	250	250	125	250	250
4d	250	125	250	250	125
4e	250	125	125	62.5	62.5
4f	250	250	125	125	62.5
4g	500	500	500	500	500
4h	250	125	125	250	125
4i	growth	growth	growth	growth	growth
4l	500	500	500	growth	growth
7	growth	growth	growth	500	growth
DMSO*	275	137.5	137.5	275	550

* – Concentration for DMSO was calculated based on its density value 1.1 mg/mL.

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. ^{1}H NMR-spectra were recorded on a Varian Mercury MR-400 instrument using DMSO-d_6 (for **4a-i**) or $CDCl_3$ (for **4l**, **7**) as solvents and TMS as an internal standard. The ^{13}C 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-R-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine-3-carbonitrile 5,5-dioxides 4a-i

To the solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 Mol), malononitrile **2** (0.066g, 0.001 Mol) and appropriate aliphatic aldehyde **3a-g,i** (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-4*H*-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).

***2-Amino-6-ethyl-4,6-dihydropyrano[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). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.02, $NCH_2C\underline{H}_3$); 3.28 (2H, s, CH pyran); 3.98 (2H, q, *J* = 7.02, $NC\underline{H}_2CH_3$); 7.23 (2H, s, NH_2); 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. $C_{14}H_{13}N_3O_3S$. Calculated, %: C 55.43; H 4.32; N 13.85; S 10.57.

***2-Amino-6-ethyl-4-methyl-4,6-dihydropyrano [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). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.02, $NCH_2C\underline{H}_3$); 1.36 (3H, d, *J* = 6.71, $CHC\underline{H}_3$); 3.53 (1H, q, *J* = 6.61, CH pyran); 3.98 (2H, q, *J* = 7.02, $NC\underline{H}_2CH_3$); 7.21 (2H, br. s., NH_2); 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. $C_{15}H_{15}N_3O_3S$. Calculated, %: C 56.77; H 4.76; N 13.24; S, 10.10.

***2-Amino-4,6-diethyl-4,6-dihydropyrano[3,2-c] [2,1]benzothiazine-3-carbonitrile 5,5-dioxide* (4c).** Yield – 0.25 g (75%), colourless prisms. M. p. – 193-195°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.80 (3H, t, *J* = 7.4, $CHCH_2C\underline{H}_3$); 1.15 (3H, t, *J* = 7.0, $NCH_2C\underline{H}_3$); 1.59-1.82 (2H, m, $CHC\underline{H}_2CH_3$); 3.62 (1H, t, *J* = 3.9, CH pyran); 3.99 (2H, q, *J* = 7.0, $NC\underline{H}_2CH_3$); 7.24 (2H, s, NH_2); 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. $C_{16}H_{17}N_3O_3S$. Calculated, %: C 57.99; H 5.17; N 12.68; S 9.68.

***2-Amino-6-ethyl-4-propyl-4,6-dihydropyrano [3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide* (4d).** Yield – 0.25 g (73%), colourless prisms. M. p. – 190-192°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.84 (3H, t, *J* = 7.21, $CH_2CH_2C\underline{H}_3$); 1.15 (3H, t, *J* = 6.97, $NCH_2C\underline{H}_3$); 1.28 (2H, sxt, *J* = 7.5, $CH_2C\underline{H}_2CH_3$); 1.56-1.75 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.59 (1H, t, *J* = 4.16, CH pyran); 3.99 (2H, q, *J* = 6.68, $NC\underline{H}_2CH_3$); 7.24 (2H, br. s., NH_2); 7.33 (1H, t, *J* = 7.58, H-9); 7.50-7.57 (1H, m, H-7); 7.58-7.66 (1H, m, H-8); 7.83 (1H, d, *J* = 7.83, H-10). Found, %: C 59.32; H 5.81; N 12.38; S 9.03. $C_{17}H_{19}N_3O_3S$. Calculated, %: C 59.11; H 5.54; N 12.17; S, 9.28.

***2-Amino-6-ethyl-4-butyl-4,6-dihydropyrano [3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide* (4e).** Yield – 0.18 g (50%), colourless prisms. M. p. – 178-180°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.80 (3H, t, *J* = 6.71, $CH_2CH_2CH_2C\underline{H}_3$); 1.14 (3H, t, *J* = 7.02, NCH_2CH_3); 1.18-1.33 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$); 1.57-1.78 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$); 3.60 (1H, t, *J* = 4.43, CH pyran); 3.99 (2H, q, *J* = 7.02, $NC\underline{H}_2CH_3$); 7.24 (2H, s, NH_2) 7.33 (1H, t, *J* = 7.63,

H-9); 7.50-7.57 (1H, m, H-7); 7.58-7.65 (1H, m, H-8); 7.83 (1H, dd, *J*=7.93, 1.22, H-10). Found, %: C 59.97; H 5.72; N 11.40; S 9.07. $C_{18}H_{21}N_3O_3S$. Calculated, %: C 60.15; H 5.89; N 11.69; S, 8.92.

***2-amino-6-ethyl-4-(propan-2-yl)-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide* (4f).** Yield – 0.25 g (73%), colourless prisms. M. p. – 213-215°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.72 (3H, d, *J* = 6.59, CH(C$\underline{H}_3$)$_2$); 1.01 (3H, d, *J* = 6.86, CH(C$\underline{H}_3$)$_2$); 1.15 (3H, t, *J* = 7.00, NCH$_2$C$\underline{H}_3$); 2.11 (1H, dtd, J = 13.52, 6.70, 6.70, 2.74, C$\underline{H}$(CH$_3$)$_2$); 3.46 (1H, d, *J* = 2.47, CH pyran); 4.01 (2H, q, *J* = 7.14, NC$\underline{H}_2$CH$_3$); 7.29-7.39 (3H, m, NH$_2$, H-9); 7.52-7.59 (1H, m, H-7); 7.59-7.67 (1H, m, H-8); 7.86 (1H, d, *J* = 7.68, H-10). Found, %: C 59.11; H 5.54; N 12.17; S 9.28. $C_{17}H_{19}N_3O_3S$. Calculated, %: C 59.43; H 5.77; N 11.81; S, 9.03.

***2-Amino-6-ethyl-4-(2-methylpropyl)-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide* (4g).** Yield – 0.10 g (59%), colourless prisms. M. p. – 172-174°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.83 (3H, d, *J* = 6.85, CH$_2$CH(C$\underline{H}_3$)$_2$); 0.92 (3H, d, *J* = 6.60, CH$_2$CH(C$\underline{H}_3$)$_2$); 1.16 (3H, t, *J* = 7.09, NCH$_2$C$\underline{H}_3$); 1.46-1.61 (2H, m, C$\underline{H}_2$CH(CH$_3$)$_2$); 1.80-1.92 (1H, m, CH$_2$C$\underline{H}$(CH$_3$)$_2$); 3.51 (1H, dd, *J* = 7.95, 4.03, CH pyran); 3.99 (2H, q, *J* = 6.93, NC$\underline{H}_2$CH$_3$); 7.29 (2H, s, NH$_2$); 7.33 (1H, t, *J* = 7.70, H-9); 7.50-7.55 (1H, m, H-7); 7.58-7.65 (1H, m, H-8); 7.86 (1H, dd, *J* = 7.95, 1.34, H-10). Found, %: C 60.03; H 5.98; N 11.45; S 8.63. $C_{18}H_{21}N_3O_3S$. Calculated, %: C 60.15; H 5.89; N 11.69; S, 8.92.

***1,3-bis(2-amino-6-ethyl-4,6-dihydropyrano [3,2-c][2,1]benzothiazine-3-carbonitrile-4-yl 5,5-dioxide)propan* (4h).** Yield – 0.21 g (61%), a light yellow powder. M. p. > 250°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.13 (6H, t, *J* = 6.59, 2×NCH$_2$C$\underline{H}_3$); 1.30-1.42 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$); 1.58-1.70 (2H, m, CH$_2$CH$_2$C$\underline{H}_2$) 1.72-1.83 (2H, m, C$\underline{H}_2$ CH$_2$CH$_2$); 3.57 (2H, t, *J* = 4.10, 2×CH pyran); 3.94 (4H, q, *J* = 7.14, 2×NC$\underline{H}_2$CH$_3$); 7.21 (4H, s, 2×NH$_2$); 7.33 (2H, t, *J* = 7.55, H-9, H-9'); 7.52 (2H, d, *J* = 8.51, H-7, H-7'); 7.59-7.65 (2H, m, H-8, H-8'); 7.81 (2H, d, *J* = 7.96, H-10, H-10'). Found, %: C 57.72; H 4.39; N 13.25; S 10.14. $C_{31}H_{30}N_6O_6S_2$. Calculated, %: C 57.57; H 4.68; N 12.99; S, 9.92.

***2-Amino-6-ethyl-4-(1-phenylprop-1-en-2-yl)-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-3-carbonitrile 5,5-dioxide* (4i).** Yield – 0.33 g (79%), white needles. M. p. – 198-200°C (EtOH). ^{1}H NMR-spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 6.86, NCH$_2$C$\underline{H}_3$); 1.74 (3H, s, =C-C$\underline{H}_3$); 3.92-4.01 (2H, m, NC$\underline{H}_2$CH$_3$); 4.26 (1H, s, CH pyran); 6.50 (1H, s, =C$\underline{H}$-C$_6$H$_5$); 7.17-7.39 (8H, m, H-9, NH$_2$, C$_6$H$_5$); 7.53 (1H, d, *J* = 8.23, H-7); 7.59-7.66 (1H, m, H-8); 7.87 (1H, d, *J* = 7.68, H-10). Found, %: C 65.71; H 5.18; N 10.29; S 7.52. $C_{23}H_{21}N_3O_3S$. Calculated, %: C 65.85; H 5.05; N 10.02; S 7.64.

The procedure for the synthesis of 2-amino-6-ethyl-4-[(2R)-2,6-dimethylhept-5-en-1-yl]-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-3-carbonitrile 5,5-dioxide (4l)

To the solution of 1-ethyl-1*H*-2,1-benzothiazin-4 (3*H*)-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) **3l** (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 **4j** 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 **4l**.

Yield – 0.10 g (23%), a white powder. M. p. – 137-139°C. ^{1}H NMR-spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.87-1.12 (3H, m); 1.13-1.46 (5H, m); 1.47-1.79 (8H, m); 1.81-2.03 (3H, m); 3.70-3.81 (1H, m, CH pyran); 3.97-4.13 (2H, m, NC$\underline{H}_2$CH$_3$); 4.71 (1H, s, NH$_2$)*; 4.98-5.17 (1H, m, $\underline{H}$C=C(CH$_3$)$_2$); 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. $C_{23}H_{29}N_3O_3S$. 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]benzothiazine 7,7-dioxide (7)

Heat the solution of 1-ethyl-1*H*-2,1-benzothiazin-4 (3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 Mol) and citronellal ((R)-3,7-dimethyloct-6-enal) **3l** (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). ^{1}H NMR-spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, d, *J* = 6.60, CHC$\underline{H}_3$); 1.05-1.20 (6H, m, C(C$\underline{H}_3$)$_2$, H-3, H-4, H-6); 1.27 (3H, t, *J* = 6.95, NCH$_2$C$\underline{H}_3$); 1.42-1.53 (4H, m, C(C$\underline{H}_3$)$_2$, H-2a); 1.57-1.67 (1H, m, H-5); 1.79-1.88 (2H, m, H-3, H-4); 2.49 (1H, td, *J* = 11.07, 2.81, H-6a); 2.73 (1H, d, *J* = 12.72, H-6); 3.89-4.06 (2H, m, NC$\underline{H}_2$CH$_3$); 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). ^{13}C NMR-spectrum (100 MHz, $CDCl_3$): δ (ppm) 13.92, 19.73, 22.25, 27.24, 32.29, 34.65, 34.95,

*When $CDCl_3$ was used instead of DMSO-d_6 in ^{1}H NMR experiments involving **4l**, the signal of 2-NH$_2$ group shifts upfield significantly.

38.69, 42.05, 47.37, 80.16, 114.02, 117.92, 121.21, 122.89, 124.76, 130.34, 137.50, 149.76.

The general method for the study of the antimicrobial activity (*double serial dilution method in the liquid growth medium*)

Into the six test-tubes add 1 mL of the broth. After that add 1mL of the compound studied in DMSO solution in the concentration of 1000 μg/mL into the first test-tube and mix thoroughly the solution obtained. Transfer 1 mL of the solution from the first test-tube into the second one. Thoroughly mix the solution in the second test-tube, transfer 1 mL of the resulting solution into the third test-tube and so on up to the sixth test-tube. Pour 1 mL of the solution from the sixth test-tube to have the equal volume in all of the test-tubes. Thus, the concentrations of the compounds studied are 500, 250, 125, 62.5, 31.25, 15.62 μg/mL in the test-tubes from the first to the sixth one.

Dilutions of DMSO as the reference drug are prepared in the similar way without using of the compounds under research. Thereby, the concentrations of DMSO in the reference solutions are 550, 275, 137.5, 68.75, 34.38, 17.19 μg/mL (taking into account the density of DMSO – 1.1 mg/mL).

Inocula of the bacterial and fungal cultures were prepared according to optical turbidity standard of 0.5 ME from a daily agar culture. Transfer the microbial suspension (microbe loading – 150×10^6 microbes per mL of the growth medium) with the dilutions of the compounds and DMSO prepared into the growth medium. Keep the test-tubes with bacterial cultures in thermostat for 24 h at 37°C, and the test-tubes containing *C. albicans* culture in thermostat for 48 h at 25°C. Examine carefully for the presence of turbidity. The minimum concentration when no growth is observed is taken as the MIC value.

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