

# СИНТЕЗ ТА АНАЛІЗ БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН

Recommended by Doctor of Pharmacy, Professor S. V. Kolisnyk

UDC 547.588.11:54.057:006.034

<https://doi.org/10.24959/nphj.18.2196>

O. V. Bevz<sup>1,2</sup>, I. V. Ukrainets<sup>1</sup>, O. V. Vashchenko<sup>3</sup>, V. A. Georgiyants<sup>1</sup>, L. V. Budianska<sup>3</sup>

<sup>1</sup>National University of Pharmacy

<sup>2</sup>Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines

<sup>3</sup>Institute for Scintillation Materials of NAS of Ukraine

## Obtaining of the pharmacopoeial reference sample of the mandelic acid isopropyl ester

In accordance with the requirements of the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) each monograph for a drug must include the test for related impurities. Impurities in a medicinal product may appear as initial, intermediate or side products of the synthesis and during storage.

**Aim.** To obtain the impurity of the pregabalin substance – a high-purity isopropyl ester of mandelic acid in order to provide the domestic pharmaceutical market with the pharmacopoeial reference sample of the State Pharmacopoeia of Ukraine (RS SPhU) in the framework of the program for import substitution of reference samples.

**Materials and methods.** To obtain RS SPhU of the mandelic acid isopropyl ester the traditional methods of organic synthesis, X-ray diffraction analysis, <sup>1</sup>H and <sup>13</sup>C NMR-spectroscopy, absorption spectrophotometry in the infrared region, thermogravimetry, the capillary method for determining the melting point, thin-layer and liquid chromatography were used, determination of water was performed by K. Fischer titration.

**Results and discussion.** The simple method for the synthesis of 1-methylethyl-(2RS)-2-hydroxy-2-phenylacetate with mandelic acid and 2-propanol in the presence of catalytic amounts of inorganic acids, as well as its subsequent purification with a final yield of over 90 % have been proposed.

**Conclusions.** As a result of the study isopropyl ester of mandelic acid has been synthesized, and the effective method of its purification providing a high degree of purity of the target compound has been selected. By its characteristics the substance obtained fully complies with the requirements of the LGC international certificate as a RS and can be used for the qualitative and quantitative determination of a related impurity in the pregabalin substance.

**Key words:** synthesis; isopropyl ester of mandelic acid; pregabalin impurity D; pharmacopoeial reference sample of the State Pharmacopoeia of Ukraine

O. V. Бевз, I. V. Українець, O. V. Ващенко, V. A. Георгіянц, Л. В. Будянська

### Одержання фармакопейного стандартного зразка ізопропілового естеру мигдальної кислоти

Відповідно до умов Міжнародної ради з узгодження технічних вимог до лікарських засобів (ICH) до кожної монографії на лікарський засіб необхідно включати тест на випробування супутніх домішок. Домішки у лікарському засобі можуть з'являтися як вихідні, проміжні чи побічні продукти синтезу, так і при зберіганні.

**Мета роботи** – одержати домішку субстанції прегабаліну – ізопропіловий естер мигдальної кислоти високої чистоти для забезпечення вітчизняного фармацевтичного ринку фармакопейним стандартним зразком Державної фармакопеї України (ФСЗ ДФУ) в рамках програми імпортозаміщення стандартних зразків (СЗ).

**Матеріали та методи.** Для одержання ФСЗ ДФУ ізопропілового естеру мигдальної кислоти використовували традиційні методи органічного синтезу, рентгеноструктурний аналіз, <sup>1</sup>H та <sup>13</sup>C ЯМР-спектроскопію, абсорбційну спектрофотометрію в інфрачервоній області, термогравіметрію, капілярний метод визначення температури плавлення, тонкошарову та рідинну хроматографію, а визначення води проводили титруванням за методом К. Фішера.

**Результати та їх обговорення.** Запропонований простий у виконанні метод синтезу 1-метилетил-(2RS)-2-гідрокси-2-фенілацетату з мигдальної кислоти і 2-пропанолу в присутності каталітичної кількості неорганічних кислот, а також його наступного очищення з кінцевим виходом понад 90 %.

**Висновки.** У результаті дослідження синтезовано ізопропіловий естер мигдальної кислоти та підібрано ефективний метод його очищення, який забезпечує високий ступінь чистоти цільової сполуки. За своїми характеристиками одержана речовина повністю відповідає вимогам, що висуваються до неї міжнародним сертифікатом LGC як до ФСЗ, та може бути використана для якісного та кількісного визначення супровідної домішки в субстанції прегабаліну.

**Ключові слова:** синтез; ізопропіловий естер мигдальної кислоти; прегабаліну домішка D; фармакопейний стандартний зразок Державної фармакопеї України

Е. В. Бевз, И. В. Украинец, О. В. Ващенко, В. А. Георгиянц, Л. В. Будянская

### Получение фармакопейного стандартного образца изопропилового эфира миндальной кислоты

В соответствии с условиями Международного совета по согласованию технических требований к лекарственным средствам (ICH) в каждую монографию на лекарственное средство необходимо включать тест на испытание сопутствующих примесей. Примеси в лекарственном средстве могут появляться как исходные, промежуточные или побочные продукты синтеза, так и при хранении.

**Цель работы** – получить примесь субстанции прегабалина – изопропиловый эфир миндальной кислоты высокой чистоты для обеспечения отечественного фармацевтического рынка фармакопейным стандартным образцом Государственной фармакопеи Украины (ФСО ГФУ) в рамках программы импортозамещения стандартных образцов (СО).

**Материалы и методы.** Для получения ФСО ГФУ изопропилового эфира миндальной кислоты использовали традиционные методы органического синтеза, рентгеноструктурный анализ,  $^1\text{H}$  и  $^{13}\text{C}$  ЯМР-спектроскопию, абсорбционную спектрофотометрию в инфракрасной области, термогравиметрию, капиллярный метод определения температуры плавления, тонкослойную хроматографию и жидкостную хроматографию, а определение воды проводили титрованием полумикрометодом по К. Фишеру.

**Результаты и их обсуждение.** Предложен простой в исполнении метод синтеза 1-метилэтил-(2RS)-2-гидрокси-2-фенилацетата из миндальной кислоты и 2-пропанола в присутствии каталитического количества неорганических кислот, а также его последующей очистки с конечным выходом более 90 %.

**Выводы.** В результате исследования синтезирован изопропиловый эфир миндальной кислоты и подобран эффективный метод его очистки, который обеспечивает высокую степень чистоты целевого продукта. По своим характеристикам полученное вещество полностью соответствует требованиям, предъявляемым к нему международным сертификатом LGC как к ФСО и может быть использовано для качественного и количественного определения сопутствующей примеси в субстанции прегабалина.

**Ключевые слова:** синтез; изопропиловый эфир миндальной кислоты; прегабалина примесь D; фармакопейный стандартный образец Государственной фармакопеи Украины

Substances, new drugs and generic drugs within their shelf-life are regularly checked for the presence and amount of related impurities since they can greatly affect the quality, and hence, the safety of medicines. The reference sample (RS) of any given impurities is a tool that allows to simply and effectively solving the analytical problems. As a rule, all these impurities are presented in the catalogs of international manufacturers of various chemical products, including RS. However, the presence in the catalogs does not always mean the opportunity to actually purchase RS in the required time. Moreover, the delivery of a foreign reagent even in the case of stock availability can take 1.5-2 months, which sometimes endangers the entry of the drug into the market. Exactly this situation has recently created in Ukraine at several domestic pharmaceutical companies with the anticonvulsant drug Pregabalin [1]. The cause is a banal lack of RS to determine impurity D (1-methylethyl-(2RS)-2-hydroxy-2-phenylacetate or isopropyl ester of mandelic acid), which need for standardization was introduced by the European Pharmacopoeia in 2016 [2]. To avoid similar situations in the future, or at least minimize their negative effects the Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines started the program of replacement of imported RS by RS of the State Pharmacopoeia of Ukraine (RS SPhU). This program will allow supplying customers with the necessary RS during the day in any point of Ukraine, and even significantly cheaper than imported ones. Our study on the synthesis of mandelic acid isopropyl ester, which would fully meet the quality criteria for RS by its characteristics, has been performed in the framework of this program.

**The aim** was to develop the preparative method for the synthesis of isopropyl ester of mandelic acid with such quality indicators that would fully satisfy the requirements for RS by the International Organization for Standardization (ISO) (sections 30-35 in the part of reference samples) and the general monograph 5.12 "Reference samples" of the European Pharmacopoeia and the SPhU [3-5].

#### Materials and methods

When performing the experimental part of the work the traditional method of organic synthesis was used. The target product was synthesized by a simple method from commercially available reagents. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR-spectra of the compounds synthesized were recorded on a "Varian Mercury-400" device (400 and 100 MHz, respectively) in DMSO- $d_6$  solution with TMS as an internal standard. The thermal analysis was performed using a "Mettler TA 3000" device. Each sample was subjected to a single temperature scan with the heating rate of 5 °C/min in the atmosphere of inert gas (argon, 20 ml/min) preventing oxidation of the sample. Determination of the melting point by the capillary method was performed a "Buchi B-535" device. The IR absorption spectrum was recorded on an "IRAffinity-1S" device according to the conditions described in the SPhU 2.2.24. The purity of the target compound was determined by liquid chromatography using "Varian ProStar" chromatograph on a Supelco discovery RP-amide C16 column, 250 × 4.6 mm, 5 μm, the flow rate – 1.0 ml/min; spectrophotometric detection was performed at the wavelength of 210 nm. Thin-layer chromatography was performed using ethanol solutions of test samples and the reference sample

(mandelic acid), they were applied to the TLC Silica gel 60 F<sub>254</sub> plates and chromatographed by the ascending technique using the mobile phase – butanol : formic acid : water (4 : 1 : 5), developer – 0.4 % solution of bromocresol green. Determination of water was performed by K. Fischer titration in accordance with the SPhU 2.5.12, Hydranal-5 (Sigma-Aldrich) was titrated on a “870 KF Titrino plus” device. To conduct the studies the measuring glassware of class A and reagents meeting the requirements of the SPhU, as well as “Sartorius MC 210 S” analytical balance were used.

**Isopropyl ester of mandelic acid (1).** To the solution of 15.22 g (0.1 Mol) of (2RS)- 2-hydroxy-2-phenylacetic acid in 50 ml of 2-propanol add 0.5 ml of concentrated sulfuric acid and boil under reflux for 5 h. Remove the excess of 2-propanol under reduced pressure. Dilute the reaction mixture with cold water and add sodium carbonate to pH 8. Extract the oily precipitate of ester 1 with methylene chloride (3 × 30 ml). Combine the organic extracts, then distill the solvent with simultaneous removal of water as an azeotrope (in the end under reduced pressure). Distill the residue in vacuum with a reflux condenser not less than 20 cm, collect the fraction with a boiling point of 88-90 °C / 4 mm Hg. Keep ester 1 obtained in the form of a colorless transparent oily liquid at a temperature of approximately +5 °C for a few hours until the whole reaction mixture turns into a white crystalline substance. Yield – 17.67 g (91 %). M. p. – 33.9 °C. The retention factor R<sub>f</sub> of the main spot is 0.38, additional spots are not observed. For comparison: R<sub>f</sub> of mandelic acid under the same conditions is 0.65. The <sup>1</sup>H NMR-spectra (400 MHz, DMSO-d<sub>6</sub>): δ 7.35 (2H, d, J = 7.4, H-2,6), 7.31 (2H, t, J = 7.3, H-3,5), 7.25 (1H, t, J = 6.8, H-4), 5.96 (1H, d, J = 5.3, OH), 5.07 (1H, d, J = 5.3, CHO), 4.85 (1H, m, CH(Me)<sub>2</sub>), 1.16 (3H, d, J = 6.2, Me), 1.03 (3H, d, J = 6.2, Me). The <sup>13</sup>C NMR-spectra (100 MHz, DMSO-d<sub>6</sub>): δ 172.5, 140.2, 129.4, 128.6, 72.8, 68.2, 21.6, 21.3.

**Cocrystal of mandelic acid isopropyl ester with CaCl<sub>2</sub> (4).** To the combined organic extracts (see the previous example) add granular anhydrous CaCl<sub>2</sub>, mix thoroughly and leave for a day at room temperature. Filter CaCl<sub>2</sub>, wash on the filter with methylene chloride, after that distill the solvent (in the end under reduced pressure). As a result, cocrystal 4 as a white crystalline hygroscopic substance is obtained. Yield – quantitative. M. p. >300 °C. The <sup>1</sup>H NMR-spectra (400 MHz, DMSO-d<sub>6</sub>): 7.43-7.31 (m, 5H, H arom.), 7.35 (2H, d, J = 7.4, H-2,6), 7.31 (2H, t, J = 7.3, H-3,5), 7.25 (1H, t, J = 6.8, H-4), 6.10 (1H, d, J = 5.3, OH), 5.05 (1H, d, J = 5.3, CHO), 4.83 (1H, m, CH(Me)<sub>2</sub>), 1.12 (3H, d, J = 6.2,

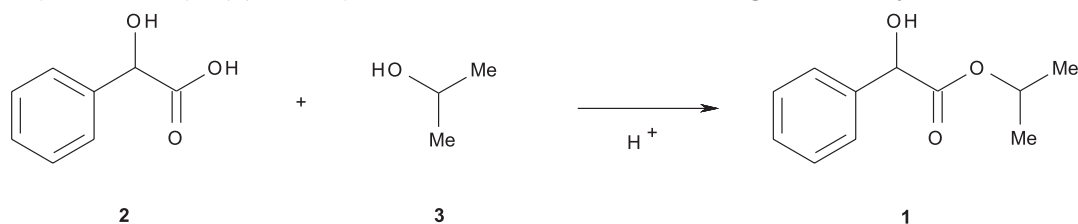
Me), 1.00 (3H, d, J = 6.2, Me). The <sup>13</sup>C NMR spectra (100 MHz, DMSO-d<sub>6</sub>): δ 172.5, 140.2, 129.4, 128.6, 72.8, 68.2, 21.6, 21.3.

### Results and discussion

Isopropyl ester of mandelic acid is the known substance, and to date two fundamentally different ways of obtaining it have been described. They are the interaction of phenylglyoxal with 2-propanol in the presence of yttrium (III) chloride [6], or esterification of D-mandelic acid with the same alcohol under the effect of Lewis acids (boron trifluoride etherate) [7]. These ways are certainly interesting, give good yields and, apparently, one of them could easily be used for solving the synthetic task set. However, the need for the use of the given inaccessible catalysts, in our opinion, is unlikely reasonable in the synthesis of the chemically simple compound. Besides, there is no information on purity of compounds obtained in these ways. Therefore, they have more theoretical value than practical one, at least in respect of the synthesis of isopropyl ester of mandelic acid.

The attempt was made to obtain RS SPhU of mandelic acid isopropyl ester (1) using a more simple method shown good results in the synthesis of alkyl- $\alpha$ -hydroxy carboxylates [8], namely by esterification of racemic mandelic acid (2) in the classic version, i.e. by boiling in the excess of 2-propanol (3) and in the presence of the catalytic amounts of anhydrous mineral acid (hydrochloric or sulfuric) (Scheme 1).

Monitoring by thin-layer chromatography (controlled by the presence of the initial mandelic acid in the reaction mixtures) showed that esterification fully completed in approximately 5 hours regardless of the nature of the catalyst. After completion of the reaction the excess of 2-propanol was distilled, water was added, the catalyst was neutralized with the solution of sodium carbonate, and the resulting mandelic acid isopropyl ester (1) was extracted with methylene chloride. As a rule, before further manipulation it is necessary to remove residual water from organic extracts, and it can be done with a variety of agents. A granular anhydrous calcium chloride, which is characterized by the ability to dry organic solvents with a relatively small amount effectively [9] is used in our work, and, besides, it is very easy to work with. However, its tendency to form solvates with lower alcohols is also known [10]. Although compound (1) has a hydroxyl group in its structure, but it is unlikely to be correct to name it a lower alcohol. We had some expectations regarding the use of calcium chloride for its dehydration. Indeed, treatment of the resulting solution of mandelic acid isopropyl ester (1) in methylene chloride with a granular anhydrous calcium chloride at



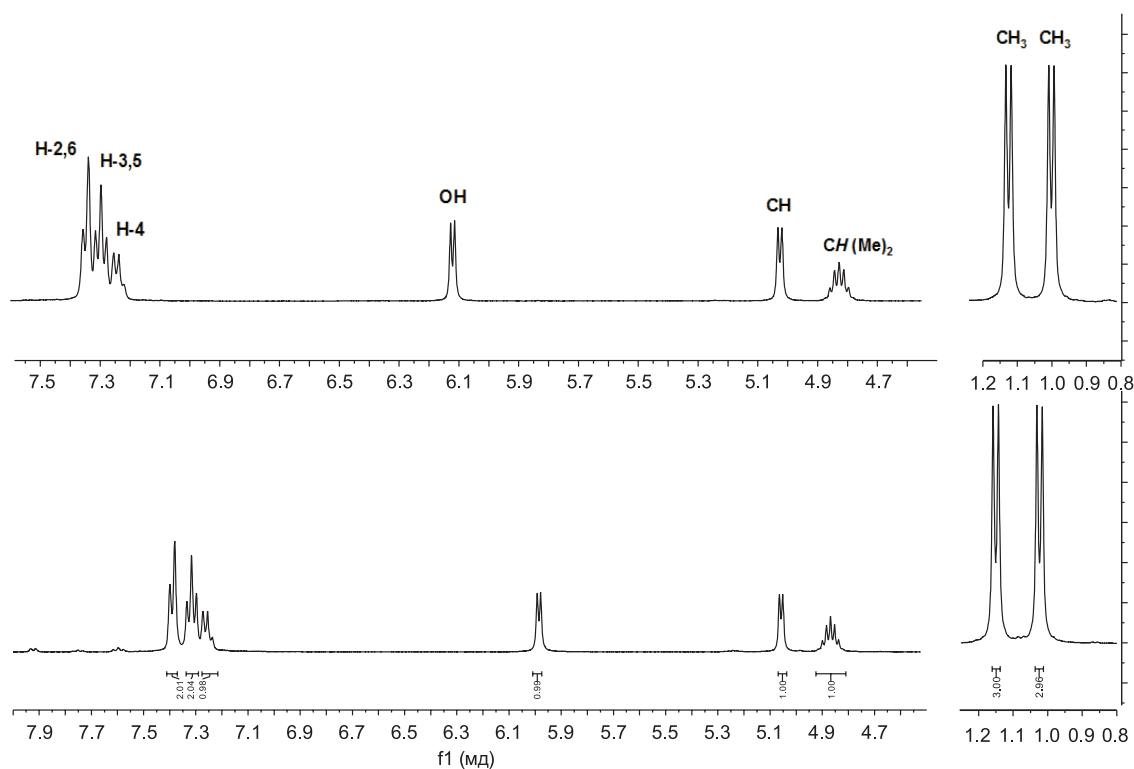


Fig. 1. The  $^1\text{H-NMR}$ -spectra of isopropyl ester of mandelic acid dried over  $\text{CaCl}_2$  (top) and its C3 (bottom)

first glance did not lead to any surprises –only clarification of the solution typical for such operations was visually observed due to binding of water.

However, after distilling methylene chloride it was found that the product obtained according to its characteristics did not correspond to the properties of the target ester (**1**) – we failed to distill it under reduced pres-

sure (4 mm Hg) since it remained a white crystalline substance even when heated up to 200 °C. Under normal conditions this compound generally has a melting point above 300 °C (for comparison – M. p. of ester **1** is only 34 °C) and rapidly absorbs moisture from the air.

At the same time, its  $^1\text{H-NMR}$ -spectrum appeared to be virtually identical to the spectrum of mandelic acid

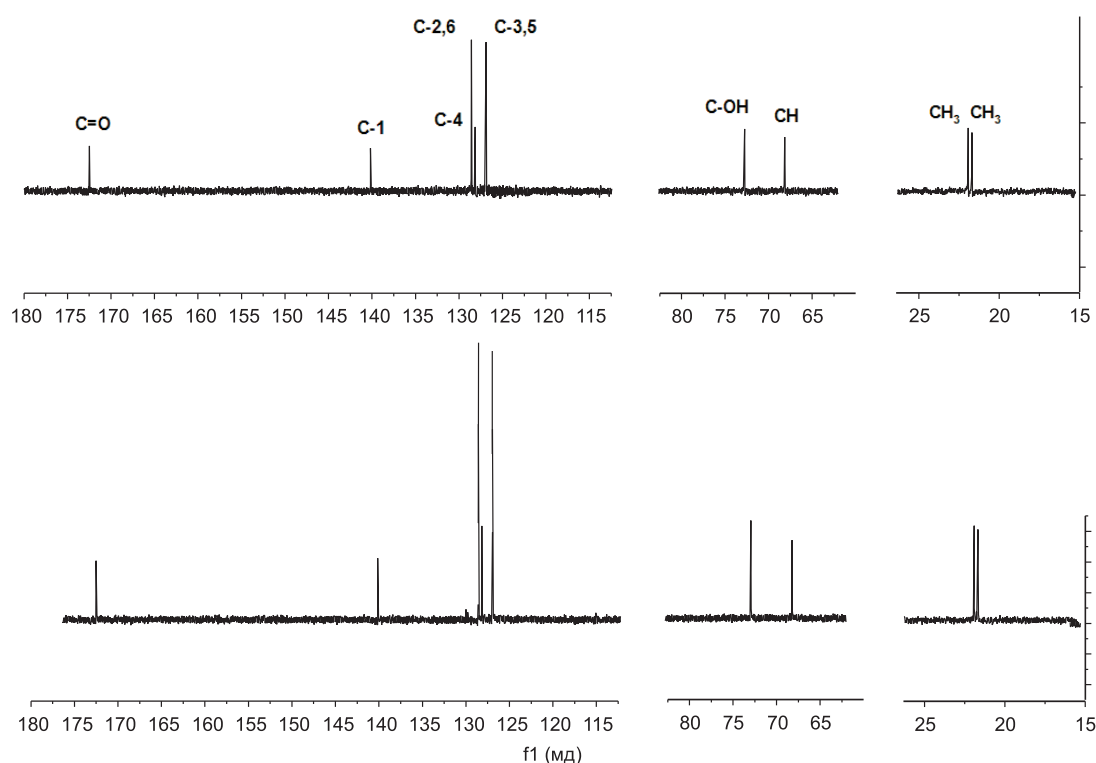


Fig. 2. The  $^{13}\text{C-NMR}$  spectra of isopropyl ester of mandelic acid dried over  $\text{CaCl}_2$  (top) and its C3 (bottom)



isopropyl ester RS (Fig. 1). It contains the signals of all proton-containing functional groups, and their intensity, multiplicity, and chemical shifts coincide. Only the signal of the alcoholic hydroxyl (6.10 ppm) is slightly displaced to a weak field relative to the same signal of RS (5.96 ppm). This fact (together with the above data) could be interpreted as the confirmation of participation of the alcoholic hydroxyl group in formation of a compound of the solvate type with calcium chloride. However, this conclusion is not quite correct since it is well known that the chemical shifts of the “active” protons (OH, NH, SH) even of the same substance can greatly vary depending on conditions of the spectrum registration (concentration, temperature, etc.) [11].

In these cases,  $^{13}\text{C}$ -NMR-spectroscopy is more informative since carbon atoms are very sensitive to even minor changes in their chemical surrounding, which affects their chemical shifts [12]. However, this method has not explained the situation with the structure of the compound obtained – its  $^{13}\text{C}$ -NMR-spectrum also coincided with the spectrum of mandelic acid isopropyl ester RS (Fig. 2). However, it should be remembered that the real cause for this result may be not the structure of the product studied, but only the specific effect of the solvent used (DMSO- $d_6$ ).

At the same time, conventional analytical qualitative and quantitative analyses show that calcium chloride is still present in the isolated substance and in rather large quantities – its content is 34.4 %. Based on this fact it can be assumed that ester 1 forms an adduct with calcium chloride in the ratio of 1 : 1 (it is possibly a solvate although, in our opinion, the name of cocrystal is more close to the truth). The highly branched spatial structure of mandelic acid isopropyl ester studied earlier [13] could promote to formation of this cocrystal (Fig. 3). By the way, in the solution cocrystals usually form a common mixture with the unrelated components [14], and it is in good agreement with the results of our NMR studies.

Another interesting and important aspect of the analytical problem, which we had somewhat unexpectedly

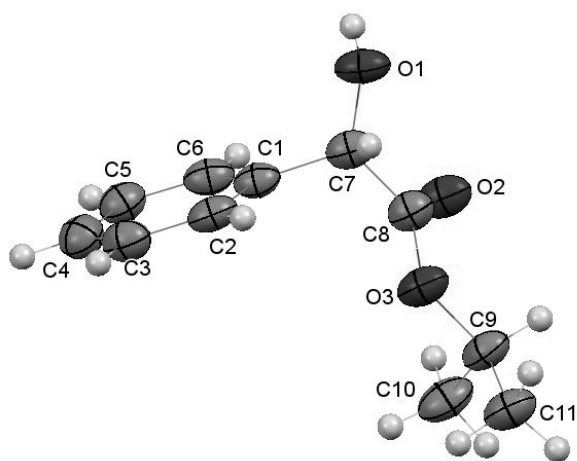


Fig. 3. The structure of the molecule of ester 1 in presentation of atoms by ellipsoids of thermal vibrations with 50% probability

Table 1

The melting points of calcium chloride and its crystalline hydrates [15]

Crystalline hydrates of calcium chloride	Melting point
$\text{CaCl}_2$	772-775 °C
$\text{CaCl}_2 \cdot \text{H}_2\text{O}$	260 °C
$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	176 °C
$\text{CaCl}_2 \cdot 4\text{H}_2\text{O}$	45.5 °C
$\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$	30 °C

to solve, is determination of the water content in the isolated product – if it enters the molecule of the cocrystal and, if so, in what form and in what quantity.

Using K. Fischer titration it was found that the total amount of all water in the sample was only 1.75 %, while a derivatographic attempt to trace the loss of moisture in the dynamics gave a very different result. Thus, it follows from the derivatogram in Fig. 4 (curve 1) that the sample gradually loses its weight immediately after the start of heating. At a temperature of approximately 110 oC the process significantly accelerates and ends with a peak on the differential thermogravimetric curve at 168 oC. After that weight loss abruptly stops, but at 175 oC it recovers again reaching its maximum at 183 °C. If all weight lost by the sample in the given temperature range is taken as water, then there will be an incredibly high result – 24.75 %. The cause for this effect became clear after studying the thermal behavior of mandelic acid isopropyl ester RS (Fig. 4, curve 2). It appeared to be thermally stable and easily volatile substance, and thus virtually nullified the results of the derivatographic studies.

Nevertheless, more careful and detailed analysis derivatograms has allowed us to obtain useful information. In particular, the peak on the differential thermogravimetric curve 1 at 168 °C can indicate only about the loss of water by the hydrate form of calcium chloride. Only four forms are known (Tab. 1), but only one of them is a dihydrate, which losing one molecule of water in simi-

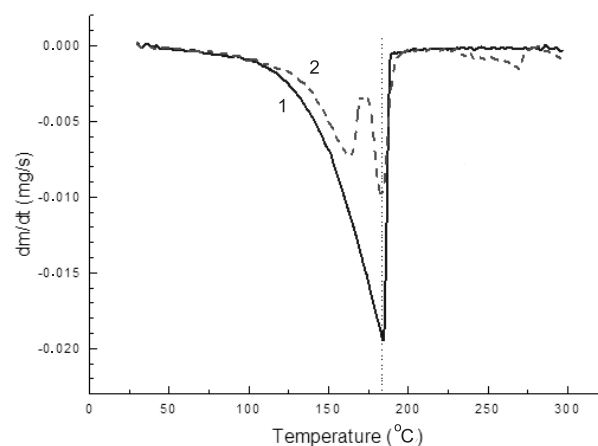
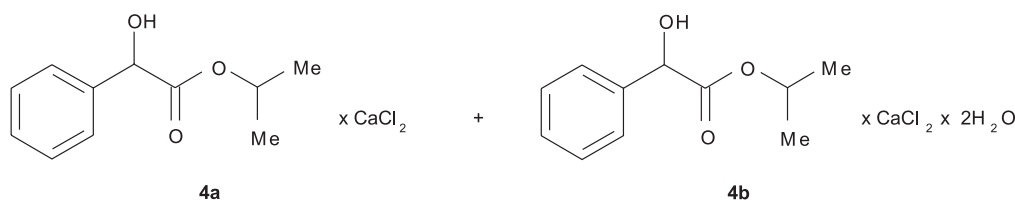


Fig. 4. Derivatograms of isopropyl ester of mandelic acid dried over  $\text{CaCl}_2$  (1) and its C3 (2)



Scheme 2

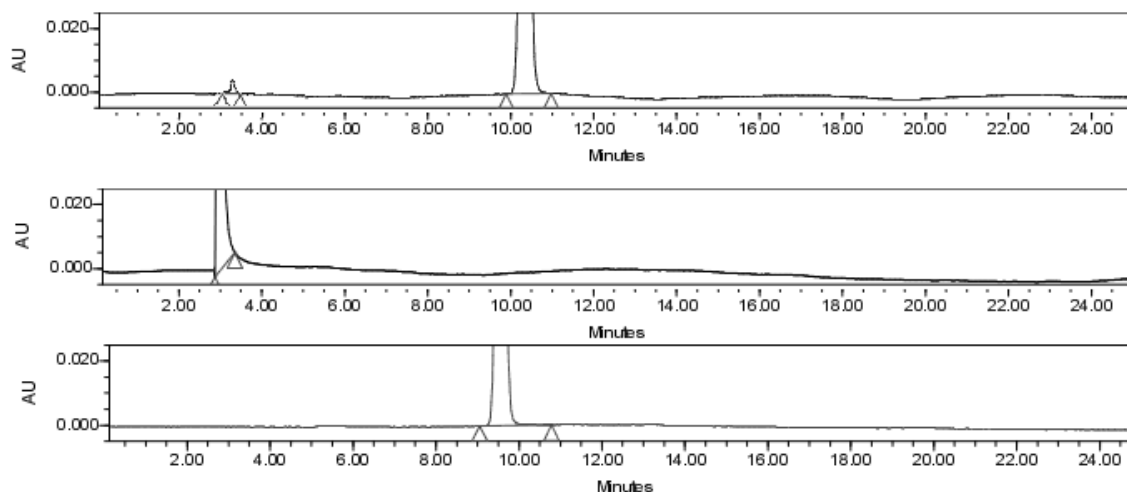


Fig. 5. Chromatograms: ester 1 after the conventional vacuum distillation (top); mandelic acid (in the middle); ester 1 after vacuum distillation with a reflux condenser (bottom)

lar conditions is converted into a monohydrate, is fully consistent with the experimental data. Unfortunately, the quantitative determination of water is not considered here since all measurements associated with the weight loss are masked by evaporation of isopropyl ester of mandelic acid. However, its thermal stability and volatility can play a very positive role. Thus, the peak at 183 °C on the derivatogram 1 (Fig. 4), which fully coincides with a similar peak on the derivatogram 2, shows that from this point the sample no longer contains isopropyl ester of mandelic acid. And there is no calcium chloride monohydrate in the residue; thus, nothing prevents to the quantitative determination of water. Simple calculations show that in the temperature range from 240 to 285 °C (another indication that we are dealing with a

monohydrate) 0.86 % of the initial weight is lost, it is 1.72 % calculated with reference to calcium chloride dihydrate (the result of water determination by K. Fischer semi-micro method – 1.75 %).

Therefore, based on the whole complex of the analytical studies conducted it can be unambiguously said that mandelic acid isopropyl ester (**1**) easily forms co-crystals both with calcium chloride **4a**, and with its dihydrate **4b**, and their real ratio can obviously vary within a wide range depending on the amount of water present in the reaction mixture (Scheme 2).

Since anhydrous calcium chloride (even granular) turned out to be totally unsuitable for drying the solution of mandelic acid isopropyl ester in methylene chloride, it was decided to perform this operation by even

Table 2

#### The results of the tests conducted

The quality indicator	The LGC certificate data [16]	The results obtained
Description	A white powder	A white crystalline powder
Identification:		
X-ray analysis	-	satisfied
<sup>1</sup> H NMR spectroscopy	-	satisfied
<sup>13</sup> C NMR spectroscopy	-	satisfied
Melting point	34°C	33.9°C
IR spectroscopy	satisfied	satisfied
Determination of purity by liquid chromatography	100 %	100 %
Water (Karl Fischer semi-micro method)	< 0.05 %	< 0.05 %
Certified content of C <sub>11</sub> H <sub>14</sub> O <sub>3</sub>	100.0%	100.0%

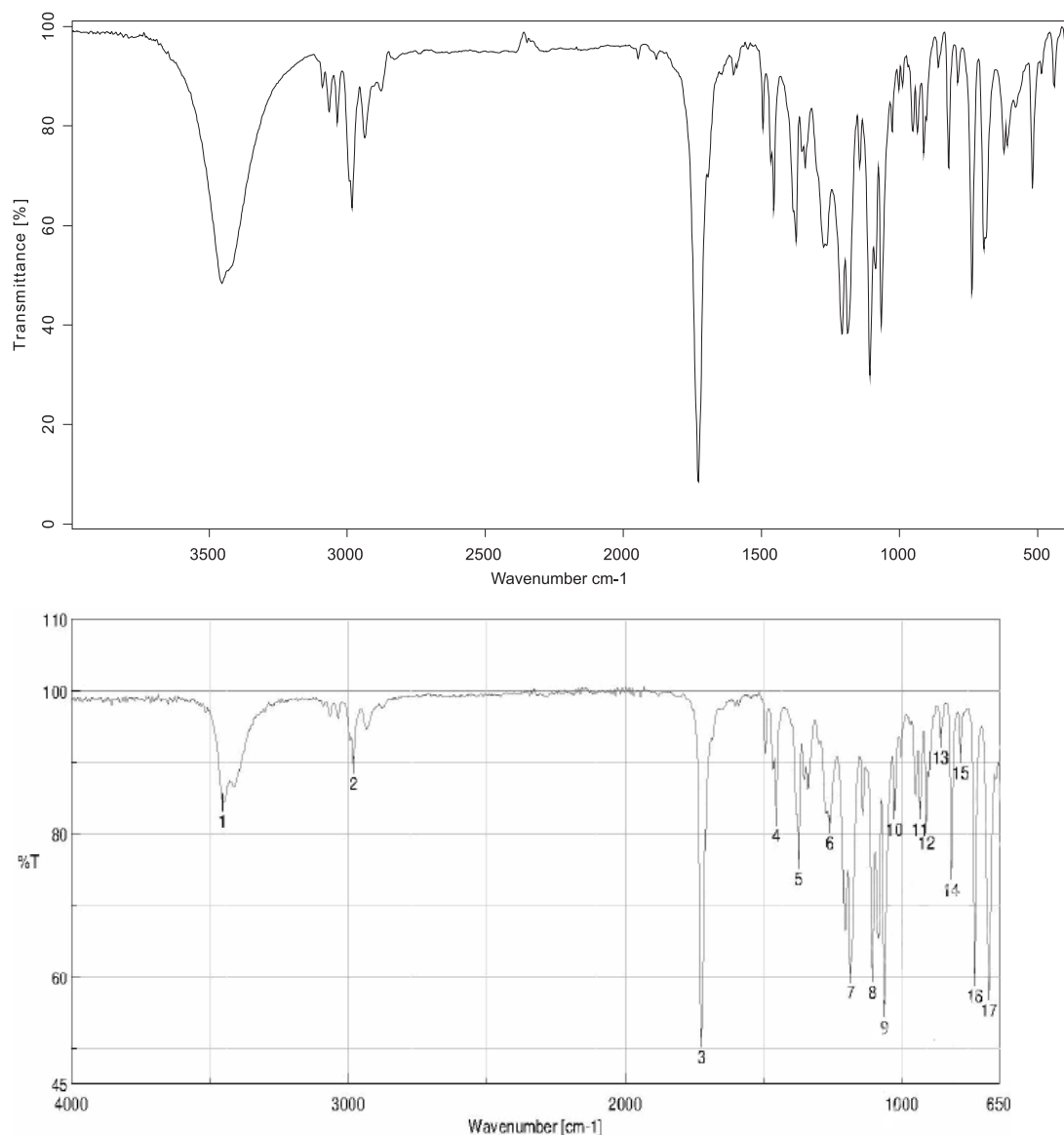


Fig. 6. The IR spectra of the isopropyl ester of mandelic acid: the synthesized one (top), the ester from the LGC certificate (bottom)

more simple method – removal of water as an azeotrope with the organic solvent. However, according to the data of the chromatographic studies (Fig. 5) under these conditions ester **1** undergoes the partial hydrolysis to the initial mandelic acid (**2**), but its content was so low (1.1 %) that this adverse process can be neglected.

Moreover, vacuum distillation with a reflux condenser allows to completely get rid of unwanted impurity of mandelic acid. Thus, the target isopropyl ester of mandelic acid with the purity of 100.0 % was obtained (Fig. 5).

In the end the IR-spectrum of ester **1** was recorded for its comparison with the standard IR-spectrum given for this compound in the LGC certificate. As clearly seen from Fig. 6, they are absolutely identical.

The results of all analytical tests for the isopropyl ester of mandelic acid synthesized are summarized in Tab. 2 compared to the characteristics of RS from the LGC certificate. These data indicate that it fully complies with the requirements for RS and can be used as RS SPhU to determine the corresponding related impurity in the pregabalin substance.

#### CONCLUSIONS

It has been shown that the common reaction of mandelic acid with 2-propanolol in the presence of mineral acids can be successfully used for the synthesis of high-purity isopropyl ester of mandelic acid, which meets all the requirements for pharmacopoeial reference samples by its parameters.

**Conflict of Interests:** authors have no conflict of interests to declare.

## REFERENCES

1. Леонтьев, Д. А. Система фармакопейных стандартных образцов Государственной фармакопеи Украины: концепция создания и текущее состояние / Д. А. Леонтьев, Н. В. Воловик, А. И. Гризодуб // Фармац. журн. (Узбекистан). – 2015. – № 2. – С. 29–37.
2. European Pharmacopoeia Supplement – 8.7–th ed. – Strasbourg : European Department for the Quality of Medicines, 2016. – P. 5801–5803.
3. ISO Guide 34:2009(E) : General requirements for the competence of reference material producers. – 3–rd ed. – Geneva: International Organization for Standardization. ISO copyright office, 2009. – 34 p.
4. Державна фармакопея України : в 3–х т. / Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів». – 2–вид. – Х. : Український науковий фармакопейний центр якості лікарських засобів, 2015. – Т. 1. – 1128 с.
5. European Pharmacopoeia Supplement – 9.3–th ed. – Strasbourg : European Department for the Quality of Medicines, 2017.
6. Likhari, P. R. YC13–Catalyzed Highly Selective Conversion of Arylglyoxal to  $\alpha$ –Aryl– $\alpha$ –Hydroxyacetic Ester : Dramatic Influence of Base / P. R. Likhari, A. K. Bandyopadhyay // Synlett. – 2000. – Vol. 2000, Issue 04. – P. 538–540. doi: 10.1055/s–2000–6569
7. Identification and Quantification of Aerosol Polar Oxygenated Compounds Bearing Carboxylic and/or Hydroxyl Groups. 1. Method Development / M. Jaoui, T. E. Kleindienst, M. Lewandowski, E. O. Edney // Analytical Chem. – 2004. – Vol. 76, Issue 16. – P. 4765–4778. doi: 10.1021/ac049919h
8. Houston, T. A. Boric acid catalyzed chemoselective esterification of  $\alpha$ –hydroxycarboxylic acids / T. A. Houston, B. L. Wilkinson, J. T. Blanchfield // Org. Lett. – 2004. – Vol. 6, Issue 5. – P. 679–681. doi: 10.1021/ol036123g
9. Patel, D. A. Synthetic, spectroscopic, magnetic and thermal aspects of drug based metal complexes derived from 1st row transition metal ions / D. A. Patel, A. A. Patel, H. S. Patel // Arabian J. of Chem. – 2017. – Vol. 10. – P. S2217–S2224. doi: 10.1016/j.arabjc.2013.07.056
10. Organikum : Organisch–chemisches / H. G. O. Becker, W. Berger, G. Domschke et al. – Wiley–VCH Verlag GmbH & Co. KGaA : Weinheim, Germany, 2015. – P. 46–51.
11. Günther, H. NMR Spectroscopy : Basic Principles, Concepts and Applications in Chemistry / H. Günther. – 3–rd ed. – Wiley–VCH : Weinheim, Germany, 2013. – P. 85–148.
12. 200 and More NMR Experiments : A Practical Course / ed. by S. Berger, S. Braun. – 3–rd ed. – Weinheim : Wiley–VCH, 2004. – 838 p.
13. Crystal structure of isopropyl 2–hydroxy–2–phenylacetate: a pharmacopoeia reference standard / I. Isaiev, S. Shishkina, I. Ukrainets, E. Bevez // Acta Crystallographica Section E Crystallographic Communications. – 2017. – Vol. 73. – P. 771–773. doi: 10.1107/s2056989017005862
14. Co–Crystals : A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients / A. V. Yadav, A. S. Shete, A. P. Dabke et al. // Indian J. Pharm. Sci. – 2009. – Vol. 71, Issue 4. – 359 p. doi: 10.4103/0250–474x.57283
15. Pradyot, P. Handbook of Inorganic Chemicals / P. Pradyot. – McGraw–Hill Companies, 2003. – P. 161–163.
16. LGC Certificate of Analysis. Reference Standard. Propan–2–yl (2RS)–2–Hydroxy–2–phenylacetate (Isopropyl Mandelate). – Available at : [https://hybris-static-assets-production.s3-eu-west-1.amazonaws.com/sysmaster/pdfs/ha1/h83/9439015829534/en\\_ST-WB-CERT-2387565-1-1-1](https://hybris-static-assets-production.s3-eu-west-1.amazonaws.com/sysmaster/pdfs/ha1/h83/9439015829534/en_ST-WB-CERT-2387565-1-1-1)

## REFERENCES

1. Leontev, D. A., Volovyk, N. V., Gryzodub, A. I. (2015). *Farmatsevticheskii zhurnal (Uzbekistan)*, 2, 29–37.
2. *European Pharmacopoeia Supplement*, 8.7–th ed. (2016). Strasbourg: European Department for the Quality of Medicines, 5801–5803.
3. *ISO Guide 34:2009(E): General requirements for the competence of reference material producers*. (2009). Geneva: International Organization for Standardization. ISO copyright office, 34.
4. *Derzhavna Farmakopeia Ukrainy, v 3–kh tomakh*. (2015). Kharkiv: Ukrainyskyi naukovyi farmakopeynyi tsentr yakosti likarskykh zasobiv, 1, 1128.
5. *European Pharmacopoeia Supplement*, 9.3–th ed. (2017). Strasbourg: European Department for the Quality of Medicines.
6. Likhari, P. R., Bandyopadhyay, A. K. (2008). YC13–Catalyzed Highly Selective Conversion of Arylglyoxal to  $\alpha$ –Aryl– $\alpha$ –Hydroxyacetic Ester: Dramatic Influence of Base. *Synlett*, 2000 (04), 538–540. doi: 10.1055/s–2000–6569
7. Jaoui, M., Kleindienst, T. E., Lewandowski, M., Edney, E. O. (2004). Identification and Quantification of Aerosol Polar Oxygenated Compounds Bearing Carboxylic or Hydroxyl Groups. 1. Method Development. *Analytical Chemistry*, 76 (16), 4765–4778. doi: 10.1021/ac049919h
8. Houston, T. A., Wilkinson, B. L., Blanchfield, J. T. (2004). Boric Acid Catalyzed Chemoselective Esterification of  $\alpha$ –Hydroxycarboxylic Acids. *Organic Letters*, 6 (5), 679–681. doi: 10.1021/ol036123g
9. Patel, D. A., Patel, A. A., Patel, H. S. (2017). Synthetic, spectroscopic, magnetic and thermal aspects of drug based metal complexes derived from 1st row transition metal ions. *Arabian Journal of Chemistry*, 10, S2217–S2224. doi: 10.1016/j.arabjc.2013.07.056
10. Becker, H. G. O., Berger, W., Domschke, G. et al. (2015). *Organikum: Organisch–chemisches*. Wiley–VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 46–51.
11. Günther, H. (2013). *NMR Spectroscopy: Basic Principles, Concepts and Applications in Chemistry*, 3rd ed. Wiley–VCH: Weinheim, Germany, 85–148.
12. Berger, S., Braun, S. (2004). *200 and More NMR Experiments: A Practical Course*, 3rd edition. Wiley–VCH, Weinheim, Germany, 838.
13. Isaiev, I., Shishkina, S., Ukrainets, I., Bevez, E. (2017). Crystal structure of isopropyl 2–hydroxy–2–phenylacetate: a pharmacopoeia reference standard. *Acta Crystallographica Section E Crystallographic Communications*, 73 (5), 771–773. doi: 10.1107/s2056989017005862
14. Yadav, A., Shete, A., Dabke, A., Kulkarni, P., Sakhare, S. (2009). Co–crystals: A novel approach to modify physicochemical properties of active pharmaceutical ingredients. *Indian Journal of Pharmaceutical Sciences*, 71 (4), 359. doi: 10.4103/0250–474x.57283
15. Pradyot, P. (2003). *Handbook of inorganic chemicals*. McGraw–Hill Companies, 161–163.
16. LGC Certificate of Analysis. Reference Standard. Propan–2–yl (2RS)–2–Hydroxy–2–phenylacetate (Isopropyl Mandelate). Available at: [https://hybris-static-assets-production.s3-eu-west-1.amazonaws.com/sysmaster/pdfs/ha1/h83/9439015829534/en\\_ST-WB-CERT-2387565-1-1-1.PDF](https://hybris-static-assets-production.s3-eu-west-1.amazonaws.com/sysmaster/pdfs/ha1/h83/9439015829534/en_ST-WB-CERT-2387565-1-1-1.PDF)



**Information about authors:**

Bevz O. V., postgraduate student of the Department of Pharmaceutical Chemistry, National University of Pharmacy. Junior researcher of the Department of Validation and Reference Standards, Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines. E-mail: bevz.helen@gmail.com. ORCID: 0000-0002-7695-3612

Ukrainets I. V., Doctor of Chemistry (Dr.habil), professor of the Department of Pharmaceutical Chemistry, National University of Pharmacy.  
E-mail: igor.v.ukrainets@gmail.com

Vashchenko O. V., Candidate of Physical and Mathematical Sciences (Ph.D.), senior researcher of the Institute for Scintillation Materials of NAS of Ukraine.  
E-mail: olga\_v@isma.kharkov.ua. ID ORCID: <http://orcid.org/0000-0002-7447-9080>

Georgiyants V. A., Doctor of Pharmacy (Dr.habil), professor, head of the Department of Pharmaceutical Chemistry, National University of Pharmacy.  
E-mail: vgeor@ukr.net

Budianska L. V., PhD student of the Institute for Scintillation Materials of NAS of Ukraine. E-mail: l.budjanskaja92@gmail.com.  
ORCID: <http://orcid.org/0000-0003-4967-1035>

**Відомості про авторів:**

Бевз О. В., аспірант кафедри фармацевтичної хімії, Національний фармацевтичний університет. Молодший науковий співробітник відділу валідації та стандартних зразків, Український науковий фармакопейний центр якості лікарських засобів. E-mail: bevz.helen@gmail.com. ORCID: 0000-0002-7695-3612

Українець І. В., д-р хім. наук, професор кафедри фармацевтичної хімії, Національний фармацевтичний університет. E-mail: igor.v.ukrainets@gmail.com

Вашченко О. В., канд. фізико-математичних наук, старший наук. співробітник, Інститут сцинтиляційних матеріалів НАНУ. Email: olga\_v@isma.kharkov.ua

Георгіянт В. А., д-р фарм. наук, професор, завідувачка кафедри фармацевтичної хімії, Національний фармацевтичний університет. E-mail: vgeor@ukr.net.  
ORCID: 0000-0001-8794-8010

Будянська Л. В., аспірант, Інститут сцинтиляційних матеріалів НАНУ. E-mail: l.budjanskaja92@gmail.com

**Информация об авторах:**

Бевз Е. В., аспирант кафедры фармацевтической химии, Национальный фармацевтический университет. Младший научный сотрудник отдела валидации и стандартных образцов, Украинский научный фармакопейный центр качества лекарственных средств. E-mail: bevz.helen@gmail.com

Украинец И. В., д-р хим. наук, профессор кафедры фармацевтической химии, Национальный фармацевтический университет.  
E-mail: igor.v.ukrainets@gmail.com

Вашченко О. В., канд. физико-математических наук, старший научный сотрудник, Институт сцинтилляционных материалов НАНУ.

E-mail: olga\_v@isma.kharkov.ua. ORCID: <http://orcid.org/0000-0002-7447-9080>

Георгиянт В. А., д-р фарм. наук, профессор, заведующая кафедрой фармацевтической химии, Национальный фармацевтический университет.

E-mail: vgeor@ukr.net

Будянская Л. В., аспирант, Институт сцинтилляционных материалов НАНУ. E-mail: l.budjanskaja92@gmail.com. ORCID: <http://orcid.org/0000-0003-4967-1035>

*Надійшла до редакції 09.11.2017 р.*