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## Synthesis of hydrazone derivatives of isonicotinic acid under microwave activation conditions

In the article the results of studying the reaction of the interaction of isonicotinic acid hydrazide with various derivatives of aromatic aldehydes under conditions of microwave activation in an alcohol medium were described. The results of studying the dependences of the hydrazone yield on the duration of the activation time at various microwave irradiation powers in comparison with the classical method have been presented. It was found that the main factors affecting the nature of the synthesis and the yields of the target products were the power and time of microwave activation, as well as the structural features of the reactants. For all studied reactions, the optimal conditions for obtaining the target product have been shown. As a result of a comparative analysis of the results obtained for the synthesis of new isonicotinic hydrazones, it was determined that the use of microwave irradiation contributed to an increase in the yield of the product and a decrease in the reaction time by 3-4 times than according to traditional technology. The authenticity of each product is unambiguously proved by comparing the melting point, as well as by analyzing the physico-chemical characteristics with previously synthesized hydrazone derivatives of isonicotinic acid obtained by classical synthesis methods. The structure of all synthesized compounds was studied by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, as well as data from two-dimensional COSY (<sup>1</sup>H-<sup>1</sup>H) spectra and HMQC (<sup>1</sup>H-<sup>13</sup>C). The developed microwave method for the synthesis of hydrazone derivatives of isonicotinic acid complies with the principles of the concept of «Green Chemistry».

*Keywords:* hydrazide of isonicotinic acid, hydrazone, aromatic aldehydes, microwave activation.

### Introduction

According to the World Health Organization (WHO), tuberculosis remains one of the most common and dangerous diseases. Currently, every third inhabitant of the earth is infected with it, i.e. over 2 billion people. Every year, 8 million people fall ill with active tuberculosis, two million die. More than 90 % of the disease is registered in developing countries. At the same time, 75 % of the working-age population is among the patients. Thus, the prevention and treatment of tuberculosis is an important political, economic, social task of any state [1, 2].

Over the past 50 years, research on the synthesis of new anti-TB drugs based on carboxylic acid hydrazides has been carried out in the world. A review of literature data on available anti-tuberculosis drugs shows that the majority of anti-tuberculosis drugs used in medical practice contain a hydrazide fragment in their structure [2–5].

Despite the large number of publications on the synthesis of various hydrazide derivatives, their properties and structure, they are currently promising for further study and improvement [2–6]. In this series of compounds, various derivatives of isonicotinic acid hydrazide (INH), exhibiting a wide spectrum of biological activity, are of particular interest. To date, many different derivatives have been synthesized on the basis of INH with various variations of anti-tuberculosis activity. For example, the tuberculosis drug ftivazide developed in 1951 in the Soviet Union has been widely used in clinical practice to date [6–8]. However, the problem of drug resistance of many pathogenic bacteria and viruses to medicines used for treatment requires constant search and expansion of the arsenal of new highly effective and low-toxic drugs. In recent years, interest in hydrazones has increased again, which is associated with the discovery of high anticancer activity and other types of activities in a number of derivatives of hydrazine compounds [9–11].

Currently, the search strategy for chemical compounds with anti-tuberculosis activity is carried out in several directions. These are chemical modification of known anti-tuberculosis drugs, optimization of

pharmacokinetics by obtaining polymeric forms of anti-tuberculosis drugs, developing new composition of dosage forms and synthesizing new classes of organic compounds with anti-tuberculosis properties [11–13].

For a number of years, the Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan has been carrying out research on the search for new bioactive compounds based on isonicotinic acid hydrazide and optimal methods for their preparation. One-step methods of obtaining known anti-TB drugs, namely 4-pyridinecarboxylic acid hydrazide («isoniazid»), 4-pyridinecarboxylic acid [(4-hydroxy-3-methoxyphenyl)methylene]hydrazide («ftivazide») and other drugs with high yields have been implemented. Syntheses were carried out using microwave activation technology [14]. Microwave (MW) activation of organic reactions is one of the new directions in chemical synthesis [15–18]. Chemical transformations occur with the use of microwave radiation with the participation of solid dielectrics and liquids. The developed methods are consistent with the principles of the concept of «Green Chemistry» [19].

In continuation of the studies [20, 21] we present the results of studying the effect of microwave exposure on the synthesis of certain hydrazone derivatives of isonicotinic acid in the article.

### Experimental

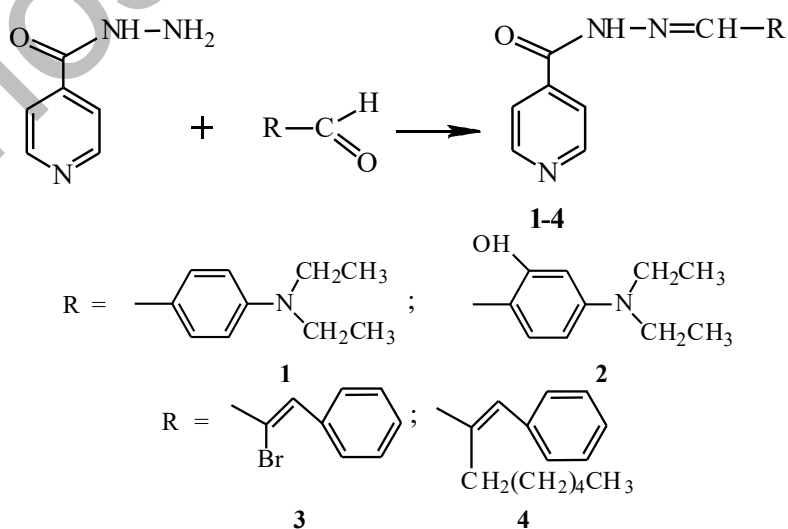
The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds (1–4) were recorded in DMSO- $d_6$  using a JNN-ECA 400 spectrometer (400 and 100 MHz on  $^1\text{H}$  and  $^{13}\text{C}$  nuclei) from Jeol, Japan. The survey was carried out at room temperature using a DMSO solvent. Chemical shifts are measured relative to signals of residual protons or carbon atoms of a deuterated solvent.

Syntheses of the new isonicotinic acid hydrazones under classical conditions were carried out at a 1:1 ratio of initial reactants in an alcohol medium and the reaction time was from 2 to 6 hours with heating (65–75 °C) in a flask with reflux condenser. Similar reactions in the microwave field were carried out in the reactor for microwave synthesis Monowave 300 manufactured by «Anton Paar» with a maximum radiation power of 350 W and a frequency of 2455 MHz.

Synthesis products were isolated and purified by standard, well-known methods. The authenticity of the product is unambiguously proved by comparing the melting point, analyzing the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra with previously synthesized compounds under the conditions of the classical method. Purity was monitored by thin layer chromatography.

### Results and Discussion

In this paper, we studied the possibility of optimizing the synthesis of a number of new hydrazone derivatives of isonicotinic acid under microwave (MW) activation conditions in comparison with the classical method. To this end, we conducted a series of experiments to determine the optimal conditions for the synthesis of compounds (1–4). In order to establish the optimal condition, an alcoholic solution of INH and the corresponding aldehyde was placed in a 1:1 ratio in a glass container. The reaction mixture was irradiated with microwaves of 75, 150 and 350 watts. The conditions of the microwave synthesis reaction were selected by varying the time and radiation power.



Comparative results of the optimal conditions for the synthesis of the studied hydrazones (1–4) at different irradiation powers are shown in Table 1.

Table 1

**Yields of hydrazones (1–4) under conditions of MW activation at different powers (W) and classical heating (CH), the reaction time is 2 hours**

Comp. No.	Compound name	Microwave activation			
		MW radiation power, W	MW time, min	yield, %	
				MW	CH
1	N-(4-(diethylamino) benzylidene)-isonicotinohydrazide	75	70	50	
		150	30	97	85
		350	20	85	
2	N-diethylamino-2-hydroxybenzylidene-isonicotinohydrazide	75	90	65	
		150	60	80	66
		350	30	78	
3	N-(2-bromo-3-phenyl) allylidene)-isonicotinohydrazide	75	60	80	
		150	70	82	70
		350	90	74	
4	N'-(2-benzylidenoctylidene)-isonicotinohydrazide	75	70	85	
		150	40	95	78
		350	60	80	

As follows from the analysis of the obtained data, the duration of the synthesis and the yields of these compounds (1–4) depend on the power and time of the microwave heating. During the interaction of 4-diethylaminobenzaldehyde with INH under microwave irradiation, the maximum yield of N-(4-(diethylamino)benzylidene) isocotinohydrazide 1 (97 %) was found to occur at a power of 150 W and an irradiation time of 30 minutes. Under conditions of classical synthesis, the highest yield of product 1 is 85 % with a reaction time of 160 minutes, i.e. the reaction rate in terms of microwave activation is reduced by 5.3 times.

Similar results were obtained for the remaining reactions. The highest yield of the final product under the conditions of microwave activation with an irradiation power of 150 W was for hydrazone 4 (95 %), which can be explained by the structural features of the reactants. Figure 1 shows the dependence of the influence of the duration of activation time on the hydrazone yield at different microwave activation powers in comparison with the classical method.

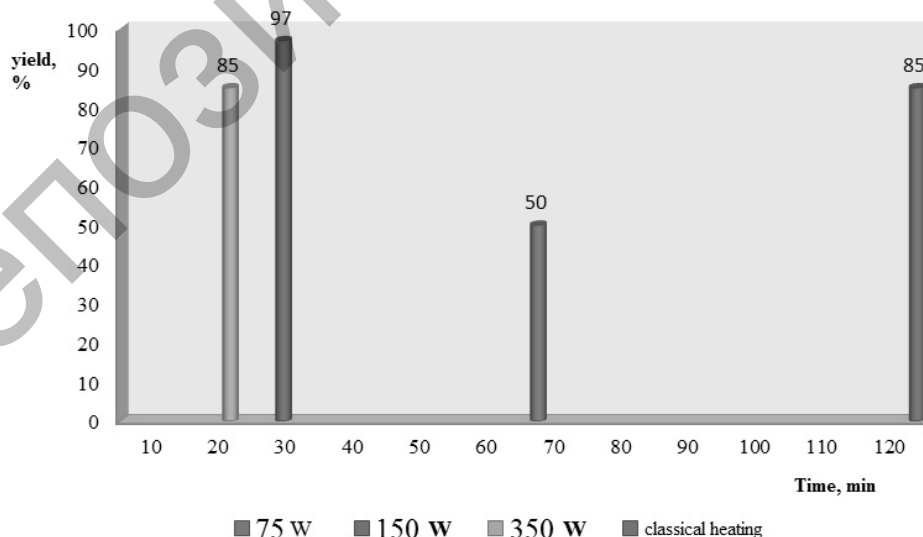


Figure 1. The effect of MW power on the duration of the synthesis and on the yield of N-(4-(diethylamino)benzylidene)isonicotinohydrazide 1

The structure of compounds (1–4) was also confirmed by the methods of two-dimensional NMR spectroscopy COSY ( $^1\text{H}$ - $^1\text{H}$ ) and HMQC ( $^1\text{H}$ - $^{13}\text{C}$ ), which makes it possible to establish spin-spin interactions of a homo- and heteronuclear nature (Fig. 2, 3). The observed correlations in the molecule are presented in the diagrams. In the spectra of  $^1\text{H}$ - $^1\text{H}$  COSY compounds, spin-spin correlations are observed through three bonds of neighboring aliphatic protons in the N-diethyl fragment of  $\text{H}^{20,22}$ - $\text{H}^{19,21}$  (1.03; 3.33 and 3.32; 1.05) of the benzylidene core  $\text{H}^{14,16}$ - $\text{H}^{13,17}$  (6.65; 7.48 and 7.48; 6.66) and the pyridine ring  $\text{H}^{3,5}$ - $\text{H}^{2,6}$  cross-peaks with coordinates at 7.76; 8.72 and 8.71; 7.77 (Fig. 2, 3). The heteronuclear interactions of protons with carbon atoms through one bond were established using  $^1\text{H}$ - $^{13}\text{C}$  HMQC spectroscopy for pairs:  $\text{H}^{20,22}$ - $\text{C}^{20,22}$  (1.03; 12.93),  $\text{H}^{14,16}$ - $\text{C}^{14,16}$  (6.63; 111.53),  $\text{H}^{13,17}$ - $\text{C}^{13,17}$  (7.45, 129.54),  $\text{H}^{3,5}$ - $\text{C}^{3,5}$  (7.76; 121.92) and  $\text{H}^{2,6}$ - $\text{C}^{2,6}$  (8.70; 150.73).

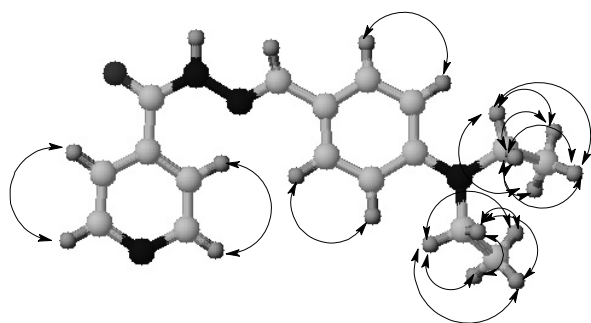


Figure 2. Scheme of correlations of COSY ( $^1\text{H}$ - $^1\text{H}$ ) of compound (1)

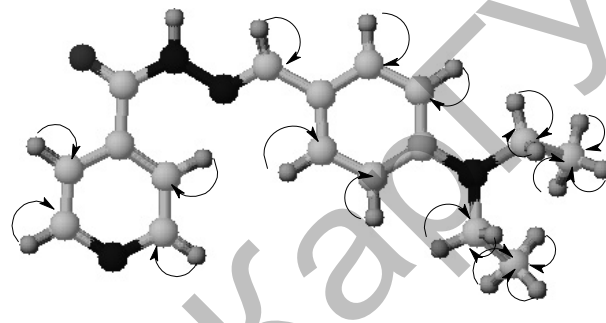


Figure 3. Scheme of correlations of HSCQ ( $^1\text{H}$ - $^{13}\text{C}$ ) of compound (1)

In order to establish the spatial structure of the molecule N-(4-(diethylamino)benzylidene)isonicotinhydrazide 1, its X-ray diffraction study was carried out. For structure 1, X-ray diffraction data, cell parameters and reflection intensities were obtained at 100 K using an Agilent Supernova, Dual Source, Cu at zero diffractometer equipped with an Atlas CCD detector using  $\alpha$  scanning and  $\text{MoK}\alpha$  ( $\alpha = 0.71073 \text{ \AA}$ ) radiation. Images were interpreted and integrated using the CrysAlisPro program [22]. The experimental data were processed by the Olex2 program [23], the structure was decoded by direct methods using the ShelXL program, and refined using ShelXS [24, 25] using the least squares method on  $F^2$ . Non-hydrogen atoms were anisotropically refined and hydrogen atoms in the upper mode and isotropic temperature factors were fixed at 1.2 times  $U$  (eq) of the parent atoms (1.5 times for methyl groups). A general view of the molecule 1 is shown in Figure 4.

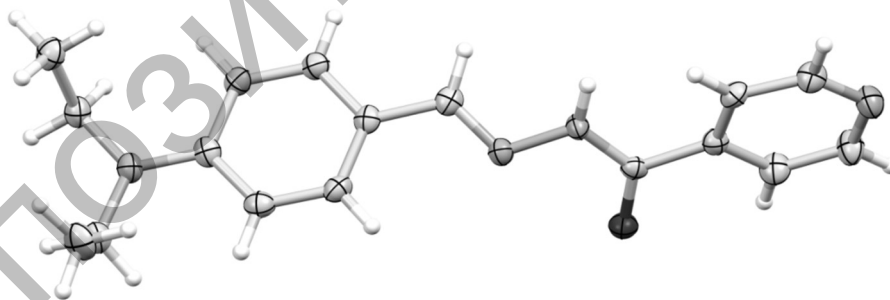


Figure 4. Molecular structure of the compound (1)

From the data obtained it follows that the bond lengths and bond angles in compound (1) are close to normal. The monoclinic crystals, space group  $Ia$  (N 9),  $a = 9.16383$  (17),  $b = 9.45505$  (11),  $c = 18.6806$  (2)  $\text{\AA}$ ,  $\beta = 102.704$  (15) $^\circ$ .  $V = 1578.94$  (4)  $\text{\AA}^3$ ,  $Z = 4$ ,  $T = 100.0$  (1) K,  $(\text{C}_{17}\text{H}_{20}\text{N}_4\text{O})$ ,  $M = 296.37$  g/mol,  $d_{\text{comp}} = 1.247$  g/cm $^3$ ,  $\mu = 0,643$  mm $^{-1}$ . The scan area is  $9.7 \leq 2\theta \leq 150.86$ , the number of reflections measured is 30824 ( $R_{\text{int}} = 0.0569$ ,  $R_{\text{sigma}} = 0.0200$ ), 3013 independent reflections with  $I \geq 2\sigma(I)$ ,  $\text{Goof} = 1.053$  were used in the calculations. The final divergence factors are  $R_1 = 0.0446$ ,  $wR_2 = 0.1175$  (for reflections with  $I \geq 2\sigma(I)$ ),  $R_1 = 0.0455$ ,  $wR_2 = 0.1196$  (for all reflections). Peaks of residual density:  $\Delta\rho = 0.21$  and  $-0.31$  e/ $\text{\AA}^3$ .

Tables 2 and 3 show the physico-chemical and spectral NMR  $^1\text{H}$  and  $^{13}\text{C}$  data of the synthesized substances (1–4).

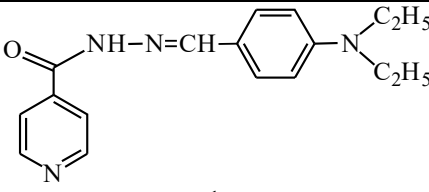
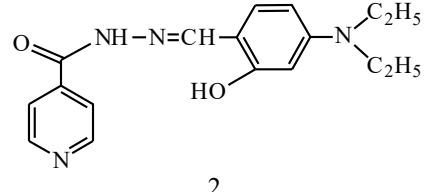
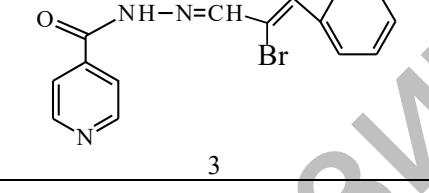
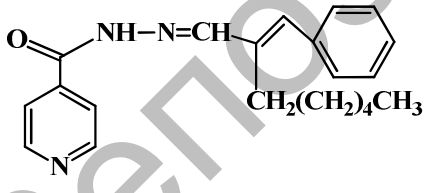
Table 2

## Physical and chemical data of the synthesized hydrazones (1–4)

Comp. No.	Compound name	Gross formula	Mol. weight	Yield, %	T. mel., °C
1	N-(4-(diethylamino) ben-zylidene) isonicotino-hydrazone	C <sub>17</sub> H <sub>20</sub> N <sub>4</sub> O	296.37	83.7	192–193
2	N-diethylamino-2-hydroxybenzylidene-isonicotinohydrazone	C <sub>17</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub>	312.37	82	224–225
3	N-(2-bromo-3-phenyl) allylidene) isonicotino-hydrazone	C <sub>15</sub> H <sub>12</sub> BrN <sub>3</sub> O	330.18	63.04	211–213
4	N'-(2-benzylidenoctylidene) isonicotinohydra-zide	C <sub>21</sub> H <sub>25</sub> N <sub>3</sub> O	335.44	98	110–112

Table 3

NMR <sup>1</sup>H and <sup>13</sup>C data of the synthesized compounds (1–4)

Compound	<sup>1</sup> H and <sup>13</sup> C NMR (ppm)
 <p>1</p>	<p>NMR <sup>1</sup>H (DMSO-d<sub>6</sub>), δ, m.p.: 1.06 t (6H, 2CH<sub>3</sub>), 3.31–3.35 m (4H, 2CH<sub>2</sub>), 6.66 d (2H, CH<sup>14,16</sup><sub>Ar</sub>, <sup>3</sup>J 8.7), 7.48 d (2H, CH<sup>13,17</sup><sub>Ar</sub>, <sup>3</sup>J 8.7), 7.77 d (2H, CH<sup>3,5</sup>, <sup>3</sup>J 4.6), 8.25 s (1H, N=CH), 8.72 d (2H, CH<sup>2,6</sup>, <sup>3</sup>J 4.6), 11.72 s (1H, NH).</p> <p>NMR <sup>13</sup>C (DMSO-d<sub>6</sub>), δ, m.p.: 12.96 (2CH<sub>3</sub>), 44.26 (2CH<sub>2</sub>), 111.56 (CH<sup>14,16</sup><sub>Ar</sub>), 120.76 (C<sup>12</sup><sub>Ar</sub>), 122.00 (CH<sup>3,5</sup>), 129.56 (CH<sup>13,17</sup><sub>Ar</sub>), 141.37 (C<sub>4</sub>, N=CH), 149.57 (CH<sup>2,6</sup>), 150.41 (C<sup>15</sup><sub>Ar</sub>), 161.48 (C=O)</p>
 <p>2</p>	<p>NMR <sup>1</sup>H (DMSO-d<sub>6</sub>), δ, m.p. (J, Hz): 1.05 t (6H, 2CH<sub>3</sub>, <sup>3</sup>J 6.9), 3.29–3.35 m (4H, 2CH<sub>2</sub>), 6.08 s (1H, CH<sup>16</sup>), 6.23 d (1H, CH<sup>14</sup>, <sup>3</sup>J 8.2), 7.19 d (1H, CH<sup>13</sup>, <sup>3</sup>J 8.7), 7.78 d (2H, CH<sup>3,5</sup>, <sup>3</sup>J 2.7), 8.40 s (1H, N=CH), 8.73 d (2H, CH<sup>2,6</sup>, <sup>3</sup>J 2.7), 11.26 s (OH), 11.99 s (NH).</p> <p>NMR <sup>13</sup>C (DMCO-d<sub>6</sub>), δ, m.p.: 13.04 (2CH<sub>3</sub>), 44.34 (2CH<sub>2</sub>), 97.89 (CH<sup>16</sup>), 104.27 (CH<sup>14</sup>), 106.77 (C<sup>12</sup>), 121.94 (CH<sup>3,5</sup>), 132.15 (CH<sup>13</sup>), 140.77 (C<sub>4</sub>), 150.84 (CH<sup>2,6</sup>), 151.32 (N=CH), 160.32 (C<sup>17</sup>-OH), 161.10 (C=O).</p>
 <p>3</p>	<p>NMR <sup>1</sup>H (DMSO-d<sub>6</sub>), δ, m.p. (J, Hz): 7.38–7.43 m (3H, CH<sup>15,17,19</sup>), 7.67 s (1H, CH<sup>13</sup>), 7.77 d (2H, CH<sup>3,5</sup>, <sup>3</sup>J 1.8), 7.84 d (2H, CH<sup>16,18</sup>, <sup>3</sup>J 6.4), 8.34 s (1H, N=CH), 8.75 d (2H, CH<sup>2,6</sup>), 12.19 s (1H, NH).</p> <p>NMR <sup>13</sup>C (DMSO-d<sub>6</sub>), δ, m.p.: 119.50 (C<sup>12</sup>), 122.07 (CH<sup>3,5</sup>), 128.99 (CH<sup>15,19</sup>), 130.34 (CH<sup>16,18</sup>), 135.04 (C<sup>14</sup>), 139.37 (CH<sup>12</sup>), 140.85 (C<sub>4</sub>), 149.53 (N=CH), 150.90 (CH<sup>2,6</sup>), 162.27 (C=O).</p>
 <p>4</p>	<p>NMR <sup>1</sup>H (DMSO-d<sub>6</sub>), δ, m.p. (J, Hz): 0.79 t (3H, CH<sub>3</sub><sup>25</sup>), 1.05–1.09 m (2H, CH<sub>2</sub><sup>23</sup>), 1.21–1.29 m (4H, CH<sub>2</sub><sup>22</sup>, CH<sub>2</sub><sup>24</sup>), 1.51 m (2H, CH<sub>2</sub><sup>21</sup>), 2.56 s (2H, CH<sub>2</sub><sup>20</sup>), 6.79 d (1H, CH<sup>13</sup>), 7.28–7.39 m (4H, CH<sup>16,18</sup>, CH<sup>15,19</sup>), 7.55 d (1H, CH<sup>11</sup>), 7.76 d (2H, CH<sup>3,5</sup>), 8.13 s (1H, CH<sup>17</sup>), 8.73 d (2H, CH<sup>2,6</sup>), 11.86 s (1H, NH).</p> <p>NMR <sup>13</sup>C (DMSO-d<sub>6</sub>), δ, m.p.: 14.46 (CH<sub>3</sub><sup>25</sup>), 22.59 (CH<sub>2</sub><sup>24</sup>), 26.22 (CH<sub>2</sub><sup>20</sup>), 28.53 (CH<sub>2</sub><sup>21</sup>), 29.45 (CH<sub>2</sub><sup>22</sup>), 31.30 (CH<sub>2</sub><sup>23</sup>), 122.04 (CH<sup>3,5</sup>), 128.43 (CH<sup>16,18</sup>), 128.96 (CH<sup>15,19</sup>), 136.58 (C<sup>14</sup>), 137.15 (CH<sup>13</sup>), 137.99 (CH<sup>12</sup>), 141.18 (C<sub>4</sub>), 149.83 (N=CH), 150.82 (CH<sup>2,6</sup>), 154.22 (CH<sup>17</sup>), 161.93 (C=O).</p>

## Conclusions

Thus, targeted synthesis of new isonicotinic acid hydrazones on the basis of isonicotinic acid hydrazone, under conditions of convection heating and microwave irradiation was carried out. As a result of a comparative analysis of the data obtained, it was determined that the use of microwave irradiation contributes to an increase in the yield of the product and a decrease in reaction time by a factor of (3–4) than according to traditional technology.

*This work was supported by the Science Committee of the Ministry of Education of the Republic of Kazakhstan (Grant N AP05131054).*

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### Микротолқынды сәулелендіру жағдайында изоникотин қышқылының гидразонды туындылары синтезі

Мақалада изоникотин қышқылы гидразидинің спирттік ортада микротолқынды активтендіру жағдайында ароматты альдегидтердің түрлі туындыларымен өзара әрекеттесуінің реакциясын зерттеу нәтижелері қарастырылған. Гидразондардың шығымының классикалық әдіспен салыстырғанда микротолқынды сәулеленудің түрлі қуаттары кезінде белсендіру уақытының ұзақтығына байланысты зерттеу нәтижелері келтірілген. Синтездің жүру жағдайына және мақсатты өнімдердің шығымына әсер ететін негізгі факторлары ол микротолқынды белсендірудің қуаты мен уақыты, сондай-ақ реакцияға түсетін заттардың құрылымдық ерекшеліктері болып табылатыны анықталды. Барлық зерттелген реакциялар үшін мақсатты өнімді алудың оңтайлы шарттары көрсетілген. Изоникотин қышқылының жаңа гидразондары

синтезінен алынған нәтижелерін салыстырмалы талдау нәтижесінде микротолқынды сәулеленуді пайдалану өнімінің шығымының артуына және реакция уақытының дәстүрлі технологияға қарағанда 3–4 есе төмендеуіне ықпал ететіні анықталды. Әрбір өнімнің түпнұсқалығы балқу температурасын салыстырумен, сондай-ақ классикалық синтез әдістерімен алынған изоникотин қышқылының бұрын синтезделген гидразонды туындыларының физика-химиялық сипаттамаларын талдаумен бірмәнді дәлелденген. Барлық синтезделген қосылыстардың құрылысы ЯМР  $^1\text{H}$ - және  $^{13}\text{C}$ -спектроскопия әдістерімен, сондай-ақ COSY ( $^1\text{H}$ - $^1\text{H}$ ) және НМҚС ( $^1\text{H}$ - $^{13}\text{C}$ ) екіөлшемді спектрлерінің деректерімен зерттелген. Рентгенқұрылымдық талдау мәліметтерімен N-(4-(диэтиламино)бензилден)изоникотиногидразидтің кристалдық құрылымының негізгі параметрлері белгіленген. Изоникотин қышқылының гидразон туындылары синтезінің әзірленген микротолқынды әдісі «жасыл химия» тұжырымдамасының қағидаттарына сәйкес келеді.

*Кілт сөздер:* изоникотин қышқылының гидразиді, гидразон, ароматты алдегидтер, микротолқынды сәулелендіру.

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### Синтез гидразоновых производных изоникотиновой кислоты в условиях микроволновой активации

В статье рассмотрены результаты изучения реакции взаимодействия гидразида изоникотиновой кислоты с различными производными ароматических альдегидов в условиях микроволновой активации в спиртовой среде. Приведены результаты изучения зависимостей выхода гидразонов от продолжительности времени активации при различных мощностях микроволнового облучения в сравнении с классическим методом. Установлено, что основными факторами, влияющими на характер протекания синтеза и выходы целевых продуктов, являются мощность и время микроволновой активации, а также структурные особенности реагирующих веществ. Для всех изученных реакций показаны оптимальные условия получения целевого продукта. В результате сравнительного анализа полученных результатов синтеза новых гидразонов изоникотиновой кислоты было определено, что использование микроволнового облучения способствует увеличению выхода продукта и снижению времени реакции в 3–4 раза, чем по традиционной технологии. Подлинность каждого продукта однозначно доказана сопоставлением температуры плавления, а также анализом физико-химических характеристик с ранее синтезированными гидразоновыми производными изоникотиновой кислоты, полученных методами классического синтеза. Строение всех синтезированных соединений исследовано методами ЯМР  $^1\text{H}$ - и  $^{13}\text{C}$ -спектроскопии, а также данными двумерных спектров COSY ( $^1\text{H}$ - $^1\text{H}$ ) и НМҚС ( $^1\text{H}$ - $^{13}\text{C}$ ). Данными рентгеноструктурного анализа установлены основные параметры кристаллической структуры N-(4-(диэтиламино)бензилден)изоникотиногидразида. Разработанный микроволновой метод синтеза гидразоновых производных изоникотиновой кислоты соответствует принципам концепции «зеленая химия».

*Ключевые слова:* гидразид изоникотиновой кислоты, гидразон, ароматические альдегиды, микроволновая активация.

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