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DEVELOPMENT OF QUALITY CONTROL METHODS OF PROMISING ANTICONVULSANT

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Попередніми дослідженнями вчених НФАУ доведена перспективність пошуку потенційних антиконвульсантів в ряду похідних 1,3,4-тіадіазолу[1-3]. На кафедрі медичної хімії НФаУ синтезована сполука N-(5-етил-[1,3,4]-тіадіазол-2-іл)-2-нітробензамід, яка в умовах експерименту показала високу протисудомну активність на коразоловій моделі судом у порівнянні з класичним антиконвульсантом – «Депакіном». Сполука запатентована та запропонована для подальших доклінічних досліджень. Одним з найважливіших етапів впровадження нового лікарського засобу або субстанції в медичну практику є розробка методик контролю якості.

Мета. *Метою даної роботи була розробка методик ідентифікації, визначення домішок та кількісного визначення N-(5-етил-[1,3,4]-тіадіазол-2-іл)-2-нітробензаміду з метою подальшого застосування в стандартизації субстанції.*

Методи. *Хроматографічно чистий зразок N-(5-етил-[1,3,4]-тіадіазол-2-іл)-2-нітробензаміду, методи ІЧ-, УФ- та ^{1}Н ЯМР спектроскопії.*

Результати. *Вивчено фізико-хімічні властивості і спектральні характеристики N-(5-етил-[1,3,4]-тіадіазол-2-іл)-2-нітробензаміду, запропоновано хімічні методи ідентифікації. Підібрано оптимальні умови визначення супутніх домішок методом тонкошарової хроматографії з використанням методу внутрішньої нормалізації. Аналіз N- (5-етил-[1,3,4] -тіадіазол-2-іл) -2-нітробензаміда проводили методом абсорбційної спектрофотометрії в етанольному розчині при довжині хвилі 282 нм з показником поглинання 631. Для застосування методу були вивчені такі валідаційні характеристики, як стійкість, лінійність, коректність, стабільність аналітичних рішень, точність, збіжність, відтворюваність, розрахунок невизначеності підготовки зразків.*

Висновки. *Розроблено методи ідентифікації N- (5-етіл- [1,3,4] -тіадіазол-2-іл) -2-нітробензаміду з використанням хімічних реакцій і спектральних методів аналізу - ІЧ і УФ та ^{1}Н ЯМР -спектроскопії. Для визначення супутніх домішок в субстанції рекомендований метод ТШХ. Визначено регламентовані специфічні і неспецифічні домішки. Розроблено методику кількісного визначення субстанції методом абсорбційної спектрофотометрії в ультрафіолетовій ділянці методом питомого показника поглинання.*

Ключові слова: *фармацевтичний аналіз, ідентифікація, кількісне визначення, домішки, спектроскопія, тонкошарова хроматографія антиконвульсант.*

1. Introduction

Derivatives of 1,3,4-thiadizole, which contain various substituents of the aliphatic, aromatic and heterocyclic series at C2 and C5 atoms of the 1,3,4-thiadiazole cycle are a promising class of biologically active substances, as evidenced by extensive scientific work both domestic and foreign scholars.

Derivatives of 1,3,4-thiadiazole have a broad spectrum of biological activity, including antitumor [1, 2], antimicrobial [3, 4], antioxidant [5, 6], anti-inflammatory [7, 8], antidepressant and tranquilizing [9, 10] and antifungal activity [11, 12].

According to the results of pharmacological testing substance N- (5-ethyl-[1,3,4]-thiadiazol-2-yl)-2-nitrobenzamide showed pronounced anticonvulsant activity and was patented and recommended for further in-depth studies. Anticonvulsant activity of this substance exceeds the activity of the drug reference, since unlike Depakin, it provides a 100% protective effect at a significantly lower dose. Depakin prolonged the latent period of the convulsions, reduced their severity and the percentage of lethality at a dose of 200 mg / kg. N- (5-Ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide is able to protect animals from death at a lower dose (50 mg / kg). It protected the animals from the convulsions, which was manifested in the elongation of the latent period by the convulsions (2.3 times, $p < 0.05$) and the decrease in their severity compared with the control of an average of 2.3 times, as well as in reducing mortality (from 100 % in control to 20%, $p < 0.05$) in the dose of 50 mg/kg. In addition, the "compound leader" reduced the duration of seizure attack by 2 times compared with control and led to a further increase in the time of death of mice (1.5 times) [13].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Development of modern, unified, effective, and simple in performance methods of standardization of substances is one of the main tasks in pharmaceutical science. Current understanding of approaches to quality assurance is based on the concept that includes quality assurance of drugs from the stage of pharmaceutical development and research, through proper production, quality control, storage, sale, and provision of information to doctors and patients [14].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

Despite significant advances in the development of methods for the synthesis of 1,3,4-thiadiazol derivatives, the study of their chemical and pharmacological

properties, their analysis methods are insufficient and are of interest for further study. [15, 16]. There are number of 1,3,4 -thiadiazol derivatives original structure, which can be used as perspective anticonvulsants was obtained in National University of Pharmacy [17, 18]. Further in-depth study of these substances with anticonvulsive action requires a detailed study of the physical and chemical properties, those will give the opportunity not only to standardize such substances, but also explore the promising behavior of xenobiotics in humans, its pharmacodynamics and pharmacokinetics, which will develop well-founded recommendations for application. In addition, such studies are necessary for the development of pharmaceutical dosage form and technology of new anticonvulsant.

4. The field of research considering the general problem, which is described in the article

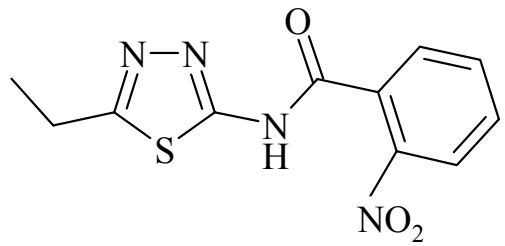
This work was carried out according to the research plan of the National University of Pharmacy for problem Ministry Health of Ukraine "Development and validation of methods for quality control of drugs and pharmaceutical industrial production" (state registration 0108U010944).

5. Formulating the goals (tasks) of the article

The aim of this work was to develop methods for the identification and quantitative determination of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide for their further application in the development of quality control techniques.

6. Presentation of the main research material (methods and objects) with the justification of the results

For preparation of the implementation of a substance, we have developed the methods of identification, tests for purity and quantitative analysis of the perspective anticonvulsant N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide.



N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide

Standardization was performed according to the existing requirements for the development of modern methods of analysis of pharmaceutical substances based on Pharmacopoeia quality [19]. The standard sample of the compound was used in standardization (the impurity content is 0.5%). While performing an identification of the substance, the standard sample of N- (5-ethyl- [1, 3, 4] -thiadiazol-2-yl) -2-nitrobenzamide was considered as an example of this substance repeatedly subjected to crystallization. Purity and identity of N- (5-ethyl- [1, 3, 4] -thiadiazol-2-yl) -2-nitrobenzamide have been confirmed by a set of instrumental methods of analysis (NMR ^{1}H, IR and UV spectroscopy, TLC). The volumetric glassware of class A, reagents that correspond to the requirements of SPHU, "AXIS" analytical balances, «Thermo Fisher Scientific EVOLUTION 60S» spectrophotometer and «Nicolet 380 FT-IR Spectrometer by Thermo Fisher Scientific», chromatographic plates with a layer of silica gel GF_{254} were used in this work.

The physical-chemical properties and spectral characteristics of N- (5-ethyl- [1, 3, 4] -thiadiazol-2-yl) -2-nitrobenzamide were studied. By its physical properties N- (5-ethyl- [1, 3, 4] -thiadiazol-2-yl) -2-nitrobenzamide is a white crystalline powder, odourless, soluble in ethanol and insoluble in water. To determine solubility the standard pharmacopoeial methods have been used [20].

The State Pharmacopoeia of Ukraine recommends to use the method of infrared spectroscopy for identification of organic compounds. The infrared spectrum of the substance was recorded on «Smart Perfomer» device in ZnSe crystal. Therefore, substances by IR spectroscopy are identified either by the standard method or by calculating positions of the main functional groups. Analysing the IR spectrum of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide (Fig. 1) a number of characteristic bands, which appear due to the presence of certain features of the chemical structure can be mentioned.

Based on the structure of the substance, bands characteristic of aromatic rings (benzene and 1, 3,4-thiadiazole), a carbonyl group (amide-1), a substituted amino group, and an ethyl radical should be observed in the IR spectrum of absorption.

It is established (Fig. 1) that the absorption bands of valence vibrations, found on the site 687-685 cm^{-1}, are characteristic of the C-S-C groups of the 1,3,4- tiadiazole ring; in the range 1425-1487 cm^{-1}, medium intensity bands are observed which correspond to deformation vibrations (δas CH_3) of the group of the ethyl radical; in the range 1523-1548 cm^{-1}, there are medium-intensity bands that are characterized by carbon-carbon bonds of the aromatic benzene ring; a band of strong intensity in the region 1682 cm-1 corresponds to a valence vibrations of carbonyl (v amide I); at 3151 cm^{-1} there is a band of substituted amino group (δ NH) [21]. Thus, the results of the conducted research indicate that the structure of the resulting compound can be confirmed by infrared spectroscopy. The presence of aromatic properties of the 1,3,4-thiadiazole cycle and the benzene ring allows the compound to be identified by absorption spectrophotometry in the ultraviolet and visible regions of the spectrum [22].

UV spectrophotometry is used at all stages of the pharmaceutical analysis (for identification, tests for purity and quantitative determination), and is one of the main general methods of analysis of substances and medicinal forms [22]. Since the claimed compound is practically insoluble in water, 95% ethyl alcohol was chosen as a solvent.

The test substance is amphoteric. Acidic character is due to the presence of the amide group, and heterocyclic atoms of Nitrogen give the molecule the basic properties. In view of this, absorption was studied in three solvents: 95% ethyl alcohol, 0.1 M solution of hydrochloric acid and 0.1 M solution of sodium hydroxide at wavelengths from 220 nm to 350 nm.

Established that, the UV absorption spectrum of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide in ethanol has the maximum at wavelengths of 264 nm (Fig. 2).

The UV spectrum of a 0.002% solution of a substance in a 0.1 M hydrochloric acid solution is characterized by a more intense and specific absorption maximum at 261 nm (Fig. 3).

In the study of the nature of the UV-spectrum of 0.002% of the substance solution in 0.1 M sodium hydroxide solution, the presence of two absorption maxima at 222 nm and 282 nm was established (Fig. 4).

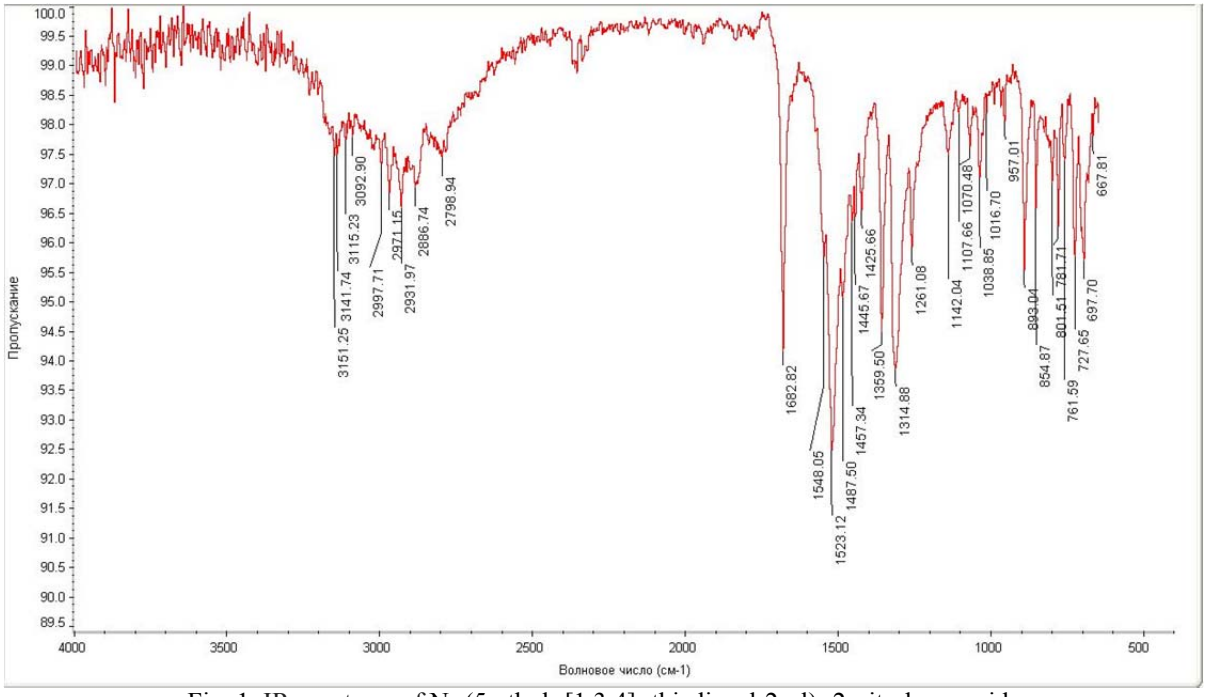


Fig. 1. IR spectrum of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide

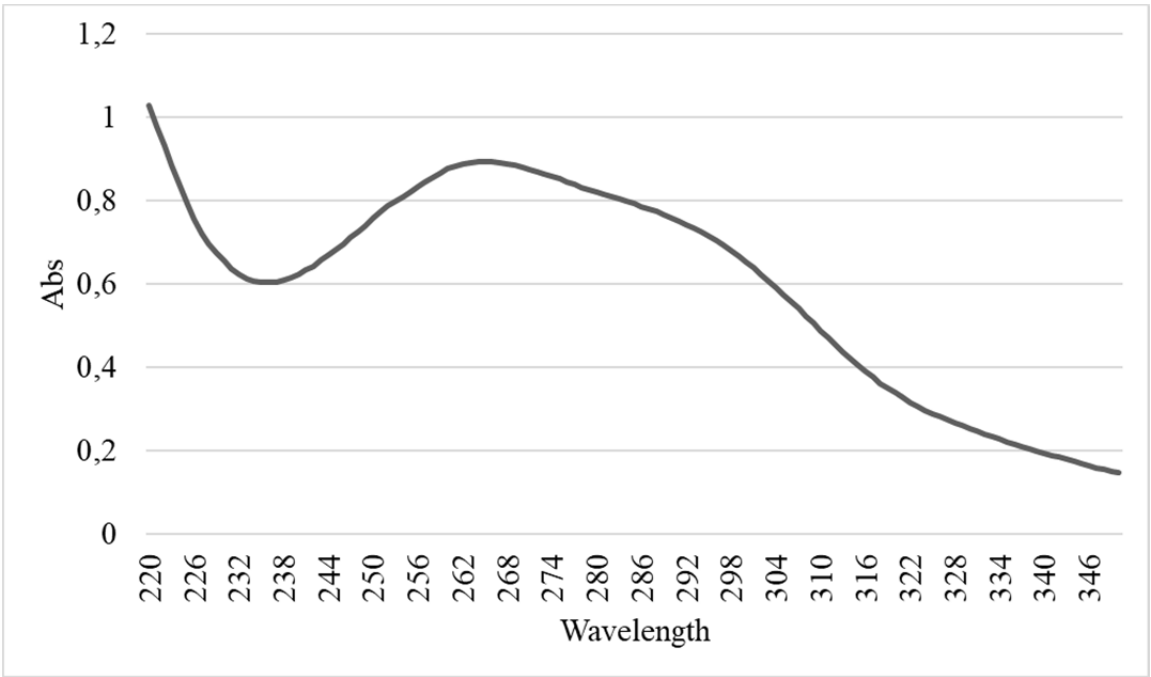


Fig. 2. The UV absorption spectrum of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide in ethanol

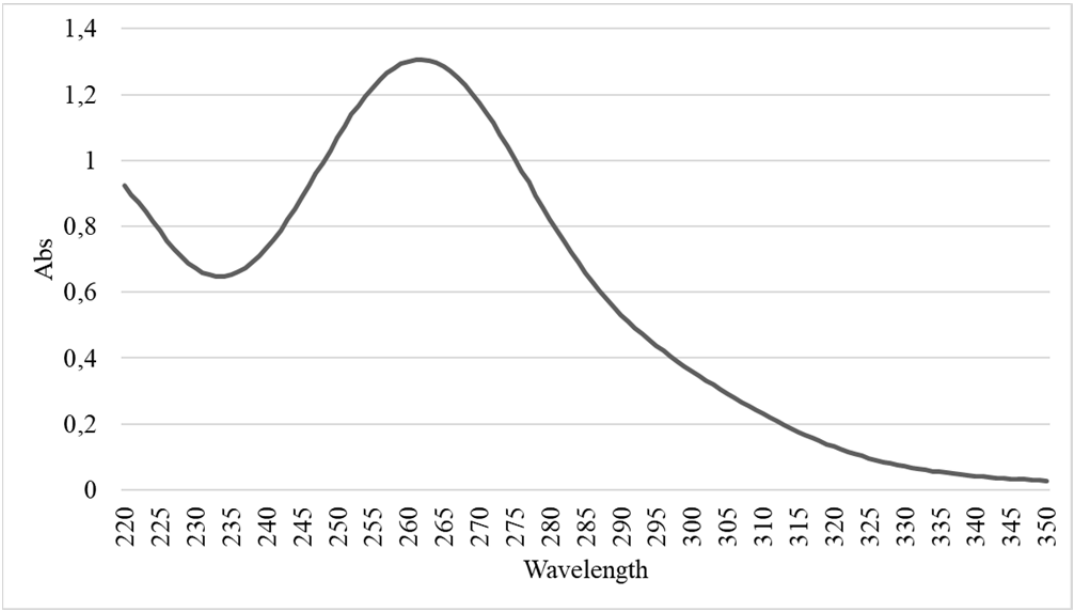


Fig. 3. The UV absorption spectrum of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide in a 0.1 M hydrochloric acid solution

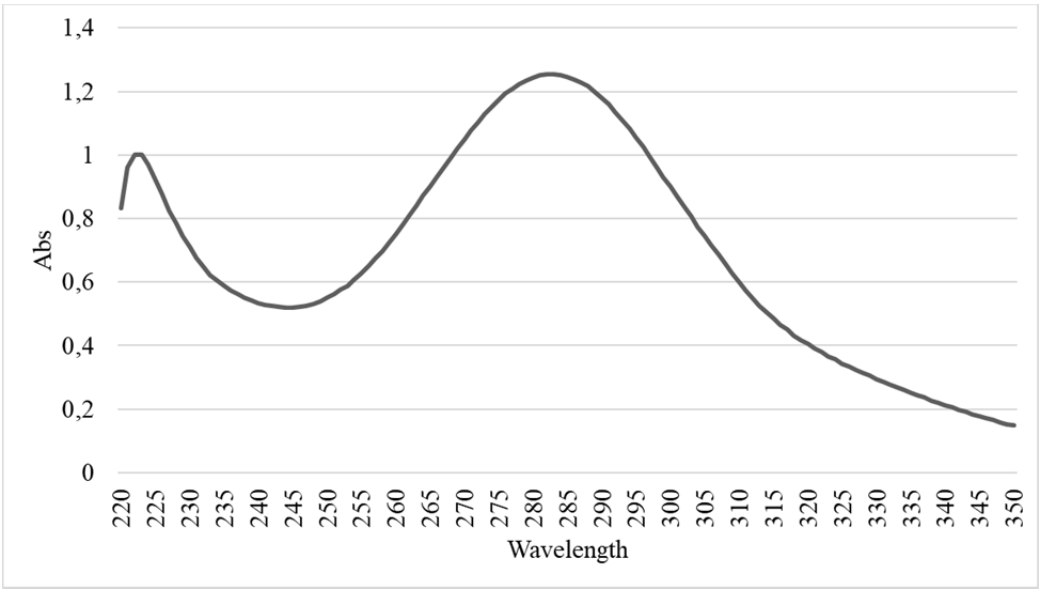


Fig. 4. The UV absorption spectrum of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide in 0.1 M of sodium hydroxide solution

The maximum absorption of the test substance in a 0.1 M solution of sodium hydroxide at a wavelength of 282 nm is more specific, therefore it was advisable to determine the subordination of alkaline solutions of matter to the main law of light absorption and to calculate the value of the specific absorption index, followed by the use of the methodology for identification and quantitative determination of the compound. It has been experimentally proved that the subordination of solutions of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide in a 0.1 M sodium hydroxide solution of the Bouguer-Lambert-Berry law takes place within the concentration of a substance from 0.0002 % to 0.0014%. The values of specific absorption rates obtained during the experiment were calculated and the results of calculations were subsequently subjected to statistical processing. The specific absorption rate at the maximum at 282 nm proposed for introduction in the project of quality control methods should be from 617 to 641.

Spectrum ^{1}H NMR of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide acid contains all signals of hydrogen containing groups which are characteristic for this substance, so the ^{1}H NMR data can be recommended for introduction in the project of quality control methods [12]. Protons of amide group appear as a singlet signal at 13,25 ppm (c, NH, 1H) and aromatic proton signals - as a multiplet at 7,87 - 8.22 ppm (м, 4H). Protons of methyl group in position 5 of 1,3,4-thiadiazol cycle are observed in the ^{1}H NMR spectrum as a triplet at 1.34 ppm (т, 3H, CH_3). Protons of methylen group – as a guadruple at 3.05 ppm (к, 2H, CH_2).

More convincing for identification of organic compounds is a combination of physical, physicochemical and chemical methods, which are based on the prop-

erties of functional groups. Chemical identification methods were proposed.

Considering N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide structure, it was logical to develop techniques for identification of compound due to the presence of anilide residue and 1,3,4-thiadiazol ring.To confirm the tertiary nitrogen atoms in the structure of the substance studied the reactions with alkaloid "precipitative" reagents. To provide the general monograph of SPHU, we consider it appropriate to use potassium bismuth iodide as a reagent that is universal to determine the tertiary Nitrogen. Test with potassium bismuth iodide can be recommended for introduction in the project methods of quality control.

Considering the fact that as starting material 2-amine-5-ethyl-1,3,4-thiadiazol in the synthesis of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide was used we tried to reproduce the reaction on aromatic amino group after hydrolysis. To confirm the presence of anilide residue in the molecule of test substance, the substance underwent acid hydrolysis and 2-amine-5-ethyl-1,3,4-thiadiazol, which was formed in the reaction have been identified by reaction of diazotization with followed azo coupling (Fig. 5).

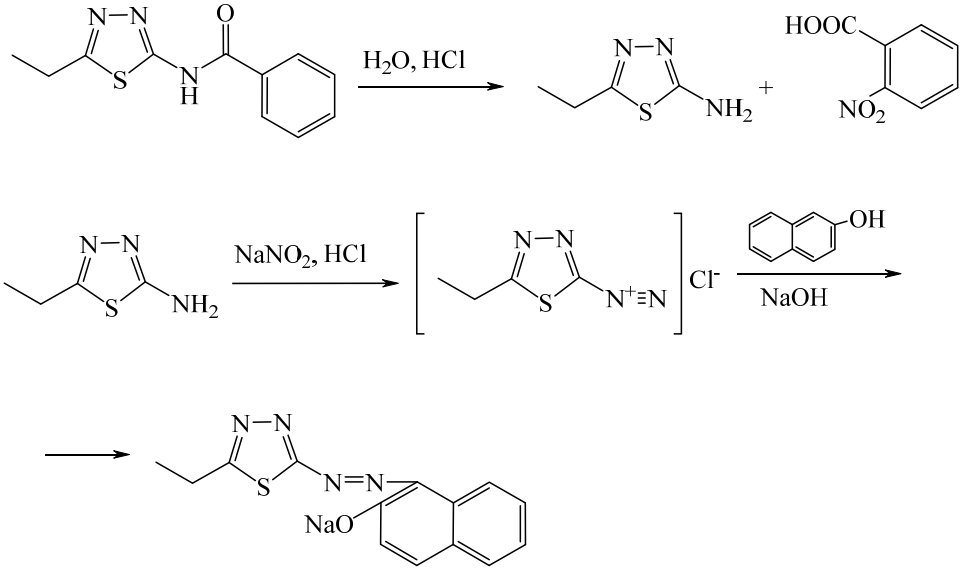


Fig. 5. Reaction of diazotization with followed azo coupling after hydrolysis of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide

The red color formed as a result of the reaction confirms that the amino group at position 2 of 1,3,4-tiadiazole is aromatic. This test can be recommended for introduction in the project methods of quality control.

The optimal conditions for the determination of potential impurities that may be present in the test compound by the method of thin-layer chromatography are selected, using the method of internal normalization. As a stationary phase, plates were offered on an aluminum basis with a layer of silica gel GF254. A mixture of solvents, toluene-acetone-ethanol-25% solution of ammonia in a ratio of 45: 45: 7: 3 was proposed as a mobile phase. The detection is proposed to be carried out in UV rays with a wavelength of 254 nm, followed by the detection of potassium iodide solution.

The assay for N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide was carried out by absorption spectrophotometry in the alcohol solution at the wavelength of 282 nm with the absorption index 631. For application of methods such validation characteristics as robustness, linearity, correctness, stability of analytical solutions, precision, convergence, reproducibility, calculation of uncertainty of samples preparation were studied [19].

The optical density of the test solution is measured at a wavelength of 282 nm relative to the compensation solution 0.1 M solution sodium hydroxide.

Calculate the content of $\mathbf{C_{11}H_{10}N_4O_3S}$ in the substance by the formula:

$$x,\% = \frac{A \cdot V^1_{m.f.} \cdot V^2_{m.f.}}{A^{1\%}_{1cn} \cdot m_{n\cdot} \cdot V_{aliquots}}$$

where – optical density of the test solution;

$A^{1\%}_{1cn}$ – the specific absorption rate, which at a wavelength of 282 nm is 631.

$V^1_{m.f.}$ – volume of the first measuring flask, ml;

$V^2_{m.f.}$ – volume of the second measuring flask, ml;

$m_{n\cdot}$ – weight of test substance for quantit *A* ative determination, g;

$V_{aliquots}$ – volume of aliquots, ml.

To confirm the correctness of the method for quantitative determination of the substance of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide, a forecast of complete uncertainty of sample preparation in accordance with the requirements of the STU was performed. The obtained data are presented in Table 1.

Table 1

Estimation of the uncertainty of sample preparation for the quantitative determination of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide

Operation of sample preparation	Parameter	Uncertainty, %
Weighing on the analytical scales of the substance N-(5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide	m_0	0.2 mg/100 mg * 100% = 0.2%
Bringing to the volume of the volumetric flask, ml	100	0.12 %
Taking aliquots ml	1	0.74%
Bringing to the volume of the volumetric flask, ml	100	0.12%
Δ_{As}		0.79%

$$\Delta_{SP} = \sqrt{\sum_i \Delta_{V,i}^2} = \sqrt{0.1^2 + 0.12^2 + 0.74^2 + 0.12^2} =$$
$$= \sqrt{0,6164} = 0.79\ \%.$$

Thus, the predicted uncertainty of sample preparation of the results of the analysis for the method of quantitative determination exceeds the critical value of 0.32%, so for the use of the method in other laboratories it is necessary to calculate the complete uncertainty of the results of the analysis:

$\Delta SP_{max} = \Delta As_{max} * 0.32 = 0.32;$

$\Delta As_{max} = 1\ \%;$

$$\Delta As = \sqrt{\Delta SP^2 + \Delta FAO^2};$$

$$\Delta FAO = 1.65 * \sqrt{\frac{S_x^2}{3}} = 1.65 * \sqrt{\frac{0.52^2}{3}} = 0.50;$$

$$\Delta As = \sqrt{0.79^2 + 0.50^2} = \sqrt{0.6241 + 0.25} =$$
$$= \sqrt{0.8741} = 0.94;$$

The total uncertainty of the results of the analysis is 0.94, which is ≤ ΔAsmax (1 %).

Robustness was studied by observing the stability of solutions in time and the effect of pH (Table 2, 3).

Table 2

Study of the stability of the analytical solution

Solution	Optical density through, min.					Medium	RSDt, %	Δt, %	max σ, %
	0	15	30	45	60				
Test Solution	0.630	0.633	0.633	0.633	0.632	0.6322	0.206	0.4397	1.54
	0.630	0.633	0.633	0.633	0.632				
	0.630	0.633	0.633	0.633	0.632				

The validation characteristics (linearity, correctness, precision) are studied, indicating the correctness of the methodology, the complete uncertainty of sample preparation does not exceed the critical value ΔSP=0.79%≤0.32%. The linearity parameters correspond to the requirements of the SFU in the range of concentrations from 80% to 120% (a=0.3103≤1.35, r=0.9998≥0.9993), the results of the correctness and convergence of the method of quantitative determination do not exceed the criteria of the acceptability of the method.

Linearity, accuracy, precision is investigated within the range of application of the analytical technique. To do this, solutions were prepared using the above method, in which the concentration of the test solution was evenly changed over the entire range of methods, in percentages: 80, 85, 90, 95, 100, 105, 110, 115, 120 % of the nominal content [19]. Based on the actual attitude, calculate the concentration of solutions. The obtained data are presented in Table 3.

The resulting linear regression equation has the form: y = 0.9999x + 0.1393, and the value of the correlation coefficient is r = 0.9999, which allows us to confirm the suitability of the method for the quantitative determination of N- (5-ethyl- [1,3,4] thiadiazol- 2-yl) -2-nitrobenzamide in the concentration range under study (Fig. 6).

The method of least squares calculated the parameters of linear dependence: the free term a, the residual standard deviation S0, the correlation coefficient r (Table 4).

Thus, the obtained results indicate that the linearity requirements are met.

According to the found / introduced data, obtained in the study of linearity, we calculated the following validation characteristics, such as precision and accuracy (Table 5).

Table 3

The results of the definition of "introduced" and "found" solution

Number of solution	1	2	3	4	5	6	7	8	9
introduced,%	80.56	85.59	90.63	95.66	100.50	105.73	110.77	115.80	120.84
found, %	80.67	85.09	90.15	95.36	99.94	105.77	110.36	115.57	120.14

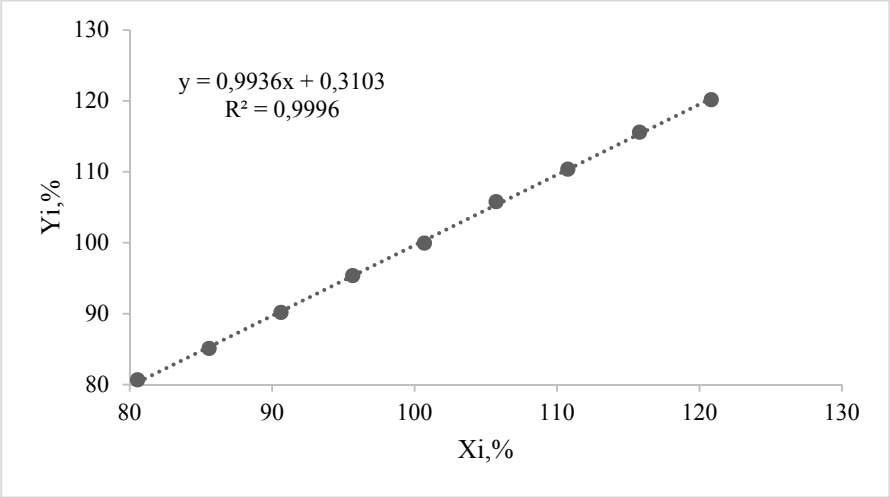


Fig. 6. Graph of linear dependence in normalized coordinates

Table 4

Metrological characteristics of linear dependence

Value	Value	Criteria (for tolerances 80-120%, number of points 9)	Conclusion (corresponds, does not corresponds)
1	2	3	4
b	0.9936	–	–
Sb	0.0070	–	–
1	2	3	4
A	0.3103	1) ≤1.8946 Sa=1.35; 2) if not executed, then ≤1.6;	Responsible for the first criterion
Sa	0.7133	–	–
S0	0.2741	–	–
S0/b	0.2758	≤0.53	corresponds
SY (RSD)	13.79	13.69	
r	0.9998	≥0.9993	corresponds

Table 5

Results of analysis of model solutions and their statistical processing (correctness and precision)

No. model solution	Added in % concentration reference solution (Xi actually %)	Optical density Ai (Ast=0,429)	Found in % concentration reference solution (Yi%)	Found % in the added Zi=100(Yi/Xi)
1	2	3	4	5
1	80.56	0.511	80.67	100.14
2	85.59	0.539	85.09	99.42
3	90.63	0.571	90.15	99.47
4	95.66	0.604	95.36	99.69
5	100.50	0.630	99.94	99.25
6	105.73	0.670	105.77	100.04
7	110.77	0.699	110.36	99.63
8	115.80	0.732	115.57	99.80
9	120.84	0.761	120.14	99.42
average Z%				99.67
relative standard deviation, Sz%				0.2716
relative confidence interval Δas%=t(95%,8)*Sz				0.4640
critical for convergence of results Δas%				1.00%
systematic error δ				0.32
criterion of uncertainty of systematic error 1) δ≤Δas/(g)^0,5=0,72/√9, 2=if not executed 1), то δ≤0,32				0.24
general conclusion about the technique				is correct

Proposed methods of identification, tests for purity and quantitative determination are included in the project on the investigated substance

7. Conclusions from the conducted research and prospects for further development of this field

The methods of identification of N- (5-ethyl- [1,3,4] -thiadiazol-2-yl) -2-nitrobenzamide with the use of chemical reactions and spectral methods of analysis - IR and UV and ^{1} H NMR spectroscopy have been developed. To determine the impurities in the substance, the TLC method have been recommended. The methods of quantitative determination of the investigated substance by the method of absorption spectrophotometry in the ultraviolet region by the method of specific absorption index have been developed.

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SEARCH OF THE PROMISING SPECIES OF SUBFAMILY *AMYGDALOIDEAE* AND *PYROIDEAE* USING THE CHEMOTAXONOMY

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Світова флора нараховує понад 1000 видів роду Crataegus L., до підроду Prunus L. належать понад 30 видів, рід Malus Mill. містить 100 видів, до підріду Cerasus Juss. відноситься понад 150 видів. Незважаючи на різноманіття видів та достатню сировинну базу, лише деяки представники цих родів достатньо досліджені та знайшли своє використання як джерела біологічно активних речовин (БАР).

Мета. *Провести хемотаксономічне дослідження представників родів Crataegus L., Prunus L., Malus Mill., Cerasus* Juss.*; встановити перспективні джерела БАР для одержання лікарських засобів.*

Методи дослідження. *Хемотаксономічне дослідження проводили з використанням методу граф-аналізу. Хемомаркерами служили фенольні сполуки та терпеноїди, ідентифіковані у генеративних та вегетативних органах представників родів Crataegus L., Prunus L., Malus Mill., Cerasus* Juss*. Ідентифікацію терпеноїдів та органічних кислот проводили хромато-мас-спектрометричним методом на хроматографі Agilent Technology 6890N з мас-спектрометричним детектором 5973N. Флавоноїди та гідроксикоричні кислоти визначали хроматографічно.*

Результати дослідження. *Встановлені хімічні профілі вегетативних та генеративних органів 34 видів роду Crataegus L., 5 видів роду Prunus L., 7 видів роду Malus Mill., 4 видів роду Cerasus Juss. Встановлені перспективні види глоду, які містять основну групу БАР роду.*

Висновки. *За результатами хемотаксономічного дослідженя представників підродів Amygdaloideae та Pyroideae встановлені перспективні джерела біологічно активних речовин (БАР) видів родів Crataegus L., Prunus L., Malus Mill. та Cerasus Juss. Встановлено, що хімічний профіль досліджених родів формують флавоноїди, терпеноїди та ароматичні кислоти. Перспективні види глоду були введені до складу фітокомплексу «Кратофіт»*

Ключові слова: *розоцвіті, глід, яблуня, вишня, слива, листя, квітки, плоди, таксон, хемотаксономія*

1. Introduction

The representatives of genus *Crataegus* L., *Malus* Mill*., Prunus* L. and *Cerasus Juss.* belong to the family *Rosaceae L. (Rose)* subfamily *Amygdaloideae* and *Pyroideae*. According to modern data *Cerasus* Juss. and *Prunus* L. belong to the *Amygdaeae*, genus *Crataegus L.* and *Malus* Mill. – *Pyreae* [1].

In the world of flora, the genus *Crataegus* L. has more than 1000 species, the *Prunus* L. – more than 30 species, the *Malus* Mill. – more than 100 species, the *Cerasus* Juss. – more than 150 species.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Despite the wide species composition, only some representatives of the genera *Crataegus* L., *Prunus* L., *Malus* Mill. and *Cerasus* Juss. thoroughly investigated. Most of the existing species are not sufficiently studied. The feature of the above genus is that their representatives are easily hybridize as within the genus and between families, which complicates their identification [2]. Because of this, the taxonomy of the