

C. CHEPTEA,¹ L.M. IVAN,² D.O. DOROHAI,² V. SUNEL,³ I. HURJUI,⁴
C.I. SAVEANU,⁵ A.I. GALACTION¹

¹“Gr. T. Popa” University of Medicine and Pharmacy, Faculty of Medical Bioengineering
(9-13, Kogălniceanu Str., Iasi 700454, Romania)

²“Al. I. Cuza” University, Faculty of Physics
(11, Carol I Blvd., Iasi 700506, Romania)

³“Al. I. Cuza” University, Faculty of Chemistry
(11, Carol I Blvd., Iasi 700506, Romania)

⁴“Gr. T. Popa” University of Medicine and Pharmacy, Faculty of Medicine
(16, University Str., Iasi 700115, Romania)

⁵“Gr. T. Popa” University of Medicine and Pharmacy, Faculty of Dental Medicine
(16, University Str., Iasi 700115, Romania)

OPTIMIZED SYNTHESIS AND SPECTRAL CHARACTERIZATION OF SOME HYDRAZONES BASED ON 5-NITROINDAZOLE WITH PHARMACOLOGICAL POTENTIAL

UDC 539

A number of new hydrazones with biological activity are synthesized on the basis of 5-nitroindazole. The most efficient conditions of their synthesis with maximum reaction yield are established. The chemical structure of new compounds is found by the elemental analysis, FTIR spectroscopy, and ¹H-NMR method. The data of spectral analysis were verified by calculations with the HyperChem software. Toxicological tests indicate that the synthesized hydrazones have the antitumor effect.

Keywords: Hydrazones, HyperChem, antitumor effect.

1. Introduction

A considerable importance has been attached recently to the synthetic methods leading to indazole derivatives because of their biological activity [1–7].

The study of a correlation between the chemical structure of substances and their biological activities has been the interest of many researchers pending the discovery of factors responsible for specific biological effects. It has been established that indazole derivatives have antibacterial [8, 9] and cytostatic [10, 11] activities. Moreover, the presence of an indazol ring in various chemical structures provides these compounds with antitumoral [12], antiinflammatory [13], antiprotozoal [14], and antimalarial activities [15].

Starting from the results published in the literature, we synthesized a new series of hydrazones derived from 5-nitroindazole with biological activity [16]. This paper describes the synthesis optimization and the spectral characterization of some new hydra-

zones based on 5-nitroindazole for introducing them in the pharmacological field.

2. Experimental

The starting compound is 5-nitroindazole-1-yl-acetylhydrazide (I) synthesized in our laboratory, which has been treated with the following aromatic aldehydes: benzaldehyde, o- and p-nitrobenzaldehydes, and o-hydroxybenzaldehyde (all from the Merck Company) [16].

The chemical structures of the synthesized compounds (II-V) were elucidated by means of the elemental and spectral analyses (FTIR, ¹H-NMR).

The synthesized compounds (II-V) were purified by repeated recrystallizations from ethanol.

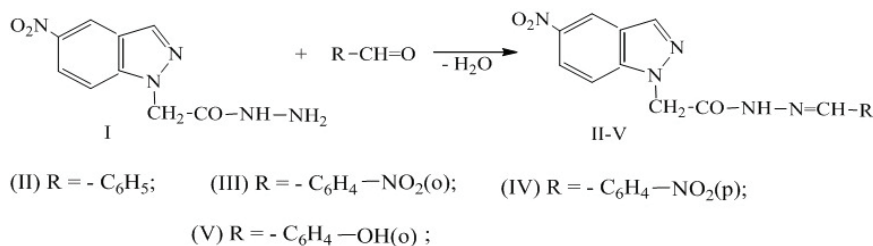
All reagents were used as-purchased (Sigma-Aldrich, Fluka, Merck, S.C. Chemical Company S.A.).

The FTIR spectra were registered using a FTIR spectrophotometer (ATR) Bruker Tensor-27; ¹H-NMR analysis was performed on a Bruker ARX 400 spectrometer (5mm QNP probe; 1H/13C/31P/19F), and elemental analysis was made with the use of an Exeter Analytical CE 440 elemental analyzer.

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Scheme 1. Reactions producing hydrazones II-V

The melting points of the obtained compounds were determined with a Mel-Temp melting point module equipped with a digital thermometer.

The reaction yields were estimated by masses of the initial and final products.

In a reaction flask containing 100 mL absolute ethyl alcohol, 0.005 moles of 5-nitroindazole-1-yl-acetylhydrazide were dissolved. Into this solution, 0.005 moles of aromatic aldehyde was added [16]. The mixture was refluxed on a water bath for 120 min, when an abundant precipitate is separated, filtered in vacuum, dried, and finally purified by the recrystallization from ethyl alcohol.

In the IR spectra of the studied compounds, the absorption IR bands at 1490–1496 cm⁻¹ that are characteristic of a CH–N group can be observed. The characteristic IR absorption bands appear at 1673–1682 cm⁻¹ for a CO–NH group, and the nitro group presents intense and very intense bands between 1342–1398 cm⁻¹ (NO₂ sym.) and 1514–1545 cm⁻¹ (NO₂ asym.), respectively. Compound V presents also a shift at 1287 cm⁻¹ specific of a C–OH bond.

The absorption bands for a monosubstituted benzene ring appear in the spectral interval 748–811 cm⁻¹.

The spectral data regarding IR spectra and NMR chemical shifts are given in Table 1.

The ¹H-NMR method confirms the structure of each of the synthesized hydrazones; the protons of the CH₂ group are present at δ = 5.81–5.86 ppm, by depending on the compound structure.

3. Biological Tests

The synthesized compounds were tested from the toxicity point of view, by establishing the values of DL₅₀.

The toxicity was estimated by intraperitoneal administration of synthesized substances, as a solution

with Tween 80, on groups of 14 mice (20 ± 5g each), using the Spearman–Kärber method [17].

The mortality of tested animals was record after 7 days (Table 2).

The obtained toxicological data confirm that the N-acyl-hydrazones possess low toxicity, which recommends them for future biological tests.

4. Results and Discussions

From the initial reactions, the dependence of the reaction yield on the temperature and the reaction time has been evidenced. Consequently, the two variables were considered as being significant. The values of the significant variables [18–21] (both for real and a-dimensional ones) and the corresponding reaction yield are given in Table 3.

In order to optimize the synthesis of hydrazones within a 3² factorial model, the experiment was organized for each reaction. The chemical reactions were repeated in a short variation domain of relevant variables, in a neighborhood spot corresponding to the estimated maximum, and the reaction yield was estimated.

The definition of significant a-dimensional variables is given in Fig. 1.

The a-dimensional variables were computed by using relation (1),

$$x_i = \frac{X_i - X_{imed.}}{\Delta X_i}; \quad i = 1, 2, \quad (1)$$

$$X_{imed.} = \frac{X_{i \min} + X_{i \max}}{2}; \quad i = 1, 2,$$

and

$$\Delta X_i = \frac{X_{i \max} - X_{i \min}}{2}; \quad i = 1, 2.$$

The real significant variable X_i ($i = 1, 2$) depending on the corresponding a-dimensional variable x_i (found by the optimization of calculations) can be expressed as follows:

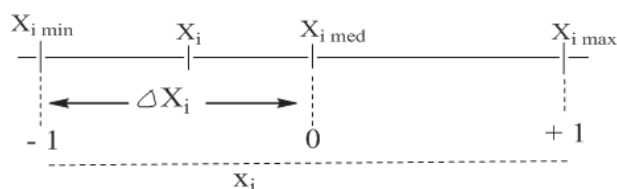
$$X_i = X_{imed.} + x_i \Delta X_i; \quad i = 1, 2. \quad (2)$$

Table 1. Elemental and spectral characteristics of N-acyl hydrazones II-V

| | II | III | IV | V |
|---|---|--|---|---|
| Colour | yellow solid | light grey solid | yellow solid | yellow solid |
| Melting point | 180–182 °C | 209–211 °C | 204–205 °C | 184–186 °C |
| Elemental analysis | C%59.83; H%4.26; N%22.05; | C%52.65; H%3.41; N%23.28; | C%52.31; H%3.59; N%23.23; | C% 56.95; H%4.12; N%21.05; |
| FTIR, (ν_{\max} cm ⁻¹) | 3000(NH); 1681 (C=O); 2850 (CHAr); 1342 (NO ₂ sym); 1516 (NO ₂ asym); 1495(C=N); 803 monosubstituted benzene ring; | 2900 (NH); 1678 (C=O); 3000 (CHAr); 1338 (NO ₂ sym); 1519(NO ₂ asym); 1496 (C=N); 799 p-disubstituted benzene ring; | 3149; 3483 (NH); 1682 (C=O); 2840 (CHAr); 1360 (NO ₂ sym); (NO ₂ asym); 1490 (C=N); 728 p-disubstituted benzene ring; | 3066 (NH); 1673 (C=O); 2978 (CHAr); 1344 (NO ₂ sym);1514 (NO ₂ asym); 1493 (C=N); 1287 (OH); 811 -disubstituted benzene ring; |
| ¹ H-NMR δ (ppm) | 5.38(s, 1H, CH); 5.86(s, 2H, CH ₂); 7.44–7.47(m, 3H, CHAr); 7.74–7.76(m, 2H, CHAr); 7.89–7.92(d, 1H, CHAr); 8.22–8.26(d, 1H, CHAr); 8.44(s, @h, CHAr); 11.85(s, 1H, NH); | 5.41 (s, 1H, CH); 5.84(s, 2H, CH ₂); 7.69(s, 1H, CHAr); 7.79–7.80(d,1H, CHAr); 7.89–7.92(d, 1H, CHAr); 8.07–8.09(m, 2H, CHAr); 8.22(s, 1H, CHAr); 8.45(s, 1H, CHAr); 8.85(s, 1H, CHAr); 12.21(s, 1H, CHAr); | 5.42 (s, 1H, CH); 5.89(s, 2H, CH ₂); 7.679s, 1H, CHAr); 7.76–7.78(d, 1H, CHAr); 7.91–7.93(d, 1H, CHAr); 8.05–8.08(m, 2H, CHAr); 8.25(s, 1H, CHAr); 8.44(s, 1H, CHAr); 8.87(s, 1H, CHAr); 12.10(s, 1H, NH); | 5.39 (s, 1H, CH); 5.81(s, 2H, CH ₂); 6.86–6.90(d, 1H, CHAr); 7.78(s, 1H, CHAr); 7.89–7.91(d, 1H, CHAr); 8.21–8.22(d, 1H, CHAr); 8.37(s, 1H, CHAr); 8.43–8.48(m, 2H, CHAr); 8.84–8.86(d, 1H, CHAr); 11.70(s, 1H, OH); 12.10(s, 1H, NH) |

Table 2. DL₅₀ Values of the synthesized compounds

| Compound | Administration route | Tested animals | DL ₅₀ (mg/kgcorp) |
|----------|----------------------|----------------|------------------------------|
| II | i.p. | mice | 1280 |
| III | i.p. | mice | 1050 |
| IV | i.p. | mice | 1025 |
| V | i.p. | mice | 1135 |

Fig. 1. Definition of the real significant a-dimensional variables ($i = 1, 2$)

A mathematic 3² factorial model has been considered. We denote the reaction yield by η ,

$$\eta = a_0 + a_1x_1 + a_2x_2 + a_{12}x_1x_2 + a_{11}x_1^2 + a_{22}x_2^2, \quad (3)$$

where are x_i ($i = 1, 2$) the significant a-dimensional variables. Model (3) can describe the response function near the optimum with enough precision.

In Table 3, we also used the orthogonal variables $x_1^2 - 2/3$ and $x_2^2 - 2/3$ introduced in [18–21] as nor-

malized variables satisfying the conditions of orthogonality.

By using the orthogonal coordinates, the reaction yield becomes [18–21]

$$\eta = \bar{\eta} - \frac{2}{3}(a_{11} + a_{22}) + a_1x_1 + a_2x_2 + a_{12}x_1x_2 + a_{11}x_1^2 + a_{22}x_2^2. \quad (4)$$

The coefficients a_{ij} from (3) are calculated using the relations

$$a_i = \frac{\sum_{k=1}^N x_{ij} \eta_k}{\sum_{k=1}^N x_{ik}^2}, \quad i = 1, 2, \quad (5)$$

Table 3. Significant variables and reaction yields

| Nr | Time (h) x_1 | Temp ($^{\circ}$ C) x_2 | $x_1 x_2$ | $x_1^2 - 2/3$ | $x_2^2 - 2/3$ | η_{II} | η_{III} | η_{IV} | η_V |
|----------|----------------|----------------------------|-----------|---------------|---------------|-------------|--------------|-------------|----------|
| 1 | 2.45(-1) | 64(-1) | 1 | 1/3 | 1/3 | 71 | 69 | 75 | 52 |
| 2 | 2.45(-1) | 66(0) | 0 | 1/3 | -2/3 | 74 | 72 | 76 | 54 |
| 3 | 2.45(-1) | 68(1) | -1 | 1/3 | 1/3 | 75 | 70 | 78 | 57 |
| 4 | 3.00(0) | 64(-1) | 0 | -2/3 | 1/3 | 74 | 70 | 76 | 54 |
| 5 | 3.00(0) | 66(0) | 0 | -2/3 | -2/3 | 82 | 74 | 77 | 57 |
| 6 | 3.00(0) | 68(1) | 0 | -2/3 | 1/3 | 76 | 76 | 78 | 59 |
| 7 | 3.15(1) | 64(-1) | -1 | 1/3 | 1/3 | 70 | 66 | 69 | 58 |
| 8 | 3.15(1) | 66(0) | 0 | 1/3 | -2/3 | 72 | 70 | 73 | 49 |
| 9 | 3.15(1) | 68(1) | 1 | 1/3 | 1/3 | 68 | 60 | 64 | 57 |
| Σ | 0 | 0 | 0 | 0 | 0 | 662 | 627 | 666 | 497 |

Table 4. Polynomial coefficients

| | a_0 | a_1 | a_2 | a_{12} | a_{11} | a_{12} |
|--------------|-------|--------|-------|----------|----------|----------|
| Compound II | 73.78 | -1.00 | 0.00 | -0.75 | -2.66 | -4.67 |
| Compound III | 62.5 | -0.5 | 0.5 | -0.75 | -3.5 | -4.16 |
| Compound IV | 79.25 | -1.00 | -1.00 | -0.25 | -1.38 | -5.33 |
| Compound V | 70.99 | -0.666 | 0.00 | -0.25 | -3.0 | -4.0 |

Table 5. Experiments in the center of the variation domain

| | $\eta_0(1)$ | $\eta_0(2)$ | $\eta_0(3)$ | $\bar{\eta}_0$ | $S_{\eta}^2/2$ | P |
|--------------|-------------|-------------|-------------|----------------|----------------|-------|
| Compound II | 74 | 74 | 73 | 73.667 | 0.333 | 0.192 |
| Compound III | 62 | 63 | 63 | 62.667 | 0.721 | 0.283 |
| Compound IV | 79 | 80 | 80 | 79.667 | 0.721 | 0.283 |
| Compound V | 71 | 71 | 70 | 70.667 | 0.721 | 0.283 |

Table 6. t_i -student coefficients

| | a_0 | a_1 | a_2 | a_{12} | a_{11} | a_{22} |
|--------------|--------|-------|-------|----------|----------|----------|
| Compound II | 384.27 | 5.21 | 0.0 | 3.90 | 13.85 | 24.32 |
| Compound III | 220.85 | 1.77 | 1.77 | 2.65 | 12.37 | 14.70 |
| Compound IV | 280.04 | 3.53 | 3.53 | 0.88 | 4.88 | 18.83 |
| Compound V | 250.85 | 2.35 | 0.0 | 0.88 | 10.60 | 14.13 |

$$a_{ij} = \frac{\sum_{k=1}^N (x_i + x_j)_k \eta_k}{\sum_{k=1}^N (x_i x_j)_k^2}, \quad i = 1, 2, \quad (6)$$

$$a_{ij} = \frac{\sum_{k=1}^N (x_i^2 - \frac{2}{3}) \eta_k}{\sum_{k=1}^N (x_i^2 - \frac{2}{3})_k^2}, \quad i = 1, 2. \quad (7)$$

In order to express the condition of maximum efficiency, the determined coefficients must satisfy the following extremum conditions:

$$\begin{aligned} \frac{\partial \eta}{\partial x_1} &= a_1 + 2a_{11}x_1 + a_{12}x_2 = 0, \\ \frac{\partial \eta}{\partial x_2} &= a_2 + 2a_{22}x_2 + a_{12}x_1 = 0. \end{aligned} \quad (8)$$

The maximum yield is obtained for negative values of a_{11} and a_{22} . If the second-order partial derivatives of the yield are negative, the founded extremum represents a maximum.

The absolute values of the determined coefficients provides information about the intensity of the individual effects (a_1 and a_2) or about the combined effects (a_{12}). The (+) or (-) signs indicate the variable which multiplies that coefficient favors or, respectively, does not favor, the result of a chemical reaction. In Table 4, the polynomial coefficients determined for relation (4) are listed. They were computed on the basis of Table 3.

Let us check the model, by assuming that all coefficients from (4) were determined with the same accuracy P :

$$P = \sqrt{\frac{S_e}{N}}. \quad (9)$$

To determine S_e , other three experiments were organized for the center of the variability interval considered (see Table 5). The average values of the yield for the three experiments were estimated, and the square average deviations for the supplemental experiments were computed, by using the formula

$$S_e = \frac{\sum_{i=1}^3 (\eta_0(i) - \bar{\eta}_0)}{2}. \quad (10)$$

The t -student coefficients are listed in Table 6.

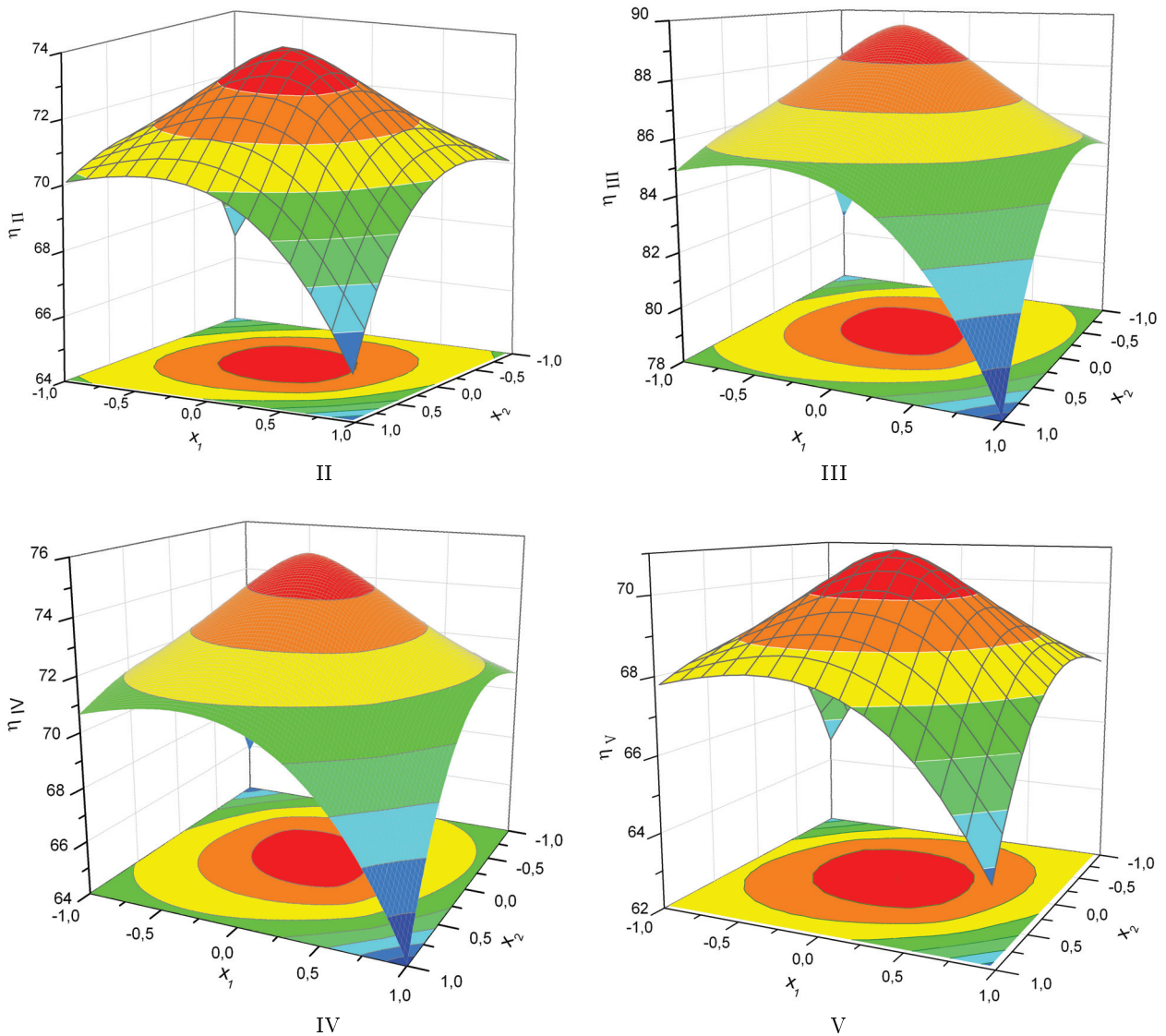


Fig. 2. Reaction yield vs. a-dimensional coordinates for compounds II-V

The significance of coefficients from Table 3 is tested using the expression for t -student coefficients in [18, 19]. A maximum error in determining the yield was fixed (as being unity), and the coefficients with lower test value than this one were neglected, because they have no significant meaning for the value of yield. Only the t -student coefficient corresponding to x_2 for compound IV shows an insignificant influence of the x_2 a-dimensional variable on the reaction yield for this compound.

The a-dimensional variable x_2 is insignificant in determining the reaction yield in the case of compound III.

The t -student coefficient a_{12} is smaller than unity for compounds IV and V. Their influence on the reaction yield is minor, so they are eliminated from the final formulae of the reaction yield.

By considering the $t_{i,j}$ -student coefficients from Table 5, the final formulae for reaction yields in obtaining compounds II-V in optimal conditions are given

in $11_{II} - 11_V$

$$\eta_{II} = 73.78 - 1.000x_1 - 0.750x_1x_2 - 2.66x_1^2 - 4.67x_2^2, \quad (11II)$$

$$\eta_{III} = 62.500 - 0.500x_1 + 0.500x_2 - 0.750x_1x_2 - 3.50x_1^2 - 4.16x_2^2, \quad (11III)$$

$$\eta_{IV} = 79.25 - 1.00x_1 - 1.000x_2 - 1.38x_1^2 - 5.33x_2^2, \quad (11IV)$$

$$\eta_V = 70.99 - 0.666x_1 - 3.000x_1^2 - 4.00x_2^2. \quad (11V)$$

The reaction yield dependences on the a-dimensional variables x_1 and x_2 are plotted in a 3D representation in Fig. 2.

The zones from Fig. 2 characterized by appropriate values of the reaction yield are presented by the same color (the same grey nuance)

The models with quadratic terms describes, with sufficient accuracy, the region, where it is supposed (and experimentally proved) that the reaction yield is maximum. The disadvantage of the method is that in order to determine the t-student coefficients in the center of the variability interval, the additional experiments should be organized.

5. Conclusions

The synthesized substances were characterized by elemental and spectral means. The synthesis reactions were optimized for establishing the conditions to obtain the highest yield of the synthesized compounds. By using a mathematic 3^2 factorial model, the most efficient reaction conditions for the synthesis of compounds II-V were obtained. The optimization is necessary to avoid the unwanted consumption of a starting compound. The toxicity of hydrazidones is established.

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*К. Кептя, Л.М. Иван, Д.О. Дорохой, В.Ш. Шунел,
І. Хуржусі, К.Ю. Севеану, А.І. Галактион*

ОПТИМІЗАЦІЯ СИНТЕЗУ
І СПЕКТРАЛЬНА ХАРАКТЕРИСТИКА НОВИХ
ГІДРАЗОНІВ НА ОСНОВІ 5-НІТРОІНДАЗОЛА
З ФАРМАКОЛОГІЧНИМ
ПОТЕНЦІАЛОМ

Резюме

Синтезовано ряд нових гідразонів з біологічною активністю на основі 5-нітроіндазола. Встановлено найбільш ефективні умови їх синтезу з максимальним виходом реакції. Хімічна структура нових сполук визначена елементним аналізом і методами інфрачервоної спектроскопії з фур'є-перетворенням і ЯМР. Дані спектрального аналізу перевірені розрахунками з програмою NucleChem. Токсикологічні тести свідчать про те, що синтезовані гідразони володіють антипухлинним ефектом.

*К. Кептя, Л.М. Иван, Д.О. Дорохой, В.Ш. Шунел,
И. Хуржуси, К.Ю. Севеану, А.И. Галактион*

ОПТИМИЗАЦИЯ СИНТЕЗА
И СПЕКТРАЛЬНАЯ ХАРАКТЕРИСТИКА НОВЫХ
ГИДРАЗОНОВ НА ОСНОВЕ 5-НИТРОИНДАЗОЛА
С ФАРМАКОЛОГИЧЕСКИМ ПОТЕНЦИАЛОМ

Резюме

Синтезирован ряд новых гидразонов с биологической активностью на основе 5-нитроиндазола. Установлены наиболее эффективные условия их синтеза с максимальным выходом реакции. Химическая структура новых соединений определена элементным анализом и методами инфракрасной спектроскопии с фурье-преобразованием и ЯМР. Данные спектрального анализа проверены расчетами с программой NucleChem. Токсикологические тесты свидетельствуют, что синтезированные гидразоны обладают антиопухолевым эффектом.