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# Synthesis of new indomethacin derivatives with 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione

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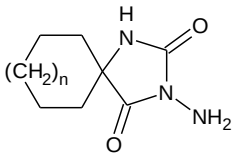
This article presents the synthesis of new amides, based on the interaction of a series of 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione with Indomethacin. The target compounds were prepared with the aim of developing new products with anti-inflammatory properties. The structures of all obtained amides were verified *via* physicochemical parameters, FTIR-ATR, Raman, $^{1}$H and $^{13}$C NMR spectroscopy.

**Keywords:** Synthesis, Indomethacin, 3-aminospirohydantoins, 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione

## INTRODUCTION

The synthesis and research of different types of biological activity of 3-aminospirohydantoins were reported in previous works of ours. The anticonvulsive effect of a series of 3-aminocycloalkanespiro-5-hydantoins with 5-, 6-, 7-, 8- and 12-membered rings (Figure 1) was investigated. The results obtained from the conducted experiments showed the absence of anticonvulsive activity. The tested cyclohexane-, cycloheptane- and cyclododecane- derivatives even induced seizures [1].




n = 0-3, 7

**Fig. 1.** 3-Aminocycloalkanespiro-5-hydantoins

The cytotoxic effect of 3-amino-9'-fluorenespiro-5-hydantoin (Figure 2) on the retinoblastoma cell line WERI-Rb-1 and its antimicrobial activity against both Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* bacteria and the yeasts *Candida albicans* were examined. It was found that this compound could not serve as potential anticancer agent, but it showed pronounced antibacterial activity against the bacteria *Escherichia coli* and no activity towards *Staphylococcus aureus* and *Candida albicans* [2].

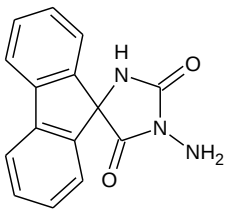



**Fig. 2.** 3-Amino-9'-fluorenespiro-5-hydantoin

An evaluation of the antimicrobial action of 3-amino-6-methyl-1,3-diazaspiro[4.5]decane-2,4-dion (Figure 3a), 3-amino-8-methyl-1,3-diazaspiro[4.5] decane-2,4-dione (Figure 3b), 3-amino-8-ethyl-1,3-diazaspiro[4.5]decane-2,4-dione (Figure 3c) and 3-amino-8-propyl-1,3-diazaspiro[4.5]decane-2,4-dione (Figure 3d) was also performed. The studied compounds showed no activity against Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella abony*, the yeasts *Candida albicans* and *Saccharomyces cerevisiae*, the molds *Penicillium chrysogenum* and *Aspergillus niger*, the plant pathogenic fungi *Fusarium oxysporum* and *Pythium ultimum* and a plant pathogenic bacterium *Pseudomonas syringae* [3].

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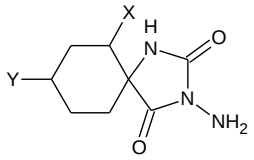



**a)** X = Me-, Y = H-; **b)** X = H-, Y = Me-; **c)** X = H-, Y = Et-; **d)** X = H-, Y = Pr-

**Fig. 3.** Substituted 3-aminocyclohexanespiro-5-hydantoins

The aim of the current research is to present the synthesis of new organic compounds with potential anti-inflammatory properties. The interaction of 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione with Indomethacin was studied for this purpose.

## EXPERIMENTAL

### *General*

All used chemicals were purchased from Merck and Sigma-Aldrich. The melting points were determined by a SMP-10 digital melting point apparatus. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 $F_{254}$, 0.2 mm Merck plates, eluent system (vol. ratio): ethyl acetate : petroleum ether = 1 : 2. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106, giving results within ± 0.2 % of the calculated values. The Attenuated Total Reflection FTIR (ATR) spectra were registered on a Bruker FT-IR VERTEX 70 Spectrometer by ATR accessory MIRacle™ with a one-reflection ZnSe element (Pike). The stirred crystals were pressed by an anvil to the reflection element and the spectra were measured from 4500 $cm^{-1}$ to 600 $cm^{-1}$ at resolution 2 $cm^{-1}$ with 16 scans. The Raman spectra (the stirred crystals placed in aluminium disc) were measured on a RAM II (Bruker Optics) with a focused laser beam of 200-500 mW power of Nd:YAG laser (1064 nm) from 4000 $cm^{-1}$ to 51 $cm^{-1}$ at resolution 2 $cm^{-1}$ with 25 scans. The NMR spectra were taken on a Bruker Avance II + 600 MHz spectrometer, operating at 600.130 and 150.903 MHz for $^{1}H$ and $^{13}C$, respectively, using the standard Bruker software. The chemical shifts were referenced to tetramethylsilane (TMS). The measurements in DMSO-$d_6$ solutions were carried out at ambient temperature.

### *Synthesis of amides **4a-4h** (Scheme 1) [4]*

A mixture of Indomethacin (3.58 g, 0.01 mol, Figure 4) and 0.01 mol of the corresponding 3-aminospirohydantoins (**3a-3d** and **3f-3h**) and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione (**3e**, 2.05 g, 0.01 mol) was dissolved in 50 ml of tetrahydrofuran with stirring at room temperature. *N,N′*-dicyclohexylcarbodiimide (DCC, 2.06 g, 0.01 mol) was added to the reaction mixture and the latter was left overnight. After this interaction, the *N,N′*-dicyclohexylcarbamide formed was filtered off and 1 ml of glacial acetic acid was added to the filtrate for removing of the unreacted reagent. After filtration, the solvent was evaporated to dryness and the amides obtained (**4a-4h**) were recrystallized from ethanol.

## RESULTS AND DISSCUSION

The synthesis of the target compounds (**4a-4h**) was performed in accordance with Scheme 1. The cycloalkanespiro-5-hydantoins (**2a-2d**) and 5-methyl-5-phenylimidazolidine-2,4-dione (**2e**) were synthesized by the Bucherer-Lieb method [5], based on the interaction between the corresponding ketones (**1a-1e**), sodium cyanide, ammonium carbonate and ethanol. The 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (**2f**) and spiro[fluorene-9,4'-imidazolidine]-2',5'-dione (**2h**) were obtained in accordance with Nagasawa et *al*. [6]. The 3',4'-dihydro-2*H*,2'*H*,5*H*-spiro [imidazolidine-4,1'-naphthalene]-2,5-dione (**2g**) was prepared in accordance with Marinov et *al*. [7] through a modification of the method reported by Sarges et *al*. [8]. The 3-aminoderivatives (**3a-3h**) were synthesized by a treatment of compounds **2a-2h** with concentrated hydrazine hydrate, following a modificated technique [4] of the previously published procedures [1, 2, 7, 9]. Compounds **3a-3h** were subjected to an interaction with Indomethacin (Figure 4) in accordance with the DCC-method [10], resulted in the formation of the corresponding amides (**4a-4h**).

The physicochemical parameters, FTIR-ATR, Raman and NMR spectral data of the synthesized compounds (**4a-4h**) are listed in Tables 1-4 respectively.

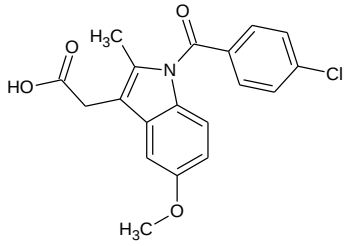
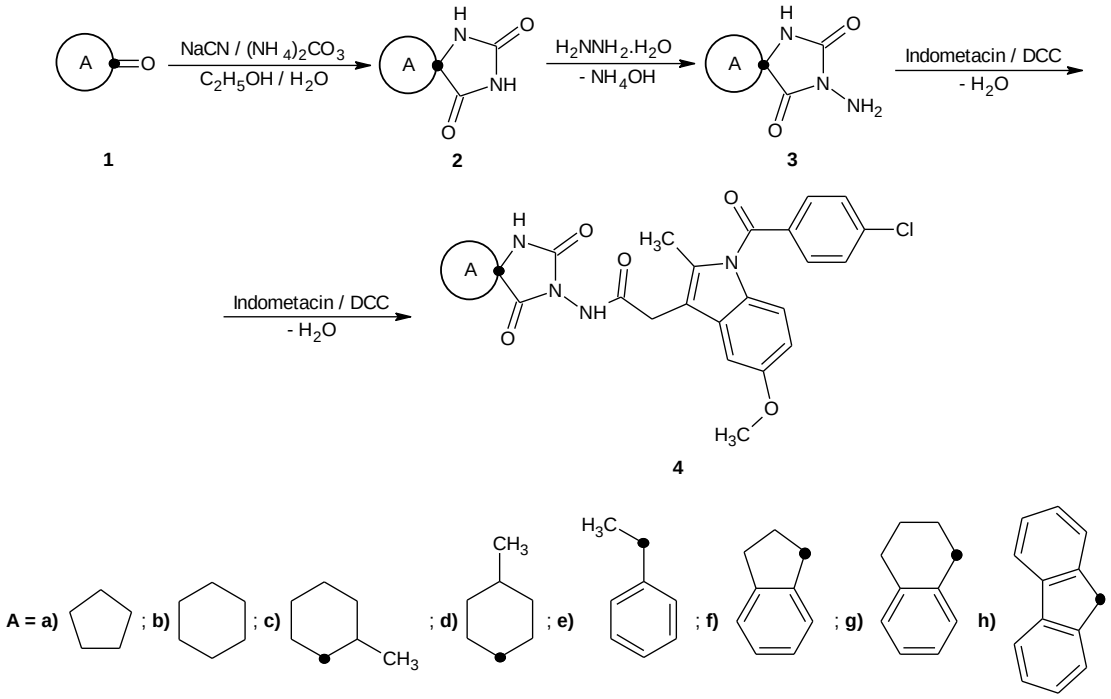



**Fig. 4.** Indomethacin (INN, BAN), Indomethacin (AAN, USAN, BAN), /Systematic name: 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-indol-3-yl]acetic acid/




**Scheme 1.** Synthesis of amides **4a-4h**

**Table 1.** Physicochemical parameters of compounds **4a-4h**

| №* | Systematic name | Yield, % | M. p., °C | $R_f$** |
|---|---|---|---|---|
| **4a** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(2,4-dioxo-1,3-diazaspiro[4.4]nonan-3-yl)acetamide | 85 | 224-225 | 0.65 |
| **4b*** ** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(2,4-dioxo-1,3-diazaspiro[4.5]decan-3-yl)acetamide | 89 | 234-235 | 0.57 |
| **4c** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(6-methyl-2,4-dioxo-1,3-diazaspiro[4.5]decan-3-yl)acetamide | 83 | 188-189 | 0.45 |
| **4d** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(8-methyl-2,4-dioxo-1,3-diazaspiro[4.5]decan-3-yl)acetamide | 92 | 236-237 | 0.52 |
| **4e** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(4-methyl-2,5-dioxo-4-phenylimidazolidin-1-yl)acetamide | 94 | 148-149 | 0.63 |
| **4f** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)-acetamide | 87 | 186-187 | 0.54 |
| **4g** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(2,5-dioxo-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-1-yl)acetamide | 91 | 207-208 | 0.51 |
| **4h** | 2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(2',5'-dioxospiro[fluorene-9,4'-imidazolidine]-1'-yl)acetamide | 84 | 181-182 | 0.46 |

* The compounds numbering is in accordance with Scheme 1.
** Eluent system (vol. ratio): ethyl acetate : petroleum ether = 1 : 2.
*** Ref. 4.

**Table 2.** FTIR-ATR spectral data ($cm^{-1}$) of compounds **4a-4h**

| № | $\nu_{NH}$ | $\nu_{CH\ (arom.)}$ | $\nu_{aliph.}$ | | $\nu_{C=O}$ | $\nu_{C=O}$ (amide) | $\nu_{CC}$ (arom.) | $\nu_{CN}$ |
|---|---|---|---|---|---|---|---|---|
| | | | $\nu_{as}$ | $\nu_{s}$ | | | | |
| **4a** | 3279 | 3022 | 2933 | 2854 | 1798, 1736, 1706 | 1681 | 1596 | 1371 |
| **4b*** | 3253 | 3001 | 2926 | 2856 | 1800, 1735, 1705 | 1681 | 1599 | 1372 |
| **4c** | 3165 | 3057 | 2932 | 2859 | 1766, 1731, 1708 | 1647 | 1590 | 1343 |
| **4d** | 3266 | 3019 | 2929 | 2856 | 1786, 1727, 1683 | 1656 | 1591 | 1356 |
| **4e** | 3280 | 3015 | 2930 | 2857 | 1795, 1741, 1692 | 1678 | 1595 | 1369 |
| **4f** | 3221 | 3008 | 2931 | 2852 | 1794, 1737, 1715 | 1690 | 1592 | 1378 |
| **4g** | 3223 | 3014 | 2931 | 2855 | 1792, 1737, 1715 | 1687 | 1593 | 1379 |
| **4h** | 3282 | 3018 | 2930 | 2853 | 1798, 1740, 1687 | 1660 | 1573 | 1358 |

* Ref. 4.

**Table 3.** Raman spectral data ($cm^{-1}$) of compounds **4a-4h**

| № | mW | $\nu_{max}$, $cm^{-1}$ |
|---|---|---|
| **4a** | 250 | 3069, 2930, 1679, 1591, 1446, 1372, 1259, 1224, 1150, 1089, 831, 756, 412 |
| **4b*** | 200 | 3068, 3002, 2928, 2852, 1782, 1738, 1680, 1590, 1577, 1447, 1393, 1350, 1222, 1182, 1124, 1066, 830, 736, 663 |
| **4c** | 250 | 3072, 2930, 1728, 1689, 1680, 1649, 1616, 1580, 1457, 1395, 1226, 1093, 742, 413 |
| **4d** | 200 | 3070, 2932, 1682, 1651, 1610, 1458, 1396, 1369, 1356, 1223, 1090, 739, 411 |
| **4e** | 500 | 3069, 2929, 1693, 1679, 1613, 1579, 1456, 1396, 1369, 1089, 904, 754, 401 |
| **4f** | 250 | 3068, 2932, 1667, 1652, 1620, 1591. 1447, 1394, 1366, 1226, 1090, 758, 409 |
| **4g** | 200 | 3068, 2929, 1787, 1651, 1626, 1593, 1580, 1459, 1434, 1387, 1266, 1177, 1090, 973, 760, 741, 402 |
| **4h** | 200 | 3070, 2945, 1672, 1648, 16109, 1583, 1458, 1395, 1372, 1229, 1089, 739, 416 |

* Ref. 4.

**Table 4.** NMR spectral data of compounds **4a-4h**

| № | $^1$H NMR (DMSO-$d_6$), $\delta$ / ppm |
|---|---|
| **4a** | 1.22-1.73 (m, 4H, $CH_2$), 2.15 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 6.68-7.58 (m, 7H, CH), 7.70 (s, 1H, NH, urea), 8.79 (s, 1H, NH, sec. amide) |
| **4b** | 1.39-1.86 (m, 10H, $CH_2$), 2.22 (s, 3H, $CH_3$), 3.38 (s, 3H, $CH_3$), 6.16-6.77 (m, 3H, CH, indole), 7.43-7.64 (m, 4H, CH, benzene), 7.83 (s, 1H, NH, urea), 8.95 (s, 1H, NH, sec. amide) |
| **4c** | 1.08 (s, 3H, $CH_3$), 1.42-1.95 (m, 8H, $CH_2$, cyclohexane), 2.29 (s, 3H, $CH_3$), 2.47 (s, 2H, CH, cyclohexane), 3.30 (s, 2H, $CH_2$), 3.76 (s, 3H, $CH_3$), 6.18-6.73 (m, 3H, CH, indole), 7.42-7.68 (m, 4H, CH, benzene), 7.87 (s, 1H, NH, urea), 9.10 (s, 1H, NH, sec. amide) |
| **4d** | 1.11 (s, 3H, $CH_3$), 1.54 (s, 1H, CH, cyclohexane), 1.38-1.89 (m, 8H, $CH_2$, cyclohexane), 2.33 (s, 3H, $CH_3$), 3.35 (s, 2H, $CH_2$), 3.82 (s, 3H, $CH_3$), 6.29-6.81 (m, 3H, CH, indole), 7.48-7.76 (m, 4H, CH, benzene), 7.94 (s, 1H, NH, urea), 10.2 (s, 1H, NH, sec. amide) |
| **4e** | 1.85 (s, 3H, $CH_3$), 2.23 (s, 3H, $CH_3$), 3.55 (s, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$), 6.56-7.02 (m, 7H, CH), 7.49 (m, 5H, CH), 7.71 (s, 1H, NH, urea), 8.84 (s, 1H, NH, sec. amide) |
| **4f** | 2.25 (s, 3H, $CH_3$), 2.49 (s, 2H, $CH_2$, indane), 3.02 (s, 2H, $CH_2$, indane), 3.43 (s, 2H, $CH_2$), 6.68-6.91 (m, 3H, CH, indole), 7.24-7.36 (m, 4H, CH, indane), 7.41-7.63 (m, 4H, CH, benzene), 7.87 (s, 1H, NH, urea), 8.58 (sec. amide) |
| **4g** | 1.51 (s, 2H, $CH_2$, 1,2,3,4-tetrahydronaphtalene), 1.72 (s, 3H, $CH_3$), 2.07 (s, 2H, $CH_2$, 1,2,3,4-tetrahydronaphtalene), 2.73 (s, 2H, $CH_2$, 1,2,3,4-tetrahydronaphtalene), 3.01 (s, 2H, $CH_2$), 3.75 (s, 3H, $CH_3$), 6.13-6.92 (m, 3H, CH, indole), 6.95-7.15 (m, 4H, CH, 1,2,3,4-tetrahydronaphtalene), 7.20-7.61 (m, 4H, CH, benzene), 7.94 (s, 1H, NH, urea), 8.99 (s, 1H, NH, sec. amide) |

**Table 4 - continuation.**

| № | $^{1}$H NMR (DMSO-$d_6$), $\delta$ / ppm |
|---|---|
| **4h** | 2.15 (s, 3H, $CH_3$), 3.27 (s, 2H, $CH_2$), 3.76 (s, 3H, $CH_3$), 6.22-6.71 (m, 3H, CH, indole), 7.39-7.47 (m, 4H, CH, benzene), 7.31-7.88 (m, 8H, CH, fluorene), 8.11 (s, 1H, NH, urea), 9.8 (s, 1H, NH, sec. amide) |
| | **$^{13}$C NMR (DMSO-$d_6$), $\delta$ / ppm** |
| **4a** | 191.1 (C=O), 175.7 (C=O, amide), 168.4 (C=O, spirohyd. ring), 156.1 (C=O, spirohyd. ring), 138.1 (CH, indole), 136.1 (CH, indole), 134.5 (CH, benzene), 129.3 (CH, benzene), 113.3 (CH, indole), 66.5 (spiro C-atom), 55.8 ($CH_3$), 29.2 ($CH_2$), 25.8 ($CH_2$), 25.1 ($CH_2$), 13.7 ($CH_3$) |
| **4b** | 189.9 (C=O), 176.6 (C=O, amide), 165.7 (C=O, spirohyd. ring), 156.4 (C=O, spirohyd. ring), 132.2 (CH, benzene), 139.6 (CH, benzene), 114.4 (CH, indole), 108.3 (CH, indole), 104.9 (CH, indole), 62.4 (spiro C-atom), 56.3 ($CH_3$), 33.1 ($CH_2$, cyclohexane), 29.2 ($CH_2$, cyclohexane), 26.9 ($CH_2$, cyclohexane), 19.8 ($CH_2$, cyclohexane), 13.4 ($CH_3$) |
| **4c** | 192.3 (C=O), 178.6 (C=O, amide), 167.6 (C=O, spirohyd. ring), 158.2 (C=O, spirohyd. ring), 132.6 (CH, benzene), 129.6 (CH, benzene), 114.3 (CH, indole), 108.3 (CH, indole), 104.5 (CH, indole), 69.1 (spiro C-atom), 58.8 ($CH_3$), 35.4 (CH, cyclohexane), 30.8 ($CH_2$, cyclohexane), 27.2 ($CH_2$, cyclohexane), 25.3 ($CH_2$, cyclohexane), 20.5 ($CH_2$, cyclohexane), 17.4($CH_2$), 13.2 ($CH_3$) |
| **4d** | 195.2 (C=O), 178.6 (C=O, spirohyd. ring), 171.3 (C=O, amide), 158.2 (C=O, spirohyd. ring), 133.4 (CH, benzene), 130.6 (CH, benzene), 115.4 (CH, indole), 110.1 (CH, indole), 105.7 (CH, indole), 64.1 (spiro C-atom), 58.3 ($CH_3$), 31.6 ($CH_2$, cyclohexane), 29.4 ($CH_2$), 28.6 (CH, cyclohexane), 26.4 ($CH_2$, cyclohexane), 19.3 ($CH_3$), 14.1 ($CH_3$) |
| **4e** | 188.1 (C=O), 172.6 (C=O, amide), 168.4 (C=O, hyd. ring), 156.1 (C=O, hyd. ring), 138.1 (CH, indole), 135.6 (CH, indole), 134.6 (CH, benzene), 131.6 (CH, benzene), 131.2 (CH, benzene), 130.6 (CH, benzene), 115.0 (CH, benzene), 111.7 (CH, indole), 68.3 (C), 55.8 ($CH_3$), 29.9 ($CH_2$), 25.3($CH_3$), 13.6 ($CH_3$) |
| **4f** | 190.5 (C=O), 172.3 (C=O, amide), 167.9 (C=O, spirohyd. ring), 158.2 (C=O, spirohyd. ring), 132.3 (CH, benzene), 130.6 (CH, benzene), 129.5 (CH, indane), 126.3 (CH, indane), 115.5 (CH, indole), 108.3 (CH, indole), 106.1 (CH, indole), 68.5 (spiro C-atom), 55.8 ($CH_3$), 32.1 ($CH_2$, indane), 25.8 ($CH_2$, indane), 24.8 ($CH_2$, aliph.), 13.7 ($CH_3$) |
| **4g** | 189.6 (C=O), 174.1 (C=O, amide), 168.4 (C=O, spirohyd. ring), 157.8 (C=O, spirohyd. ring), 138.2 (CH, benzene), 136.1 (CH, benzene), 134.5 (CH, 1,2,3,4-tetrahydronaphthalene), 131.7 (CH, 1,2,3,4-tetrahydronaphthalene), 130.7 (CH, indole), 129.5 (CH, indole), 112.3 (CH, indole), 65.2 (spiro C-atom), 55.8 ($CH_3$), 39.6 ($CH_2$, 1,2,3,4-tetrahydronaphthalene), 39.4 ($CH_2$, 1,2,3,4-tetrahydronaphthalene), 29.5 ($CH_2$, 1,2,3,4-tetrahydronaphthalene), 27.6 ($CH_2$), 13.7 ($CH_3$) |
| **4h** | 192.6 (C=O), 171.3 (C=O, amide), 168.2 (C=O, spirohyd. ring), 158.4 (C=O, spirohyd. ring), 132.3 (CH, benzene), 130.1 (CH, benzene), 129.2 (CH, fluorene), 128.4 (CH, fluorene), 127.1 (CH, fluorene), 125.9 (CH, fluorene), 113.3 (CH, indole), 108.4 (CH, indole), 104.3 (CH, indole), 67.2 (spiro C-atom), 56.6 ($CH_3$), 29.4 ($CH_2$), 12.8 ($CH_3$) |
| | **$^{13}$C DEPT 135 (DMSO-$d_6$), $\delta$ / ppm** |
| **4a** | 138.1 (CH, indole), 136.1 (CH, indole), 134.5 (CH, benzene), 129.3 (CH, benzene), 113.3 (CH, indole), 55.8 ($CH_3$), 29.2 ($CH_2$), 25.8 ($CH_2$), 25.1 ($CH_2$), 13.7 ($CH_3$) |
| **4b** | 132.2 (CH, benzene), 139.6 (CH, benzene), 114.4 (CH, indole), 108.3 (CH, indole), 104.9 (CH, indole), 56.3 ($CH_3$), 33.1 ($CH_2$, cyclohexane), 29.2 ($CH_2$, cyclohexane), 26.9 ($CH_2$, cyclohexane), 19.8 ($CH_2$, cyclohexane), 13.4 ($CH_3$) |
| **4c** | 132.6 (CH, benzene), 129.6 (CH, benzene), 114.3 (CH, indole), 108.3 (CH, indole), 104.5 (CH, indole), 58.8 ($CH_3$), 35.4 (CH, cyclohexane), 30.8 ($CH_2$, cyclohexane), 27.2 ($CH_2$, cyclohexane), 25.3 ($CH_2$, cyclohexane), 20.5 (cyclohexane), 17.4 ($CH_2$), 13.2 ($CH_3$) |
| **4d** | 133.4 (CH, benzene), 130.6 (CH, benzene), 115.4 (CH, indole), 110.1 (CH, indole), 105.7 (CH, indole), 58.3 ($CH_3$), 31.6 ($CH_2$, cyclohexane), 29.4 ($CH_2$), 28.6 (CH, cyclohexane), 26.4 ($CH_2$, cyclohexane), 19.3 ($CH_3$), 14.1 ($CH_3$) |
| **4e** | 138.1 (CH, indole), 135.6 (CH, indole), 134.6 (CH, benzene), 131.6 (CH, benzene), 131.2 (CH, benzene), 130.6 (CH, benzene), 115.0 (CH, benzene), 111.7 (CH, indole), 55.8 ($CH_3$), 29.9 ($CH_2$), 25.3 ($CH_3$), 13.6 ($CH_3$) |
| **4f** | 132.3 (CH, benzene), 130.6 (CH, benzene), 129.5 (CH, indane), 126.3 (CH, indane), 115.5 (CH, indole), 108.3 (CH, indole), 106.1 (CH, indole), 55.8 ($CH_3$), 32.1 ($CH_2$, indane), 25.8 ($CH_2$, indane), 24.8 ($CH_2$, aliph.), 13.7 ($CH_3$) |

**Table 4 - continuation.**

| № | $^1$H NMR (DMSO-$d_6$), $\delta$ / ppm |
|---|---|
| **4g** | 138.2 (CH, benzene), 136.1 (CH, benzene), 134.5 (CH, 1,2,3,4-tetrahydronaphthalene), 131.7 (CH, 1,2,3,4-tetrahydronaphthalene), 130.7 (CH, indole), 129.5 (CH, indole), 112.3 (CH, indole), 55.8 ($CH_3$), 39.6 ($CH_2$, 1,2,3,4-tetrahydronaphthalene), 39.4 ($CH_2$, 1,2,3,tetrahydronaphthalene), 29.5 ($CH_2$, 1,2,3,4-tetrahydronaphthalene), 27.6 ($CH_2$), 13.7 ($CH_3$) |
| **4h** | 132.3 (CH, benzene), 130.1 (CH, benzene), 129.2 (CH, fluorene), 128.4 (CH, fluorene), 127.1 (CH, fluorene), 125.9 (CH, fluorene), 113.3 (CH, indole), 108.4 (CH, indole), 104.3 (CH, indole), 56.6 ($CH_3$), 29.4 ($CH_2$), 12.8 ($CH_3$) |

## CONCLUSIONS

Indomethacin derivatives with 3-amino-1,3-diazaspiro[4.4]nonane-2,4-dione, 3-amino-1,3-diazaspiro[4.5]decane-2,4-dione, 3-amino-6-methyl -1,3-diazaspiro[4.5]decane-2,4-dione, 3-amino-8-methyl-1,3-diazaspiro[4.5]decane-2,4-dione, 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione, 1-amino-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione, 1-amino-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro [imidazolidine-4,1'-naphthalene]-2,5-dione and 1'-aminospiro[fluorene-9,4'-imidazolidine]-2',5'-dione were successfully synthesized. The structures of the amides obtained were proven by physicochemical parameters, FTIR-ATR, Raman, $^1$H and $^{13}$C NMR spectroscopy.

## REFERENCES


1. E. Naydenova, N. Pencheva, J. Popova, N. Stoyanov, M. Lazarova, B. Aleksiev, *Il Farmaco*., 189 (2002).
2. P. Marinova, M. Marinov, Y. Feodorova, M. Kazakova, D. Georgiev, V. Lekova, P. Penchev, N. Stoyanov, *C. R. Acad. Bulg. Sci.*, **67**, 513 (2014).
3. M. Marinov, E. Naydenova, R. Prodanova, N. Markova, P. Marinova, I. Kostova, I. Valcheva, D. Draganova, M. Naydenov, P. Penchev, N. Stoyanov, *Agric. Sci.*, **19**, 117 (2016).
4. M. Marinov, I. Kostova, E. Naydenova, R. Prodanova, P. Marinova, P. Penchev, N. Stoyanov, *Univ. of Ruse "Angel Kanchev" Proc.*, **54** (10.2), 62 (2015).
5. H. T. Bucherer, V. A. Lieb, *J. Prakt. Chem.*, **141**, 5 (1934).
6. H. T. Nagasawa, J. A. Elberling, F. N. Shirota, *J. Med. Chem.*, **16**, 823 (1973).
7. M. Marinov, P. Marinova, N. Stoyanov, N. Markova, V. Enchev, *Acta Chim. Slov.*, **61**, 420 (2014).
8. R. Sarges, R. C. Schnur, J. L. Belletire, M. J. Peterson, *J. Med. Chem.*, **31**, 230 (1988).
9. R. A. Wildonger, M. B. Winstead, *J. Med. Chem.*, **10**, 981 (1967).
10. J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).


# СИНТЕЗ НА НОВИ ИНДОМЕТАЦИНОВИ ПРОИЗВОДНИ С 3-АМИНОСПИРОХИДАНТОИНИ И 3-АМИНО-5-МЕТИЛ-5-ФЕНИЛИМИДАЗОЛИДИН-2,4-ДИОН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(Резюме)

Статията представя синтез на нови амиди, основан на взаимодействието на серия от 3-аминоспирохидантоини и 3-амино-5-метил-5-фенилимидазолидин-2,4-дион с Индометацин. Целевите съединения бяха получени с цел разработване на нови продукти с противовъзпалителни свойства. Структурите на всички получени амиди бяха потвърдени чрез физикохимични параметри, FTIR-ATR, Раманова, $^1$H и $^{13}$C ЯМР спектроскопия.