DIRECTED SYNTHESIS OF POTENTIAL ANTITUMOR SUBSTANCES AMONG DERIVATIVES OF 3-MERCAPTO-4-(PYRROL-1-YL)-5-CYCLOHEXYL-1,2,4-TRIAZOLE(4H)

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Key words: 3-mercapto-1,2,4-triazole; pyrrole; derivatives; synthesis; antitumor action

Synthesis of the series of new 4-(1H-pyrrol-1-y1)-5-cyclohexyl-1,2,4-triazole(4H)-3-yl thioacetanilides from 4-aminocyclohexyl-1,2,4-triazole(4H)-3-yl thioacetanilides previously synthesized is described. The target products 3a-z have been obtained by Paal-Knorr pyrrole condensation of the initial aminocompounds 1 with 2,5-dimethoxytetrahydrofuran (2) in the acetic acid medium. The structure of the substances synthesized has been proven by elemental analysis and NMR spectra data. All compounds synthesized contain signals of the cyclohexane system protons as two multiplets in their NMR spectra at 2.39-2.33 ppm (methylene proton) and 1.76-1.29 ppm (cyclohexyl methylene groups protons). Unlike the starting compounds (1) the end products (3a-z) have no signal of 4-aminogroup proton as a singlet in the spectra at 5.87-5.92 ppm. Instead of it, signals of the pyrrole ring are present as two doublets at 7-20-7.17 and 6.32-6.29 ppm. Among activities being more probable for the substances synthesized due to preliminary PASS-prognosis were inhibition of MAO and some enzymes (Pa = 0.554-0.729). Compound (3w) was selected by the National Cancer Institute (NCI) for in vitro screening on different tumour cell lines. As result of this investigation we have noted that, unfortunately, substance 3w is not an effective inhibitor of tumour cells in the dose studied, in particular the growth percent for leukemia cells for more sensitive lines is 68.48 (RPMI-8226); 69.30 (HL-60(TB)); for non-small cell lung cancer – 63.06 (HOP-92); for melanoma – 47.82 (SK-MEL-5); 67.37 (UACC-62); for renal cancer – 56.66 (UO-31). Sensitivity of all cancer cell lines for the colon, CNS, ovarian, prostate and breast cancer was approximately at the control level.

ЦІЛЕСПРЯМОВАНИЙ СИНТЕЗ ПОТЕНЦІЙНИХ ПРОТИПУХЛИННИХ СУБСТАНЦІЙ В РЯДУ ПОХІДНИХ 3-МЕРКАПТО-4-(1Н-ПИРОЛ-1-ІЛ)-5-ЦИКЛОГЕКСИЛ-1,2,4-ТРИАЗОЛУ(4Н)

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Ключові слова: 3-меркапто-1,2,4-триазол; пиррол; производные; синтез; противоопухолевое действие

Описано синтез серії нейтральних 4-(1Н-пірол-1-іл)-5-циклогексил-1,2,4-триазолу(4Н)-3-ілтіоацетанілідів. Цільові речовини 3а-z отримані піррольною конденсацією Паал-Кнорра з вихідних аміносполук 1 та 2,5-диметокситетрагідрофурану (2) в середовищі оцтової кислоти. Структура синтезованих речовин доведена за допомогою елемент-аналізу і даних спектрів ЯМР

1H сигналы системы циклогексановых протонов в виде двух мультиплетов при 2,39-2,33 м.д. (метиновые протоны) и 1,76-1,13 м.д (протоны метиленовых групп циклогексила). Вместо этого присутствуют сигналы протонов пиррольного кольца в виде двух триплетов при 7-20-7.17 и 6.32-6.29 м.д. Среди видов активности, ко
In our present investigation we planned to obtain chemical compounds with another structure. We have taken into account that combination in one molecule of both 1,2,4-triazole and pyrrole fragments is promising for obtaining highly active substances with different kinds of the pharmacological activity. Thus, large series of compounds with a modified aminogroup are acylated [2], aryli dene [3-6], thiosemicarbazide [7, 8] derivatives and products of their cyclization [8, 9]. Mainly the substances synthesized have the antimicrobial activity.

For our investigation we planned to obtain chemical compounds with another structure. We have taken into account that combination in one molecule of both 1,2,4-triazole and pyrrole fragments is promising for obtaining highly active substances with different kinds of the pharmacological activity [10-12]. It has been also noted that these substances possess the antitumour activity.

The abovementioned facts were prerequisites for planning modification of compounds 1 previously synthesized into the corresponding pyrrole derivatives 3 (Scheme).

For carrying out this synthesis we considered different possible methods of transformation of the aminogroup into the pyrrole cycle. The simplest way, in our opinion, is to use Paal-Knorr pyrrole condensation of 2,5-dimethoxytetrahydrofuran with amines, which usually allows to synthesize N-substituted pyrroles under very mild reaction conditions in good to excellent yields [13].

So, the end products 3a-y (Table 1) have been obtained by Paal-Knorr pyrrole condensation of the initial aminocompounds 1 with 2,5-dimethoxytetrahydrofuran 2 in the acetic acid medium. These conditions allow us to obtain substances 3a-z with good yields and purity.

The structure of the substances synthesized has been proven by elemental analysis and NMR spectra data (Table 2).

All compounds synthesized contain signals of the cyclohexane system protons as two multiplets in their NMR spectra at 2.39-2.33 ppm (methyne proton) and 1.76-1.13 ppm (cyclohexyl methylene group pro- tones). Unlike the starting compounds (1) the end products (3a-z) have no signal of 4-aminogroup proton as a singlet in the spectra at 5.87-5.92 ppm [1]. Instead of it, signals of the pyrrole ring are present as two triplets at 7.20-7.17 and 6.32-6.29 ppm due to the presence of two pairs of magnet equivalent to methyne protons in the pyrrole structure. In some cases these signals overlap with aromatic protons of substituents signals interpreted in the correspondence with their intensity and multiplicity (Table 2). All spectra also contain singlets at 9.54-10.70 ppm due to presence of amide NH-protons.

Traditionally the preliminary prediction of the possible pharmacological activity by computer prognosis (PASS programme) [14] was used as the next step of our investigation for optimizing of the pharmacological screening.

Among activities, which are more probable for the substances synthesized, there is inhibition of MAO and some enzymes (Pa = 0.554-0.729). It should be noted that there is not enough information about structures like these ones.

Due to the prognosis and logical analysis data the substances synthesized have been examined as possible anticancer agents in vitro.

Of the compounds synthesized only one (3w) was selected by the National Cancer Institute (NCI) within the Developmental Therapeutic Programme (www.dtp.nci.nih.gov) for in vitro cell line screening. Anticancer assays were performed according to US NCI protocol [15]. The compound was evaluated in one dose in the primary anticancer assay towards approximately 60 cell lines (the concentration was 10−5 M). The human tumour cell lines represent all forms of cancer (such as non-small cell lung cancer,
Yields, melting points for the substances synthesized with the general formula of

![Structure diagram]

| Comp. | R | R' | R'' | Yield | Melting point °C |
|-------|---|----|-----|-------|------------------|
| 3a    | 3-Me | H  | H   | 73.4  | 114-6            |
| 3b    | 2-Et | H  | H   | 77.2  | 130-2            |
| 3c    | 4-Et | H  | H   | 81.1  | 134-6            |
| 3d    | 4-i-Pr | H | H   | 74.4  | 138-40           |
| 3e    | 2-OMe| H  | H   | 76.5  | 118-20           |
| 3f    | 3-Cl | H  | H   | 70.8  | 125-7            |
| 3g    | 4-Cl | H  | H   | 76.4  | 192-4            |
| 3h    | 3-F  | H  | H   | 77.8  | 148-50           |
| 3i    | 4-F  | H  | H   | 80.5  | 158-60           |
| 3j    | 3-CF₃| H  | H   | 72.9  | 127-9            |
| 3k    | 4-OEt| H  | H   | 73.3  | 203-5            |
| 3l    | 4-COOEt| H | H   | 75.7  | 218-20           |
| 3m    | 2-COOEt| H| H   | 77.6  | 135-7            |
| 3n    | 4-COOEt| H| H   | 77.5  | 84-6             |
| 3o    | 4-COMe| H | H   | 72.1  | 203-5            |
| 3p    | 2-Me | 3-Me| H   | 79.4  | 164-6            |
| 3q    | 2-Me | 5-Me| H   | 77.8  | 158-60           |
| 3r    | 2-Me | 5-Me| H   | 74.3  | 160-2            |
| 3s    | 3-Me | 5-Me| H   | 75.5  | 156-8            |
| 3t    | 2-Me | 5-Cl| H   | 76.2  | 133-5            |
| 3u    | 3-Me | 4-Br| H   | 73.1  | 160-2            |
| 3v    | 2-Me | 4-Me| 6-Me| 83.3  | 166-8            |
| 3w    | 2-OMe| 4-OMe| H | 77.6  | 116-8            |
| 3x    | 3-OMe| 4-OMe| H | 73.8  | 168-70           |
| 3y    | 2-Cl | 6-Cl| H   | 71.7  | 220-2            |

As result of this investigation we have noted that, unfortunately, substance 3w is not an effective inhibitor of tumour cells in the dose studied, in particular the growth percent for leukemia cells for more sensitive lines is 68.48 (RPMI-8226); 69.30 (HL-60(TB)); for non-small cell lung cancer – 63.06 (HOP-92); for melanoma – 47.82 (SK-MEL-5); 67.37 (UACC-62); for renal cancer – 56.66 (UO-31). Sensitivity of all cancer cell lines for the colon, CNS, ovarian, prostate and breast cancer was approximately at the control level.

The next step for investigation of these compounds will be the research of the CNS activity.

### Experimental Part

Melting points were determined by the open capillary tube. NMR ¹H spectra were recorded on a Bruker WM spectrometer (300 MHz); solvents – CDCl₃ or DMSO-d₆; chemical shifts were in ppm, TMS was used as an internal standard. The purity of the compounds synthesized was monitored by TLC. The elemental analysis data correspond to the calculated ones.

N-Phenyl-2-(5-cyclohexyl-4-(1H-1-pyrrolyl)-4H-1,2,4-triazole-3-ylthio)acetanilides (3a-y, Table 1) (a general procedure). To the solution of 0.005 mole

### Table 2

| Comp. | NH, s | 1H | Ar-H | Pyrrole 2,5, 2H, t | Pyrrole 3,4, 2H, t | S-CH₂, s, 2H | CH, 1H, m | 5xCH₃, (cyclohex), 10H, m | Other |
|-------|-------|----|------|-------------------|-------------------|------------|-----------|--------------------------|-------|
| 1     | 2     | 3  | 4    | 5                 | 6                 | 7          | 8         | 9                        |       |
| 3a    | 10.26 | 7.40, 2H,m, 7.19, 3H, m, 6.90, 1H, d | 6.31           | 4.10             | 2.36, 4H (+CH₃) | 1.76-1.16 | - | -                        |       |
| 3b    | 9.69  | 7.35, 1H, d, 7.18, 5H, m | 6.31 | 4.13             | 2.36             | 1.76-1.16 | - | 2.57, 2H, κ, CH₂CH₂, 1.11, 3H, κ, CH₂ |       |
| 3c    | 10.27 | 7.48, 2H, d, 7.19, 4H, m | 6.31 | 4.10             | 2.35             | 1.75-1.15, 13H, m(CH₃) | 2.51, 2H, κ, CH₂ |       |
| 3d    | 10.26 | 7.45, 2H, d, 7.17, 4H, m | 6.31 | 4.09             | 2.36             | 1.75-1.16, 16H, m (+2x CH₂) | 2.84, 1H, κ, CH₂ |       |
| 3e    | 9.67  | 7.97, 1H,d, 7.06, 1H, m, 6.91, 1H, t | 7.20 | 6.31             | 4.14             | 2.35             | 1.76-1.16 | - | 3.32, 3H, s, OCH₃ |       |
| 3f    | 10.62 | 7.09, 7.38-7.54, m, 4H | 7.18 | 6.30             | 4.11             | 2.39             | 1.72-1.17 | - | - |       |
| 3g    | 10.41 | 8.65, 1H,d, 7.95,1 H, d, 7.63, 1H, t, 7.20, 3H, m | 6.32 | 4.11             | 2.34             | 1.73-1.17, 13H (+CH₃) | 4.31, 2H, q, CH₂CH₃ |       |
| 3h    | 10.56 | 7.57, 1H, d, 7.36, 2H, m, 6.91, 1H,t | 7.20 | 6.32             | 4.13             | 2.36             | 1.75-1.15 | - | - |       |
| 3i    | 10.41 | 7.59, 2H,m, 7.19, 4H, m | 6.31 | 4.10             | 2.36             | 1.73-1.14 | - | - | - |       |
| 3j    | 10.71 | 8.06-7.44, 4H, m | 7.20 | 6.32             | 4.14             | 2.34             | 1.71-1.15 | - | - |       |
| 3k    | 10.18 | 7.45; 6.87, dd, 4H | 7.18 | 6.30             | 4.07             | 2.34             | 1.74-1.15, 13H (+CH₃) | 3.96, 2H, q, OCH₂ |       |
of N-phenyl-2-(4-amino-5-cyclohexyl-4H-1,2,4-triazol-3-ylthio)acetanilide 2 [1] in 40 ml acetic acid add 0.005 mole of 2,5-dimethoxytetrahydrofurane. Reflux the reaction mixture for about 1 h, cool and place into 200 ml water. Collect and dry the precipitate recrystallizing it from ethanol.

Conclusions

1. Series of new N-Phenyl-2-(5-cyclohexyl-4-(1H-1-pyrrolyl)-4H-1,2,4-triazole-3-ylthio)acetanilides has been synthesized started from the corresponding amino derivatives using Paal-Knorr condensation. The structure of the compounds synthesized has been proven by elemental analysis and NMR-spectra data.

2. Due to prognosis and logical analysis data the pharmacological screening have been planned for discovering of an antitumour and CNS-agent. It has been shown that in the in-vitro investigation one of the compounds synthesized has not a high potential in the cancer cell inhibition.

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Надійшла до редакції 05.02.2014 р.