The synthesis of 3,5-dibromo-2-chlorobenzoic acid hydrazides as potential antituberculous drugs

Antitubercular drugs are used for a number of decades. In each country where research is conducted strains of mycobacteria that are resistant to one or more drugs have been registered, and it causes tuberculosis with multi-drug resistance (MDR-TB). These strains of M. tuberculosis at least are not sensitive to isoniazid and rifampicin – two most powerful first-line antitubercular drugs. MDR-TB can be treated and cured using the second choice drugs. However, these treatment options are limited and require extensive chemotherapy (the treatment duration is up to two years) with drugs which are of high cost and toxicity. In some cases, a more dangerous drug resistance may develop. Tuberculosis with extensive drug resistance (EDR-TB) is more severe form of MDR-TB caused by bacteria that do not respond to the most effective antitubercular drugs of the second choice with which there are often no any further treatment options for patients. Therefore, the search and development of drugs with the antitubercular activity are important today.

**Aim.** To synthesize and study dibromo-substituted derivatives of ortho-chlorobenzoic acids as potential substances with the antitubercular action.

**Materials and methods.** Hydrazides of 3,5-dibromo-2-chlorobenzoic acid were obtained by two methods – by hydrazinolysis of acid chlorides of the corresponding acids (method 1) and by interaction of 3,5-dibromo-2-chlorobenzoic acid with hydrazines in the presence of carbonyldiimidazole (method 2).

**Results and discussion.** It has been found that the synthesis of hydrazides by method 2 allows obtaining the target compounds with a high yield.

**Conclusions.** According to the literature data the compounds synthesized are promising for the pharmacological screening on the antitubercular activity.

**Key words:** hydrazides; ortho-chlorobenzoic acid; pharmacological screening; antitubercular activity

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In recent years in Ukraine as in many other countries there is a catastrophic situation with tuberculosis, which occupies the first place among the infectious diseases with the highest lethal consequences [1].

According to the data of the World Health Organization (WHO) [2] primary tuberculosis is identified annually more than in 10 million people, and nearly 3 million die. Currently, the appearance of the drug-resistant strains of Mycobacterium tuberculosis is the main problem in the treatment of tuberculosis [3, 4].

Therefore, the urgent task of medicinal chemistry is the search and development of more effective antitubercular drugs.

Among derivatives of ortho-chlorobenzoic acids compounds exhibiting the highest antimicrobial activity were found earlier [4–6]; therefore, it was decided to check this group of compounds for sensitivity to mycobacteria. The aim of the work is the synthesis of a new group of 3,5-dibromo-2-chlorobenzoic acid hydrazides as potential antitubercular drugs.

Materials and methods

All solvents and reagents were obtained from commercial sources. The 1H-NMR-spectra were recorded on a “Varian Mercury VX-200” spectrophotometer at 200 MHz with DMSO-d6, as a solvent, and TMS as an internal standard. Thin-layer chromatography (TLC) was performed on aluminum plates coated with silica gel (Merck, Kiesgel 60 F-254). The melting point was determined on the Kofler plate.

The IR-spectra were recorded on a “Specord M-80” spectrophotometer using potassium bromide tablets with the concentration of 1 % and on a “Testcan FTIR 8000 series” IR-spectrophotometer with Fourier transformer.

The general method for the synthesis of 3,5-dibromo-2-chlorobenzoic acid hydrazides (3-10)

**Method 1.** To 1 g (0.01 Mol) of 3,5-dibromo-2-chlorobenzoic acid (1) add 5 ml of thionyl chloride and heat for 3–4 h. Remove the excess of thionyl chloride by vacuum distillation. Use the precipitate of acid chloride (2) formed in further synthesis without additional purification.

To the solution of 0.01 Mol of the corresponding hydrazine in freshly distilled dioxane add 1.22 g (0.01 Mol) acid chloride of 3,5-dibromo-2-chlorobenzoic acid (2) when cooling, and heat at the temperature of 80 °C for 2 h. Dilute the reaction mixture with water; filter the precipitate formed and dry. Crystallize from aqueous ethanol.

**Method 2.** To 1 g (0.01 Mol) of 3,5-dibromo-2-chlorobenzoic acid (1) in freshly distilled dioxane add 0.52 g (0.2 Mol) of carbonyldimidazole and mix until emission of CO2 bubbles stops. In 45 min add 0.1 Mol of the corresponding hydrazide to the resulting transparent solution and boil for 2 h. After cooling dilute the reaction mixture with water; filter the precipitate formed, and dry. Crystallize from aqueous ethanol.

Results and discussion

The synthesis of 3,5-dibromo-2-chlorobenzoic acid hydrazides (3-10) was performed by two methods, namely – by hydrazinolysis of 3,5-dibromo-2-chlorobenzoic acid chloride (2) (method 1) and by interaction of 3,5-dibromo-2-chlorobenzoic acid (1) with hydrazines in the presence of the activator of the carboxyl group of carbonyldimidazole (method 2) (Scheme).
Method 2 is more practical and allows obtaining the target compounds with a high yield (Tab. 1). Hydrazides of 3,5-dibromo-2-chlorobenzoic acid (3-10) obtained are white crystalline substances, readily soluble in ethanol, dioxane, DMF, almost insoluble in water.

The structure of the compounds (3-10) synthesized was confirmed by the data of elemental analysis, IR- and NMR-spectroscopy. The spectral characteristics of hydrazides of 2-chloro-3,5-dibromo-benzoic acids (3-10) are presented in Table 2.

### Table 1

| Compound | R     | Yield*, % | M. p. | Found,% | Empirical formula | Calculated,% | R**<sup>**</sup> |
|----------|-------|-----------|-------|---------|-------------------|--------------|-----------------|
| 3        | H     | 67/71     | 215-217 | 38.90   | C<sub>14</sub>H<sub>16</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>3</sub> | 38.88 | 2.10 0.29 |
| 4        | 4-CH<sub>3</sub> | 71/78 | 225-227 | 40.34   | C<sub>15</sub>H<sub>18</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 40.35 | 2.48 0.34 |
| 5        | 4-OCH<sub>3</sub> | 58/64 | 241-243 | 38.94   | C<sub>15</sub>H<sub>18</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 38.95 | 2.10 0.38 |
| 6        | 4-C<sub>H</sub><sub>2</sub> | 60/65 | 251-253 | 41.72   | C<sub>15</sub>H<sub>18</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 41.73 | 2.85 0.26 |
| 7        | 4-OC<sub>H</sub><sub>3</sub> | 55/59 | 239-241 | 40.35   | C<sub>15</sub>H<sub>18</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 40.33 | 2.75 0.30 |
| 8        | 4-Cl  | 56/63     | 221-223 | 36.03   | C<sub>14</sub>H<sub>16</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 36.01 | 2.73 0.35 |
| 9        | 4-Br  | 62/65     | 243-245 | 32.89   | C<sub>14</sub>H<sub>16</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 32.88 | 1.58 0.36 |
| 10       |       | 65/70     | 237-239 | 36.01   | C<sub>13</sub>H<sub>12</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>2</sub> | 36.02 | 1.86 0.38 |

Notes: * – Numerator – yield by method 1, denominator – yield by method 2; ** – The R<sub>f</sub> values are given in the acetone-hexane system (1 : 1.5)

The structure of the compounds (3-10) synthesized was confirmed by the data of elemental analysis, IR- and NMR-spectroscopy. The spectral characteristics of hydrazides of 2-chloro-3,5-dibromo-benzoic acids (3-10) are presented in Table 2.

### Table 2

| Compound | Absorption frequency, cm<sup>-1</sup> | Chemical shifts, ppm |
|----------|--------------------------------------|----------------------|
|          | ν<sub>NH</sub> | ν<sub>amide</sub> | ν<sub>C=O</sub> | ν<sub>amide</sub> | ν<sub>C</sub> | ν<sub>NH</sub> | ν<sub>Cl</sub> | ν<sub>Br</sub> | CONH | CONNH<sub>2</sub> |
| 3        | 3366 | 3233 | 1696 | 1583 | 1596 | 1299 | 812 | 658 | 8.95 | 3.75 |
| 4        | 3345 | 3263 | 1690 | 1652 | 1583 | 1607 | 1308 | 812 | 660 | 8.75 | 3.82 |
| 5        | 3419 | 3334 | 1691 | 1646 | 1583 | 1617 | – | 812 | 788 | 598 | 9.25 | 4.25 |
| 6        | 3232 | (wide) | 1691 | 1652 | 1583 | 1600 | 1308 | 812 | 507 | 8.82 | 4.32 |
| 7        | 3242 | (wide) | 1690 | 1654 | 1585 | 1600 | 1312 | 810 | 510 | 8.92 | 3.92 |
| 8        | 3240 | (wide) | 1689 | 1649 | 1576 | 1596 | 1310 | 812 | 507 | 8.74 | 4.32 |
| 9        | 3330 | (wide) | 1695 | 1653 | 1580 | 1610 | 1315 | 807 | 600 | 9.35 | 4.42 |
| 10       | 3350 |       | 1575 | 1607 | 1305 | 817 | 510 | 9.45 | 3.95 |
and PMR-spectroscopy, and individuality was proven by the method of thin layer chromatography (Tab. 1, 2).

In the IR-spectra of 3,5-dibromo-2-chlorobenzoic acid hydrazides (3-10) the characteristic presence of two bands with the widened contour in the region of 3292-3204 cm\(^{-1}\) confirms the NH-NH group, while the bands at 810 cm\(^{-1}\) and 640 cm\(^{-1}\) indicate the presence of the covalent-bonded halogens in the molecule (\(\nu_{C-Cl}\) and \(\nu_{C-Br}\)). The band of stretching vibrations of the carbonyl group in the spectrum was interpreted in the area of 1630 cm\(^{-1}\).

In the 1H-NMR spectra of 2-chloro-3,5-dibromobenzoic acid hydrazides the signals of protons of the aromatic system at 7.70-7.32 ppm, as well as the signals of the protons of the hydrazide group at 8.77-9.55 ppm (CONH) and at 3.75-4.45 ppm (CONHNH\(_2\)) were detected.

According to the literature data [7-10] all compounds can exhibit a high antitubercular activity taking into account their chemical structure.

**CONCLUSIONS**

1. A series of new hydrazides of 3,5-dibromo-2-chlorobenzoic acid has been synthesized.

2. The compounds synthesized are promising for the pharmacological screening on the antitubercular activity.

**Conflict of Interests**: authors have no conflict of interests to declare.

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