The synthesis of the substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles as promising pharmaceutical agents with the antifungal action

One of the promising directions for development of antifungal agents is the synthesis of new chemical compounds that can be used as active pharmaceutical ingredients to produce highly effective drugs for the treatment of fungal infestations.

**Aim.** To create the combinatorial library of 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles derivatives for the total antimicrobial screening to search for new substances with the antifungal activity, and study their spectral properties.

**Materials and methods.** The methods of organic synthesis, instrumental methods of organic compound analysis were used.

**Results and discussion.** The design of the library of small molecules based on the core structure of 5-aminopyrazole has been developed. The useful and effective synthetic scheme for preparing N1-substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles and their acylation products has been proposed and approved. This approach consists of cyclization of substituted alkyl/arylsulfonamides under the action of hydrazine hydrate with further acylation and acylation of 5-aminopyrazoles obtained. The total yield of the target products is 50-85 %. The structure of all compounds synthesized has been confirmed using elemental analysis, 1H NMR- and chromatomass spectrometric methods.

**Conclusions.** The design and the synthetic scheme for obtaining 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles and products of their chemical modification have been proposed. The compounds synthesized are of certain interest as potential pharmaceutical agents and can be used to develop new antifungal agents.

**Key words:** pyrazole; combinatorial library; synthesis; pharmaceutical agents
The global spread of fungal infections trend tends to increase [1-6]. This is directly due to the high mobility of the population and because of the increasing proportion of the elderly people in its structure. It can be considered as a constant source of infections. Today more than 400 species of fungi that can cause disease in humans are known. The spectrum of potential fungal pathogens continues to expand, but the dominant clinical value remains Candida and Aspergillus spp [3]. The mortality rate for some forms of Candida infection is 38-75 %, and for invasive aspergillosis this index exceeds 95 % [3]. It should be noted that the effectiveness of the existing pharmaceutical market of antifungal drugs decreases in proportion to the increase in their use due to the spread of resistant clinical strains and is characteristic of all antimicrobial agents.

One of the promising directions for development of antifungal agents is the synthesis of new chemical compounds that can be used as active pharmaceutical ingredients to produce highly effective drugs for the treatment of fungal infestations. Modern developments in the field of chemistry of antifungal agents are new triazoles [7-9], echinocandines [9, 10], imidazoles [10] and pyrazoles [11-16].

Materials and methods

All solvents and reagents were obtained from the commercial sources. Elemental analysis was performed on a Euro EA-3000 apparatus. Melting points were obtained on a Buchi B-520 device. The NMR-spectra were recorded with a Bruker 170 Avance 500 spectrometer at 500 MHz (DMSO-d6); TMS was used as an internal standard; chemical shifts were reported in ppm. LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (215 and 254 nm) and using the C18 column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95 : 5, v/v); the linear gradient was used at the flow rate of 0.15 mL/min and the analysis cycle time of 25 min. According to LC/MS data all compounds synthesized have purity > 95 %. The TLC was performed on aluminum plates covered with silica gel (Merck, Kiesgel 60 F-254).

The substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles (3) were obtained according to the methods previously reported [17].

The general procedure for N’-alkylation 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles. To the mixture of 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles (1 mmol) and K2CO3 (3 mmol) in DMF (10 mL) add the appropriate halide (1.2 mmol). Stir the reaction mixture at 80 °C for 1 h and then cooled to the room temperature. Add water (60 mL), filter the precipitate formed, then crystallize from the mixture of ethanol/DMF (1 : 1).

The general procedure for preparation of 5-(N-diacylamino)-derivatives N’-substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles. Reflux the mixture of N’-alkylation 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazole (1.5 mmol) and the corresponding chloroanhydride of carboxylic acid (1.7 mmol) in dioxane (10 mL) for 2 h, then cool the mixture to the room temperature and dilute with water (10 mL). Filter the precipitate, wash with water (2 × 5 mL) and methyl alcohol (7 mL).

The general procedure for preparation of 5-(N,N-diacylamino)-derivatives of N’-substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles. Reflux the mixture of N’-alkylation 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazole (1.5 Mol) and the corresponding anhydride (1.7 Mol) in dioxane (10 mL) for 2 h, then cool the mixture to the room temperature and dilute with water (10 mL). Filter the precipitate and wash with water (2 × 5 mL).

Results and discussion

Recently, we described the synthesis and the antimicrobial activity of some 4-arylsulfonyl derivatives of 5-amino pyrazoles and proposed some directions of modification of the pyrazole system for enhancing their action [17]. In this paper the synthetic scheme was proposed. It allows generating structures that combine several fragments characteristic of compounds with the antifungal action. Based on the analysis using the PASS (Prediction of Activity Spectra for Substances) computer program [18] 5-aminopyrazole with the substituted sulfonyl-group in position 4 and with branched radicals in position 1 was chosen as a basic structure.

Our approach is in application of the useful and effective synthetic scheme for preparation of N’-substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles starting from substituted sulfoacetanilides shown in Tab. 1. The first stage of the reaction is the cyclization of the...
corresponding alkyl-1-[1-2] or arylsulfoacetonitriles 1-[3-6] with CS\textsubscript{2} and alkylhalogenides 2-[1-3] (Tab. 2) in dioxane for introduction of the thioalkyl moiety with the following cyclization under the action of hydrazine hydrate (Scheme). The reaction with hydrazine hydrate was carried out in propanole-2 in the presence of triethylamine traces while boiling for 3 h and led to target 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles 3-[1-12] in a good yield of 67-89\% via S,S-diacetales as intermediates. Formation of the pyrazole cycle for compounds 3 was confirmed by the presence of singlet signals of NH protons at δ 11.97…12.00 ppm and signals of the amino group at δ 5.80…6.17 ppm.

For the synthesis of N\textsubscript{1}-substituted products 5-[1-146] the alkylation reaction was used. The interaction was carried out by conventional treatment with alkyl halides 2-[1-18] and chloroacetamides 4-[1-11] (Tab. 3) in dimethylformamide (DMF) in the presence of K\textsubscript{2}CO\textsubscript{3} at 80 °C. The yields of the target products were 61-91\% depending on the nature of the reagent. The absence of signals of NH protons of \textsuperscript{1}H NMR-spectra of products 5 indicates the N\textsubscript{1}-alkylation reaction. And the presence of cross-coupling between the CH\textsubscript{2} protons of the acetamide fragment (approximately at 4.80 ppm) and the amino group (approximately at 6.50 ppm) in the NOESY spectra of target products unambiguously confirms the direction of the reaction.

Some of 5-aminopyrazoles 5 obtained were converted in high yields (70-90\%) to the corresponding N-acylamino derivatives 7-[1-54] using chloroanhydrides of carboxylic acids 6-[1-3] (Tab. 4). The use of the ex-

### Table 1

| Entry | Compound | R\textsuperscript{1} |
|-------|----------|---------------------|
| 1     | 1[1]     | Methyl              |
| 2     | 1[2]     | Ethyl               |
| 3     | 1[3]     | Phenyl              |
| 4     | 1[4]     | 4-methylphenyl      |
| 5     | 1[5]     | 4-chlorophenyl       |
| 6     | 1[6]     | 4-methoxyphenyl     |

### Table 2

| Entry | Compound | R\textsuperscript{2} and R\textsuperscript{3} |
|-------|----------|---------------------------------------------|
| 1     | 2[1]     | Methyl                                      |
| 2     | 2[2]     | Ethyl                                       |
| 3     | 2[3]     | n-propyl                                    |
| 4     | 2[4]     | i-propyl                                    |
| 5     | 2[5]     | Benzyl                                      |
| 6     | 2[6]     | 2-methylbenzyl                              |
| 7     | 2[7]     | 3-methylbenzyl                              |
| 8     | 2[8]     | 4-methylbenzyl                              |
| 9     | 2[9]     | 2,4-dimethylbenzyl                         |
| 10    | 2[10]    | 2,5-dimethylbenzyl                         |
| 11    | 2[11]    | 3-methoxybenzyl                            |
| 12    | 2[12]    | 2-fluorobenzyl                              |
| 13    | 2[13]    | 4-fluorobenzyl                              |
| 14    | 2[14]    | 2-chlorobenzyl                              |
| 15    | 2[15]    | 3-chlorobenzyl                              |
| 16    | 2[16]    | 4-chlorobenzyl                              |
| 17    | 2[17]    | 4-bromobenzyl                               |
| 18    | 2[18]    | 4-ethenylbenzyl                            |

### Table 3

| Entry | Compound | R\textsuperscript{1} |
|-------|----------|---------------------|
| 1     | 4[1]     | phenyl              |
| 2     | 4[2]     | 2-ethylphenyl       |
| 3     | 4[3]     | 2,5-dimethylphenyl  |
| 4     | 4[4]     | 3,4-dimethylphenyl  |
| 5     | 4[5]     | 3,5-dimethylphenyl  |
| 6     | 4[6]     | 4-methoxyphenyl     |
| 7     | 4[7]     | 2,4-dimethoxyphenyl |
| 8     | 4[8]     | 4-chlorophenyl       |
| 9     | 4[9]     | 4-methoxyphenyl     |
| 10    | 4[10]    | 2,4-difluorophenyl  |
| 11    | 4[11]    | 2-fluoro-4-bromophenyl |

Scheme. Preparation of substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles.
cess anhydride of carboxylic acids \(8^{[1-2]}\) in this interaction led to \(N,N\)-diacylamino derivatives \(9^{[1-28]}\). In the case of monoacylamino derivatives \(7\) in the \(^1H\ NMR\)-spectra the signal of NH-proton was observed near \(10.20 \ldots 10.30\) ppm. In the case of diacylamino derivatives \(9\) the signal of NH-proton was absent, and signals of protons of acyl fragments were observed at \(0.80 \ldots 0.85\) ppm and \(2.35 \ldots 2.55\) ppm with a double integral intensity.

The structure of all compounds obtained was confirmed using \(^1H\ NMR\)- and chromato-mass spectrometric methods.

For illustration, 8 arbitrary compounds synthesized according to Scheme are shown in Fig.

One can assume that the compounds synthesized have a broad potential of the pharmacological activity, especially as antifungal agents; and development of methods of the synthesis and the study of pharmacological properties of these compounds are important directions of pharmaceutical and medical chemistry.

5-Amino-4-phenylsulfonyl-3-methylthiopyrazole \(3^{[3]}\). Yield – \(87\) %. M. p. – \(188\) °C; \(^1H\ NMR\) \(\delta: 2.43\) (s, 1H, \(\text{SCH}_3\)), \(6.09\) (s, 2H, \(\text{NH}_2\)), \(7.56\) (m, 3H, Ar-H), \(7.89\) (d, 2H, Ar-H), \(11.97\) (br. s, 1H, NH).

5-Amino-4-(4′-chlorophenylsulfonyl)-3-ethylthiopyrazole \(3^{[8]}\). Yield – \(92\) %. M. p. – \(212\-13\) °C; \(^1H\ NMR\) \(\delta: 1.12\) (t, 3H, \(\text{CH}_3\)), \(2.87\) (q, 2H, \(\text{CH}_2\)), \(6.17\) (s, 2H, \(\text{NH}_2\)), \(7.64\) (d, 2H, Ar-H), \(7.89\) (d, 2H, Ar-H), \(12.00\) (s, 1H, NH).

5-(3,4-Dimethylphenyl)-(5-amino-4-methylsulfonyl-3-methylthiopyrazol-1-yl)acetamide \(5^{[36]}\). Yield – \(74\) %. M. p. – \(234\-36\) °C; \(^1H\ NMR\) \(\delta: 1.12\) (t, 3H, \(\text{CH}_3\)), \(2.33\) (s, 3H, \(\text{SCH}_3\)), \(4.74\) (s, 2H, \(\text{CH}_2\)), \(6.23\) (s, 2H, \(\text{NH}_2\)), \(7.03\) (d, 1H, Ar-H), \(7.22\) (d, 1H, Ar-H), \(7.31\) (s, 1H, Ar-H), \(10.10\) (s, 1H, NH); \(m/z\): \(369\) [M+].

N-(2-Fluoro-4-bromophenyl)-(5-amino-4-phenylsulfonyl-3-methylthiopyrazol-1-yl)acetamide \(5^{[63]}\). Yield – \(66\) %. M. p. – \(261\-62\) °C; \(^1H\ NMR\) \(\delta: 2.27\) (s, 3H, \(\text{SCH}_3\)), \(4.83\) (s, 2H, \(\text{CH}_2\)), \(6.50\) (s, 2H, \(\text{NH}_2\)), \(7.36\) (dd, 1H, Ar-H), \(7.61\) (s+m, 4H, Ar-H), \(7.93\) (m, 3H, Ar-H), \(10.15\) (s, 1H, NH).

1-Benzyl-5-(\(N\)-acetylamino)-4-phenylsulfonyl-3-methylthiopyrazole \(7^{[2]}\). Yield – \(71\) %. M. p. – \(253\-55\) °C; \(^1H\ NMR\) \(\delta: 2.08\) (t, 3H, \(\text{CH}_3\)), \(2.32\) (s, 3H, \(\text{SCH}_3\)), \(5.08\)

| Entry | Compound R4 | \(R^4\) |
|-------|-------------|--------|
| 1     | \(6^{[1]}\) | Methyl |
| 2     | \(6^{[2]}\) | Ethyl  |
| 3     | \(6^{[3]}\) | Propyl |

Table 4

Acid chloroanhydrides \(6^{[1-3]}\) and Acid anhydrides \(8^{[1-2]}\) 

![Examples of substituted 5-amino-3-alkylthiopyrazoles synthesized](image-url)
phenylsulfonyl-3-methylthiopyrazole 9
.

(1, 2, 3H, CH

3

, 3H, SCH

3

), 2.20 (t, 3H, CH

2

), 2.22 (m, 2H, CH

2

), 2.44 (s, 3H, SCH

3

), 5.12 (s, 2H, CH

2

), 6.84 (s, 1H, Ar-H), 7.04 (s, 2H, Ar-H), 7.57 (d, 2H, Ar-H), 7.74 (m, 3H, Ar-H), 10.20 (s, 1H, NH); m/z: 444 [M

+ ].

1-(4-Benzyl-5-(N,N-dipropionylamino)-4-phenylsulfonyl-3-methylthiopyrazole 9/5), Yield – 55 %.

CONCLUSIONS

The method of the synthesis of series of new substituted 5-amino-3-alkylthiopyrazoles has been developed.

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

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