PRODUCTS OF INTERACTION OF SUBSTITUTED 5-AMINOPYRAZOLES WITH \( \alpha \)-HALOKETONES AS POTENTIAL PHARMACEUTICAL AGENTS

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1. Introduction
Substituted pyrazoles are one of the most important heterocyclic compounds, which are mentioned and emphasized in the biological, medical and technical fields. The structural fragment pyrazole as monocyte, and as segment of polynuclear systems is part of many essential compounds of natural or synthetic origin. For example, L-α-amino-b-(pyrazolyl-N)-propanoic acid, isolated from Citrullus vulgaris, demonstrates antidiabetic effects; withasomnine from Withania somnifera demonstrates analgesic, anti-inflammatory effects, appears depressant to CNS, circulatory system; pyrazofurin functions as antitumor and antiviral agent [1]. Pyrazoles showed potent antibacterial and antifungal activity against different strains including gram-positive strains (Staphylococcus aureus [2], Streptococcus mutans [2], Bacillus subtilis [3]), gram-negative strains (Salmonella typhimurium [2] and Pseudomonas aeruginosa [4]) and fungus (Candida albicans [5], Gaeumannomyces graminis var. graminis [6], Aspergillus niger [3]). Pyrazoles are known to possess numerous chemical and biological activities such as anti inflammatory [7], antiproliferative [8], antiepileptic [9].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues
The search for new methods of synthesis of biologically active substances [10].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers
The important ability of functionally substituted pyrazoles to enter into a variety of heterocyclic reactions, as it includes the formation of binuclear compounds, which represent the most trending class of substances for biological screening [11]. For example, synthesized N\(^2\)-substituted 5-amino-4-arylsulfonyl-3-phenylamino-pyrazoles are of certain interest as potential pharmaceutical agents and can be used to develop new antifungal agents against Candida albicans [12]. 5-(N,N-Diacylamino)-derivatives of N\(^2\)-substituted 4-alkyl/arylsulfonyl-5-amino-3-alkylthiopyrazoles are of great interest for further biological screening in order to find substances with the properties associated with the action on fungal cells among them [13].

4. The field of research considering the general problem, which is described in the article
Taking into account the considerable pharmacological potential of substituted aminooazoles, we drew attention to the development of approaches to the synthesis of poly substituted imidazo[1,2-b]pyrazoles, in particular the interaction of 5-aminopyrazoles with \( \alpha \)-halogenocetones.

5. Formulation of tasks of article
Optimization of reaction of substituted 5-aminopyrazoles with \( \alpha \)-haloketones to form annealed 2,6,7-trisubstituted 1H-imidazo[1,2-b]pyrazoles.

6. Presentation of the main research material (methods and objects) with the justification of the results
6.1. Methods and objects
All reagents and solvents were obtained from the commercial sources. Melting points were obtained by a Buchi B-520 device. The NMR-spectra were recorded with a Bruker 170 Avance spectrometer at 200 MHz, 500 MHz (DMSO-d6); TMS was used as an internal standard; chemical shifts were reported in ppm. The TLC
was performed on the aluminum plates covered with a silica gel (Merck, Kiesel 60 F-254).

5-Amino-4-phenylsulfonyl-3-methylthiopyrazole 1a and 5-Amino-4-(4'-methoxy phenyl)sulfonyl-3-methylthiopyrazole 1b were obtained according to the methods previously reported [11, 13].

The general methods for preparation of imidazo[1,2-b]pyrazoles 4 a-c. Method A. To a flask with 4 ml DMF add 5-amino-4-phenylsulfonyl-3-methylthiopyrazole (0.001 mmol, 0.27 g), chloroacetone (0.0011 mmol, 0.12 g), and potassium carbonate (0.004 mmol, 0.55 g). The mixture is stirred at 50 °C for 3 hours and diluted with water (10 ml). The oily precipitate, which was formed, washed with water (5 ml) 2–3 times and separated. Then to the crude butter precipitate add 10 ml of ethanol and 0.5 ml of concentrated hydrochloric acid. The mixture is boiled for 2–4 hours and cooled. The formed precipitate was filtered, washed with ethanol, transferred into an aqueous solution of sodium bicarbonate, mix thoroughly. The precipitate is filtered, dried.

Method B. To a flask with 15 ml propanol-1 add 5-amino-4-phenylsulfonyl-3-methylthiopyrazole (0.001 mmol, 0.27 g), chloroacetone (0.0013 mmol, 0.12 g). The mixture is boiled for 8–9 hours and cooled. The formed precipitate was filtered, transferred into an aqueous solution of sodium bicarbonate, mix thoroughly. The precipitate is filtered, dried.

The procedure for preparation of N-phenyl-(2-(4'-methylphenyl)-6-methylthio-7-(4'-methoxyphenyl)sulfonyl-1H-imidazo[1,2-b]pyrazole-1-yl)acetamide 5c was obtained according to the methods previously reported [13].

6.2. Results and discussion

In previous studies, we described the interaction of 5-amino-4-aryl sulfonyl-3-alkylthiopyrazoles with (N-aryl)chloroacetamides, which leads to the formation only N'alkylation products [11]. It should be noted that during the reaction, we did not observe the impurities of the regionisomeric product or products of NH₂-alkylation. This is evidenced by the results of TLS LCMS and by the data of ¹H NMR spectroscopy (the absence of a double set of signals, signals of a free amino group, as well as the successful course of the reaction of its acylation) [13].

In this paper, we examined the interaction of 5-amino-4-aryl sulfonyl-3-methylthiopyrazoles with chloroacetone, phenacyl bromides and a-chlorocyclohexane.

Fig. 1. Preparation of substituted 1H-imidazo[1,2-b]pyrazoles

The use of the second method, the boiling of the starting reagents in propanol-1, allowed to slightly increase the yields of the final products and to exclude the stage of work with the oily product, although sometimes
the reaction did not reach the end and it was difficult to get rid of the original aminopyrazole.

Characteristic signals of the CH-proton of the pyrazole cycle in the spectra of products 4a-c are found at δ 8.19–8.32 ppm and NH-proton of imidazole fragment (δ 12.61–12.75 ppm), and a corresponding set of aromatic protons and substituent signals. Free cyclic amino group is subject to alkylation. Thus, using a standard synthetic procedure, in reaction 4c with (N-phenyl)chloroacetamide, compound 5c was received.

5-Amino-4-phenylsulfonyl-3-methylthiopyrazole 1a. Yield 87 %: M. p. 188 °C; 1H NMR δ: 2.43 (s, 1H, SCh2), 6.09 (s, 2H, NH2), 7.56 (m, 3H, Ar-H), 7.89 (d, 2H, Ar-H), 11.97 (br.s, 1H, NH).

5-Amino-4-(4'-methoxyphenyl)sulfonyl-3-methylthiopyrazole 1b. Yield 91 %: M. p. 213 – 15 °C; 1H NMR δ: 2.47 (s, 1H, SCh2), 3.75 (s, 3H, OCH3), 6.12 (s, 2H, NH2), 7.36 (d, 2H, Ar-H), 7.93 (d, 2H, Ar-H), 12.07 (br.s, 1H, NH).

2-Methyl-6-methylthio-7-phenylsulfonyl-1H-imidazo[1,2-b]pyrazole 4a. Yield 26 % (Method A), 34 % (Method B); M. p. 214 – 16 °C; 1H NMR δ: 2.08 (s, 3H, CH3), 2.28 (s, 3H, SCh2), 7.60 (m, 3H, Ar-H), 7.90 (dd, 2H, Ar-H), 8.03 (s, 1H, CH), 12.27 (br.s, 1H, NH).

2-(4'-Chlorophenyl)-6-methylthio-7-phenylsulfonyl-1H-imidazo[1,2-b]pyrazole 4b. Yield 45 % (Method B); M. p. 187 – 89 °C; 1H NMR δ: 2.49 (s, 3H, SCh2), 7.54 (m, 5H, Ar-H), 7.86 (d, 2H, Ar-H), 8.02 (m, 2H, Ar-H), 8.32 (s, 1H, CH), 12.75 (s, 1H, NH).

7. Findings from the research and prospects of further development of this area

1. The reaction of substituted 5-aminopyrazoles with α-haloketones to form annealed 2,6,7-trisubstituted 1H-imidazo[1,2-b]pyrazoles was optimized.

2. The structure of synthesized substances was confirmed by the complex of modern spectral analysis methods.

3. The obtained 2-substituted 6-methylthio-7-phenylsulfonyl-1H-imidazo[1,2-b]pyrazoles are promising enough for the further biological research.

References


QUALITY ASSESSMENT AND STABILITY STUDY OF COMPOUNDED FUROSEMIDE SYRUP

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Abstract: Dispersed solid dosage forms are often used as active pharmaceutical ingredients in preparing medicines. One of the main tasks facing the pharmacist is the affirmation of the stability of medicinal forms, which is particularly critical in the context of current drug therapy. The study focuses on the assessment of the quality and stability of compounded furosemide syrups, which are prepared in pharmacies using components of various origins and stored for different periods. The aim of the investigation was to study the physical, chemical, and microbiological stability of the obtained preparations. Material and methods: The study was conducted over a period of 30 days. The quality of the syrups was evaluated and compared to the specifications for the original medicinal substances. Results: The stability of the formulated medicinal preparations was studied using thin-layer chromatography and visual inspection. The results showed that the furosemide syrups met the required standards and did not show any significant changes in quality parameters. Conclusions: The study demonstrated that compounded furosemide syrups are stable and meet the required quality standards, providing a reliable source for maintaining patient therapy. DOI: 10.15587/2519-4852.2017.113517

1. Introduction

The need for compounded preparations as a panacea for patient-specific dosing, logistical and therapeutical quagmires in pharmacotherapy is usually faced with the challenge of affirming their stability. Dispersed solid dosage forms are often used as active pharmaceutical...