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SYNTHESIS OF (3-S-SUBSTITUTED)-1*H*-1,2,4-TRIAZOLYL-PYRIMIDINE DERIVATIVES

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In the plan of search for new chemical means of plant protection in a series of nonfused bi- and triheterocyclic systems, the synthesis of starting pyrimidinyl-trimethyl-ammonium chloride was carried out. For this under the action of 4-chloro-6-methyl-2-(methylthio)pyrimidine with trimethylamine the corresponding trimethyl-(6-methyl-2-methylthio-pyrimidin-4-yl)-ammonium chloride was synthesized. The further reaction of the latter with 3-S-substiuted 1H-1,2,4-triazoles afforded a series of compounds with combination of 1,2,4-triazole and pyrimidine cycles in the same molecule. To introduce a third heterocycle (pyrazole ring) in the molecule, the same salt was treated with 3-((1,3,5-trimethyl-1H-pyrazol-4-yl)thio)-1H-1,2,4-triazole. Currently, all synthesized compounds undergo laboratory-vegetation testing to discover among them the pesticide and growth-regulating properties.

Key words: *4-chloro-6-methyl-2-(methylthio)pyrimidine, 3-S-substiuted 1H-1,2,4-triazoles, pyrazole, heterocyclization, tautomeria.*

Introduction

Pyrimidine and 1,2,4-triazole derivatives exhibit a wide spectrum of biological activity and have application not only in medical practice but also in agriculture as chemical means of plant protection. Some of the nucleic acids, vitamins, antibiotics (amitsetin, bleomycin), certain drugs (barbiturates, pyrimidine sulfonamides, ftorafur, orotic acid), strong poison (tetrodotoxin), coenzymes (uridine diphosphate glucose) contain the pyrimidine cycle.

As a result of continuing researches in the series of substituted pyrimidines, the compounds possessing antitumor [1, 2], anti-tuberculosis [3], cardiotonic [4], anti-HIV[5], antibacterial [6] and antiviral (hepatitis C) [7] activities were discovered, some derivatives are proposed as potential antagonists of adenosine receptors [8] and protein kinase inhibitors [9].

Among the pyrimidine derivatives a series of pyrimidinamine and pyrimidine organothiophosphate insecticides, rodenticides and acaricides, pyrimidine fungicides, pyrimidinediamine, pyrimidinyloxybenzylamine, pyrimidinyloxy(thio)benzoic acid derivatives with herbicidal activity and a large series of new pyrimidinylsulfonylurea herbicides are used in agriculture [10].

The arsenal of pesticides based on 1,2,4-triazole is also very large. There are well known triazole and triazolone herbicides, triazole fungicides, triazole organothiophosphate insecticides. The compounds with combination of these two pharmacophore heterocycles – triazolopyrimidines are used as herbicides and fungicides [10]. However, the increase of environmental requirements, as well as the fact that the harmful organisms and causative agents of plant diseases eventually acquire resistance against the chemical means of plant protection, make it necessary to systematically replenish the arsenal of pesticides with the new preparations having different mechanisms of action.

Problem Statement

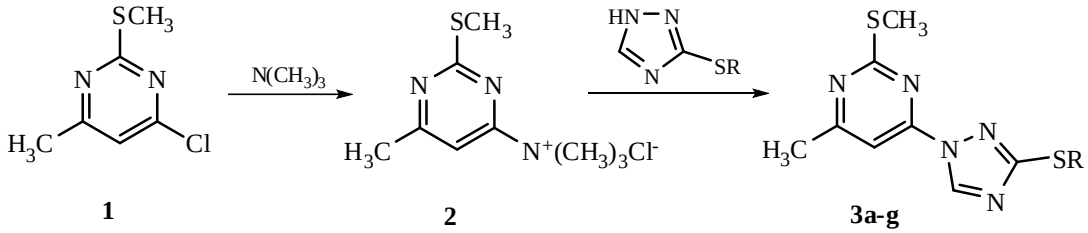
According to literature there are very few data about the biological properties for the systems, where the pyrimidine ring is directly linked to another pharmacophore heterocycle, particularly 1,2,4-triazole, which derivatives also exhibit pesticidal activity. In this regard, the targeted synthesis of new compounds with a combination of two pharmacophore heterocycles in the same molecule could lead

to new biologically active derivatives, with respect to which mentioned resistance has not yet emerged.

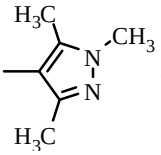
The aim of present research was the synthesis of novel series of nonfused bi- and triheterocyclic systems derivatives for further subsequent screening of their biological activity to search for new chemical means of plant protection.

Results and discussion

As the starting reagent 4-chloro-6-methyl-2-(methylthio)pyrimidine (**1**), that was synthesized according the method described in [11]. Under the action of trimethylamine it was converted into corresponding pyrimidinyl-trimethyl-ammonium chloride (**2**). The latter at mild condintions (heating at 45-50 ^{0}C in acetone medium for 2 h) reacted with a series of previously synthesized 3-S-substituted 1,2,4-triazoles and afforded the targeted compounds with combination of pyrimidine, 1,2,4-triazole (**3a-f**) and also pyrazole heterocycles (**3g**).



1 **2** **3a-g**

R = CH_3**(a)**, $CH_2C_6H_5$**(b)**, CH_2COOCH_3**(c)**; $CH_2COOC_2H_5$**(d)**, CH_2CONH_2**(e)**, CH_2CH_2O-C_6H_4-CH_3-p**(f)**,  **(g).**

3-Substituted 1,2,4-triazoles may exist in different tautomeric forms, depending on the position of mobile hydrogen atom at one of the three nitrogen atoms of the heterocycle. In our early studies based on ^{1}H and ^{13}C NMR spectral data we had proved that the substitution occurs predominantly at nitrogen atom of the first position of triazole ring [12].

Currently, all synthesized compounds undergo laboratory-vegetation testing to discover among them the pesticide and growth-regulating properties. During the preliminary screening some of the synthesized compounds have shown growth stimulant properties. These compounds are selected for deeper study and further field trials.

Experimental

The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at 30 ^{0}C on Varian Mercury-300 spectrometer with standard pulse sequences operating in the mixture of solvents DMSO-d_6 and CCl_4 (1:3) using tetramethylsilane (0.0 ppm) as internal standard. The NMR multiplicities br s, s, d, t, q, and m stand for broad singlet, singlet, doublet, triplet, quartet and multiplet, respectively. The reaction progress and purity of the obtained substances were checked by using the tlc method on "Silufol UV-254" plates and acetone/hexane mixture (2:1) as eluent. All melting points were determined in open capillaries and are uncorrected.

Compound **1** was synthesized according the method described in [2].

Trimethyl-(6-methyl-2-methylthio-pyrimidin-4-yl)-ammonium chloride (2). To a solution of compound **1** (0.01 mol) in 10 mL of absolute benzene, at 5 ^{0}C a solution of trimethylamine (0.01

mol) in 5 mL of absolute benzene was added. The reaction mixture was allowed to stand at 20 ^{0}C for 24 h. The precipitate was filtered off, washed with absolute ether and stored in desiccator. Yield: 87%; m.p. 136-137 ^{0}C. ^{1}H NMR δ ppm: 2.59 (s, 3H, CH_3); 2.60 (s, 3H, SCH_3); 7.77 (s, 1H, CH-pyrim.). Anal. Calcd for $C_9H_{16}ClN_3S$: Cl, 15.17; N, 17.98; S, 13,.72. Found: Cl, 15.03; N, 17.69; S, 13.88.

Synthesis of compounds (3a-g).

To a suspension of potassium salt of S-substituted 1,2,4-triazole (0.01 mol) in 20 mL of acetone, at 20 ^{0}C compound **2** was added by portions with continuous stirring. The mixture was allowed to stand at the same temperature overnight, then heated at 45-50 ^{0}C for 3-4 h until complete removal of trimethylamine. The solvent was evaporated, the residue was processed with water, filtered off and dried.

4-Methyl-2-(methylthio)-6-(3-(methylthio)-1*H*-1,2,4-triazol-1-yl)pyrimidine (3a). Yield: 85%; m.p. 100-102 ^{0}C. ^{1}H NMR δ ppm: 2.56 (s, 3H, CH_3); 2.60 (s, 3H, SCH_3); 7.35 (s, 1H, CH-pyrim.); 9.24 (s, 1H, CH-triazol). Anal. Calcd for $C_9H_{11}N_5S_2$: N, 27.64; S, 25.31. Found: N, 27.79; S, 25.12.

4-Methyl-2-(methylthio)-6-(3-(benzylthio)-1*H*-1,2,4-triazol-1-yl)pyrimidine (3b). Yield: 81%; m.p. 78-80 ^{0}C. ^{1}H NMR δ ppm: 2.52 (s, 3H, CH_3); 2.56 (s, 3H, SCH_3); 3.81 (s, 2H, CH_2); 7.05-7.20 (m, 5H, C_6H_5); 7.35 (s, 1H, CH-pyrim.); 9.26 (s, 1H, CH-triazol). Anal. Calcd for $C_{15}H_{15}N_5S_2$: N, 21.26; S, 19.47. Found: N, 21.12; S, 19.25.

Methyl 2-((1-(6-methyl-2-(methylthio)pyrimidin-4-yl)-1*H*-1,2,4-triazol-3-yl)thio)acetate (3c). Yield: 61%; m.p. 104-106 ^{0}C. ^{1}H NMR δ ppm: 2.54 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 3.75 (s, 3H, OCH_3); 3.83 (s, 2H, CH_2); 7.35 (s, 1H, CH-pyrim.); 9.24 (s, 1H, CH-triazol). Anal. Calcd for $C_{11}H_{13}N_5O_2S_2$: N, 22.49; S, 20.60. Found: N, 22.60; S, 20.78.

Ethyl 2-((1-(6-methyl-2-(methylthio)pyrimidin-4-yl)-1*H*-1,2,4-triazol-3-yl)thio)acetate (3d). Yield: 64%; m.p. 92-93 ^{0}C. ^{1}H NMR δ ppm: 1.25 (t, J=7.1 Hz, 3H, $OCH_2\mathit{CH_3}$); 2.55 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 3.84 (s, 2H, CH_2); 4.05 (q, J=7.1 Hz, 2H, $O\mathit{CH_2}CH_3$); 7.36 (s, 1H, CH-pyrim.); 9.26 (s, 1H, CH-triazol). Anal. Calcd for $C_{12}H_{15}N_5O_2S_2$: N, 21.52; S, 19.71. Found: N, 21.33; S, 19.49.

2-((1-(6-Methyl-2-(methylthio)pyrimidin-4-yl)-1*H*-1,2,4-triazol-3-yl)thio)acetamide (3e). Yield: 75%; m.p. 230-232 ^{0}C. ^{1}H NMR δ ppm: 2.54 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 3.85 (s, 2H, CH_2); 6.97 and 7.34 (brs, 2H, NH_2); 7.36 (s, 1H, CH-pyrim.); 9.26 (s, 1H, CH-triazol). Anal. Calcd for $C_{10}H_{12}N_6OS_2$: N, 28.36; S, 21.64. Found: N, 28.15; S, 21.41.

4-Methyl-2-(methylthio)-6-(3-((2-(p-tolyloxy)ethyl)thio)-1*H*-1,2,4-triazol-1-yl)pyrimidine (3f). Yield: 98%; m.p. 114-115 ^{0}C. ^{1}H NMR δ ppm: 2.27 (s, 3H, CH_3-tolyl); 2.54 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 3.53 (t, J=6.7, 2H, SCH_2); 4.26 (t, J=6.7, 2H, OCH_2); 6.77-7.04 (m, 4H, C_6H_4); 7.31 (s, 1H, CH-pyrim.); 9.26 (s, 1H, CH- triazol). ^{13}C NMR δ ppm: 13.40, 19.89, 23.72, 29.67, 66.02, 102.44, 113.97, 128.98, 129.20, 143.00, 153.91, 155.70, 162.83, 169.83, 171.54. Anal. Calcd for $C_{17}H_{19}N_5OS_2$: N, 18.75; S, 17.17. Found: N, 18.58; S, 17.40.

4-Methyl-2-(methylthio)-6-(3-((1,3,5-trimethyl-1H-pyrazol-4-yl)thio)-1H-1,2,4-triazol-1-yl)pyrimidine (3g). Yield: 72%; m.p. 144-146 ^{0}C. ^{1}H NMR δ ppm: 2.25 and 2.47 (s,s 6H, 2×CH_3-pyrazol); 2.54 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 3.56 (s, 3H, NCH_3); 7.37 (s, 1H, CH-pyrim.); 9.28 (s, 1H, CH-triazol). ^{13}C NMR δ ppm: 9.58, 11.42, 13.37, 23.73, 35.99, 99.52, 102.43, 142.60, 142.87,

149.63, 153.97, 163.48, 169.77, 171.44. Anal. Calcd for $C_{14}H_{17}N_7S_2$: N, 28.22; S, 18.46. Found: N, 28.38; S, 18.22.

Conclusion

A novel series of nonfused bi- and triheterocyclic systems derivatives are synthesized. During the preliminary laboratory-vegetation testing a growth-regulating activity of some substances was discovered. This fact indicates that the obtained compounds may be of interest in the search for new plant growth regulators.

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(3-S-ՏԵՂԱԿԱԼՎԱԾ)-1*Հ*-1,2,4-ՏՐԻԱԶՈԼ ՊԻՐԻՄԻԴԻՆԻ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶԸ

Ռ.Ս. Հակոբյան
Շուշիի տեխնոլոգիական համալսարան

Չկոնդենսված երկու և երեք հետերոցիկլեր պարունակող միացությունների շարքում բույսերի պաշտպանության նոր միջոցների հայտնաբերման համար որպես ելանյութ օգտագործվել է պիրիմիդինիլ-տրիմեթիլ-ամոնիումի քլորիդը: Դրա համար 4-քլոր-6-մեթիլ-2-մեթիլթիո պիրիմիդինի և տրիմեթիլամինի փոխազդեցությամբ սինթեզվել է տրիմեթիլ-(6-մեթիլ-2-մեթիլթիո-պիրիմիդին-4-իլ)ամոնիում քլորիդը: Հետագա ռեակցիան տարվել է 3-S-տեղակալված 1H-1,2,4-տրիազոլի հետ, որի արդյունքում ստացվել են չկոնդենսված պիրիմիդինի և տրիազոլի ցիկլեր պարունակող նոր միացություններ: Երրորդ հետերոցիկլի (պիրազոլի շղթա) ներմուծումը մոլեկուլա կատարվում է այդ աղի և 3-((1,3,5-տրիմեթիլ-1H-պիրազոլ-4-իլ)թիո)-1H-1,2,4-տրիազոլի փոխազդեցությամբ:

Սինթեզված բոլոր միացությունները ենթարկվել են լաբորատոր-վեգետացիոն փորձարկման՝ նրանց շարքում նոր պեստիցիդների և աճի կարգավորիչների հայտնաբերման նպատակով:

Բանալի բառեր: 4-Քլոր-6-մեթիլ-2-մեթիլթիո պիրիմիդին, 3-S-տեղակալված 1H-1,2,4-տրիազոլ, պիրազոլ, հետերոցիկլում, տաուտոմերիա:

СИНТЕЗ ПРОИЗВОДНЫХ (3-S-ЗАМЕЩЕННЫХ)-1*Н*-1,2,4,-ТРИАЗОЛ-ПИРИМИДИНОВ

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В целях обнаружения новых средств защиты растений в ряду соединений, содержащих неконденсированные два или три гетероцикла, в качестве исходного вещества использовался пиримидинил триметил аммоний хлорид. Для этого взаимодействием 4-хлор-6-метил-2-метилтио пиримидина с триметиламином ситезирован триметил-(6-метил-2-метилтио-пиримидин-4-ил)аммоний хлорид. При дальнейшем взаимодействии полученного хлорида с 3-S-замещенным 1H-1,2,4-триазолом получаются новые соединения, содержащие циклы неконденсированных пиримидина и триазола. В результате реакции полученной соли с 3-((1,3,5-триметил-1H-пиразол-4-ил)тио)-1H-1,2,4-триазолом, получается соединение, молекула которого содержит 3 гетероцикла: пиримидин, триазол, пиразол.

Все полученные соединения прошли лабораторно-вегетативное исследование в целях обноружения в них новых пестицидов и регуляторов роста растений.

Ключевые слова: 4-Хлор-6-метил-2-метилтио пиримидин, 3- S-замещенный 1H-1,2,4-триазол, пиразол, гетероциклизация, таутомерия.