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Synthesis And Bioactivity Of 5-Heteryl-1,2,4-Triazoles.

Olha A Suhak[1]*, Oleksandr I Panasenko[1], Yevhenii G Knysh[2], and Andriy A Safonov[1].

[1]Department of Toxicological and Inorganic Chemistry, Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine.
[2]Department of Management and Pharmacy Economics, Medical and Pharmaceutical Commodity Research, Zaporizhzhia State Medical University, Zaporizhzhya, Ukraine.

ABSTRACT

Despite the large number of publications devoted to the search for biologically active substances among derivatives of 1,2,4-triasole, scientific and technical literature and patents almost do not find information regarding the synthesis, physical, chemical and biological properties of S-derivatives of 4-R- 5-(thiophen-2-ylmethyl)-4H-1,2,4-triazoles. It is known that thiophene derivatives are used in agriculture for the synthesis of additives to oils and fuels, growth stimulators of plants and polymeric materials, and medical practice as drugs. The aim of this work was to analyze literary sources in order to identify the potential among derivatives of 5-heteryl-4H-1,2,4-triazole. Information search among literary data on the synthesis and biological activity of derivatives of 5-heteryl-1,2,4-triazole-3-thiol among the works of domestic and foreign scientists over the past decade. A review of literary sources on the synthesis and biological activity of derivatives of 5-heteryl-1,2,4-triazole-3-thiol. Based on the data found, the derivatives of 5-heteryl-1,2,4-triazole-3-thiol are promising compounds for the creation of new original drugs. Scientific-technical literature and patents have almost no information regarding the synthesis, physical, chemical, and biological properties of 4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazoles derivatives, therefore their study is relevant , has theoretical and practical significance.

Keywords: 1,2,4-triazole**,** synthesis, IR spectroscop*y, ^{1}H NMR spectroscopy,* activebiological

Corresponding author

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INTRODUCTION

There is a small percent of the existing domestically produced drugs and dietary supplements on the pharmaceutical market of Ukraine that can compete with the imported ones [5]. That is why the research of new low-toxic and highly effective medicines based on heterocyclic compounds is gaining a significant popularity in domestic studies, which may be confirmed due to the literature review [31].

Despite the variety of studies devoted to the search for biologically active 1,2,4-triazole derivatives [26-28], there is a mere number of technical data and patents on the synthesis, physical, chemical, and biological properties of 4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4 S-derivatives.

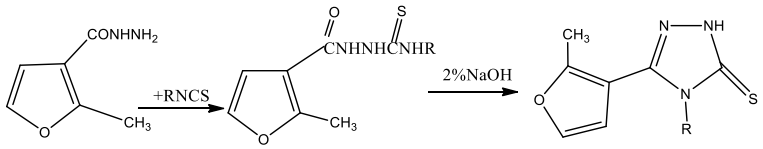
It is known that thiophene derivatives are used in agriculture, synthesis of ignition control compounds for oils and fuels, production of plant growth stimulators and polymeric materials, as well as in medical practice as drugs.

Therefore, the search for new biologically active substances among S-derivatives of4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole is important and is theoretically and practically significant.

The aim of the study was to conduct a review of the literature with purpose to unravel the potential of 5-heteryl-1,2,4-triazole derivatives.

DISCUSSION

Researchers described the synthesis of 3-(2-methylfuran-3-yl)-4-derivatives of Δ^2-1,2,4-triazolin-5-thiones [25]. In the method, derivatives of thiosemicarbazide were diluted in 2% sodium hydroxide and boiled with are flux condenser during 2 hours (Fig. 1). The reaction mixture was cooled and neutralized with hydrochloric acid. The structures of compounds were confirmed with IR, ^{1}H and^{13}C NMR spectroscopy, and elemental analysis.



R=C_6H_5, 2-$CH_3OC_6H_4$, C_6H_{11}

Fig 1: The synthesis of 3-(2-methylfuran-3-yl)-4-derivatives of Δ^2-1,2,4-triazolin-5-thiones.

In the study [27], Slovakian researchers suggested the synthesis of new derivatives of furo[3,2-b]pyrrol-5-carboxyhydrazide. On the first stage, phenylizothiocyanate in ethanol was added to 2-methyl-4H-furo[3,2-b]pyrrol-5-carboxyhydrazide. After that, cyclization was conducted by heating with a reflux condenser in a water solution of sodium hydroxide, which yielded 4-phenyl-5-(2-methyl-4H-furo[3,2-b]pyrrol-5-yl)-1,2,4-triazol-3-thione (Fig. 2). The structure was confirmed with ^{1}H NMR and IR spectroscopy.

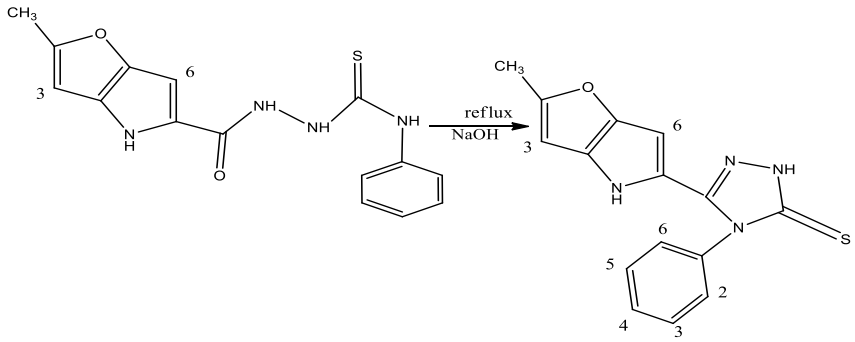


Fig 2: The synthesis of furo[3,2-b]pyrrol-5-carboxyhydrazides

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In another article [26],the team of foreign chemists continued improving methods of synthesis of initial thiols and described the preparation of 5-furan-2-yl[1,3,4]oxydazole-2-thiol and 5-furan-2-yl-4H[1,2,4]triazol-3-thiol and their derivatives. The compound of 5-furan-2-yl[1,3,4]oxydazole-2-thiol was obtained by the ring forming of hydrazide of furan-2-carboxylic acid. 5-Furan-2-yl-4H[1,2,4]triazol-3-thiol was prepared by the reaction of the appropriate 2-furoyl-theosemicarbazide and potassium hydroxide in ethanol (Fig. 3).The structures of compounds were confirmed with ^{1}H NMR, IR spectroscopy, and elemental analysis.

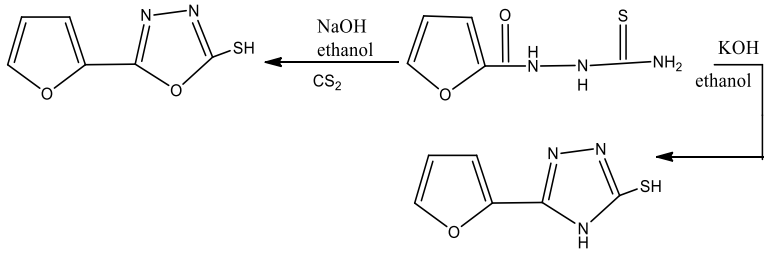
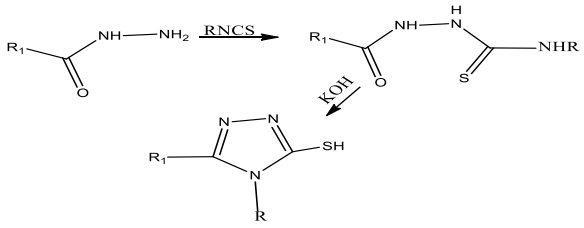


Fig 3: The synthesis of 1,2,4-triazol-3-thione

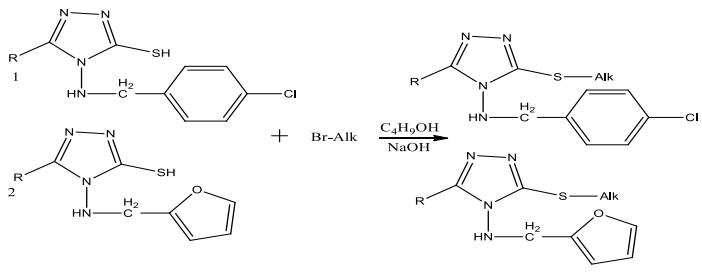
Armenian researches suggested the synthesis of new furyl-2-derivatives of 1,3,4-thiadiazoles and 1,2,4-triazoles [9]. Initial compounds for synthesis were obtained from reactions of hydrazides of furan-2-carboxylic acids with benzoyl, phenyl, benzyl, cyclohexyl, and allylizothiocyanates, which yielded in asubstituted thiosemicarbazide. 3,4-derivatives of 5-thio-1,2,4-triazoles were synthesized by boiling of thiosemicarbazides in 4.5% water alkaline solution and neutralization with acetic acid (Fig. 4). The structure was confirmed with elemental analysis, UVspectrometry,^{1}H NMR spectroscopy, mass-spectrometry, and thin-layer chromatography.



R= COC_6H_5, C_6H_5, $CH_2C_6H_5$, C_6H_{11}, CH_2 $CH=CH_2$,R_1=Het.

Fig 4: The synthesis of heteryl-derivatives of 1,2,4-triazole

With aim to expand the range of new synthetic 1,2,4-triazole derivatives, domestic researchers [14] conducted reactions of alkylation of 4-(4-chlorobenzylamino)-5-R-4H-1,2,4-triazol-3-thiols and 4-(furan-2-ylmethylamino)-5-R-4H-1,2,4-triazol-3-thiols by 1-bromoalkanes in the medium of 1-butanol and the equivalent amount of sodium hydroxide (Fig. 5). The structures of compounds were confirmed with elemental analysis, ^{1}H NMR and IR spectroscopy.



R = pyridin-3-yl, pyridin-4-yl.

Fig 5: The alkylation of 4-(4-chlorobenzylamino)-5-R-4H-1,2,4-triazol-3-thiolsand 4-(furan-2-ylmethylamino)-5-R-4H-1,2,4- triazol-3-thiols

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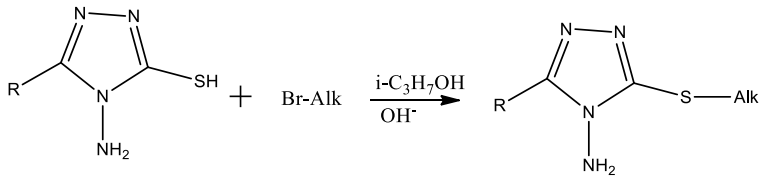
The search for new alkyl-derivatives of 1,2,4-triazole was also continued by other domestic researchers [10, 22]. A range of new 3-(alkylthio)-5-(furan-2-yl, 2-methylfuran-3-yl)-1,2,4-triazol-4-amineswere synthesized by adding 1-bromoalkane to the initial thiol in isopropanol (Fig. 6). The structures of compounds were confirmed with elemental analysis, ^{1}H NMR spectroscopy, and chromatography-mass spectrometry.



R = furan-2-yl, 2-methylfuran-3-yl, Alk- C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$.

Fig 6: The synthesis of 3-(alkylthio)-5-(furan-2-yl, 2-methylfuran-3-yl)-1,2,4-triazol-4-amines.

Reactions of arylation and heterylation of 1,2,4-triazole derivatives were studied by Chinese researchers [28]. The synthesis was held by adding benzylhalide or 2-chloro-5-chloromethylpyridine to the solution of initial thione and potassium carbonate in DMFA. The mixture was mixed at room temperature during few hours (Fig. 7). The completion of reaction was controlled with HPLC. The structures of compounds were confirmed with elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and mass spectrometry.

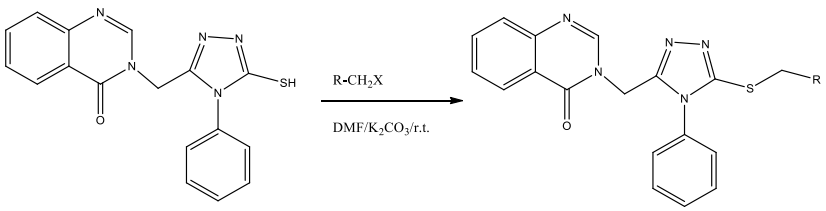
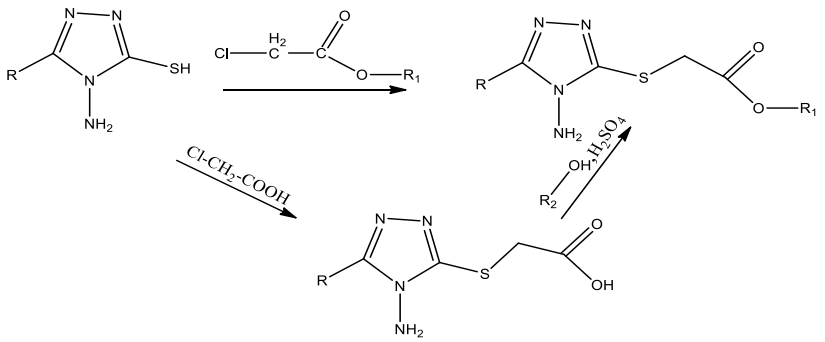


Fig7: The arylation and heterylation of 1,2,4-triazole derivatives

In the studies [3, 20], the team of domestic researchers described the specific aspects of the synthesis of esters of 2-((5-furan-2-yl, 2-methylfuran-3-yl)-4-amino-1,2,4-triazol-3-ylthio)acetic acids. Compounds were obtained by two methods. According to the first method, esters were prepared by the reaction of the initial thiols with esters of chloroacetic acid in presence of isopropanol and the equivalent amount of alkali; the second method is based on the reaction of acids with the corresponding alcohols with addition of a catalytic amount of sulfuric acid (Fig. 8). The structure was confirmed with a complex use of elemental analysis and ^{1}H NMR spectroscopy.

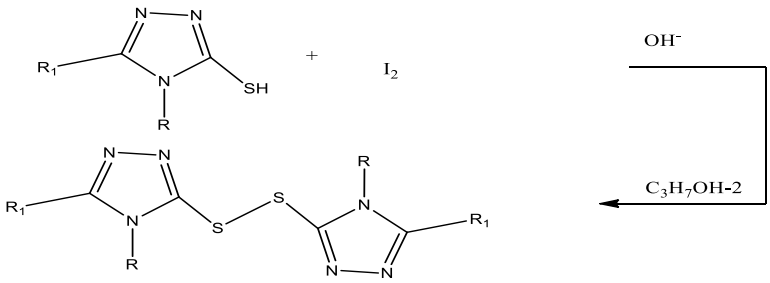


R=furan-2-yl, 2-methylfuran-3-yl, thiophene-2-yl, R_1=CH_3, C_2H_5, C_3H_7, C_3H_7(i), C_4H_9(i), C_5H_{11}(i)

Fig 8: The synthesis of esters of 2-((5-furan-2-yl, 2-methylfuran-3-yl)-4-amino-1,2,4-triazol-3-ylthio)acetic acids

The study [18] describes the synthesis of 1,2-bis(4-R-5-(2-thienyl)-4*H*-1,2,4-triazol-3-yl)disulphanes. The reaction was conductedin isopropanol with 4-R-5-(2-thienyl)-4*H*-1,2,4-triazol-3-thiones and iodine, followed by

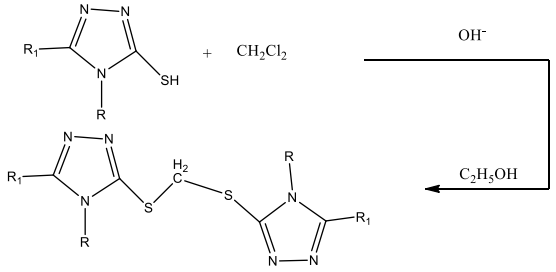
heating in alkaline medium (Fig. 9). The compounds were obtained with high quantitative yield. The structure was confirmed with spectroscopy.



R=Ar, Alk, R_1=Het.

Fig 9: The synthesis of 1,2-bis(4-R-5-(R_1)-4*H*-1,2,4-triazol-3-yl)disulphanes.

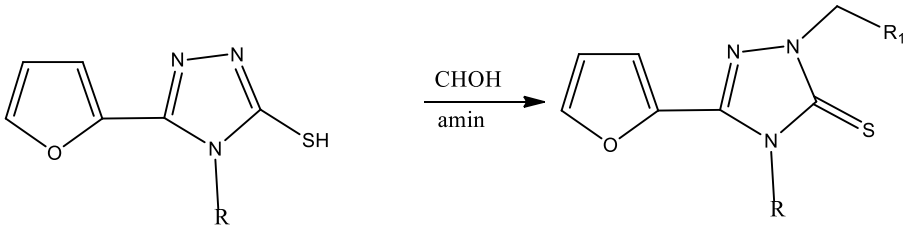
Researchers [17] managed to synthesize is(5-R-4-R_1-1,2,4-triazol-3-ylthio)methanes. The reaction was held by adding 2 moles of 5-(4-pirydyl)-4-(2-methoxyphenyl)-1,2,4-triazol-3-thione to 1 mole of dichloromehtane. The synthesis was held in ethanol alkaline medium (Fig. 10). The compounds were obtained with high quantitative yield, structures of which were confirmed with the set of modern instrumental methods of analysis (elemental analysis, ^{1}H-NMR and IR spectroscopy).



R=Ar, Alk, R_1=Het.

Fig 10: The synthesis of bis(5-R-4-R_1-1,2,4-triazol-3-ylthio)methanes

The preparation of 2-N-morpholin(pyrrolidin)methylene-4-phenyl-(benzyl-, cyclohexyl-,alyl-)-5-(furyl-2)-1,2,4-triazolinthioneswas described in the study [9]. The synthesis was conducted in terms of the reaction of the corresponding triazoles, which were dissolved in 10 mL of methanol, and morpholine or pyrrolidine in the presence of the equivalent amount of formaldehyde. The structure was confirmed with elemental analysis, UV spectrometry, ^{1}H NMR spectroscopy, mass-spectrometry, and thin layer chromatography (Fig. 11).

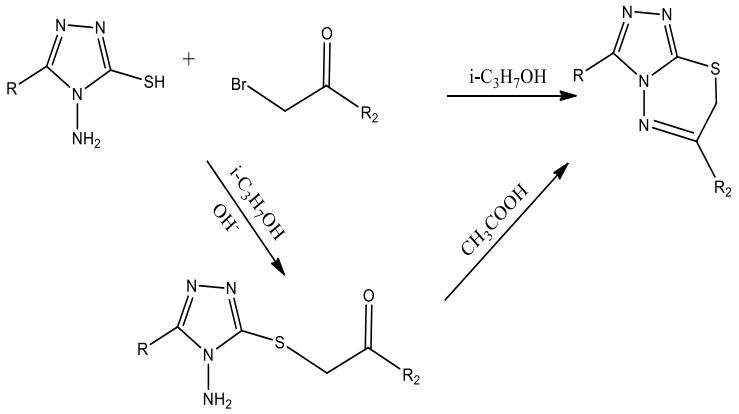


R= COC_6H_5, C_6H_5, $CH_2C_6H_5$, C_6H_{11}, CH_2 CH=CH_2, R´= 4-morpholine,pyrrolidine

Fig 11: The synthesis of 2-N-morpholin(pyrrolidin)methylene-4-phenyl-(benzyl-, cyclohexyl-,alyl-)-5-(furyl-2)-1,2,4-triazolthiones

In the next study [22], researchers continued the investigation of reactions between 1,2,4-triazol-3-thioles and α-bromoketones. The reaction of cyclization is completed in two stages if an alkaline isopropanol is

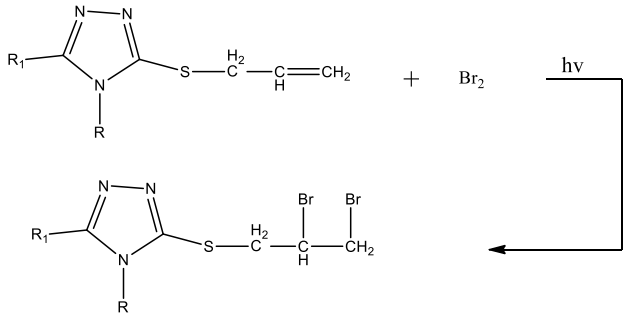
added to the solution. During the first stage, Sulphur atom is added to the structure; during the second stage, acetic acid is added to form a ring of thiadiazine. Without addition of alkali to isopropanol prior the reaction, there is only one stage of the synthesis (Fig. 12). The structure was confirmed with a complex application of elemental analysis and ^{1}H NMR and IR spectroscopy.



R=Het, R_2= Ar,

Fig 12: The synthesis of 3-(furan-2-yl, 2-methylfuran-3-yl)-6-aryl-7H-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiadiazines

In another study [17], researchers described the method of synthesis of 3-(2,3-dibromopropyl-1)thio-5-R-4-R_1-1,2,4-triazoles. The reaction of 5-(4-pyridyl)-4-R-3-alylthio-4*H*-1,2,4-triazole with bromine (Fig. 13) was held in conditions of rapid cooling and bright light. The structures of the obtained compounds were confirmed with spectroscopy.



R= alk, Ar, R_1=Het

Fig 13: The synthesis of 3-(2,3-dibromopropyl-1)thio-5-R-4-R_1-1,2,4-triazoles

Domestic researchers [16] conducted the reaction of addition of hydrogen chloride to 3-alylthio-5-R_1-4-R-1,2,4-triazoles. The authors reviewed two ways of addition with preparation of two isomers: 3-(2-chloropropyl)thio-5-R_1-4-R-1,2,4-triazole and 3-(3-chloropropyl)thio -5-R_1-4-R-1,2,4-triazole (Fig. 14).

The results of complex studies point out that the chlorine is added to the C_2 atom of the propyl substituent.

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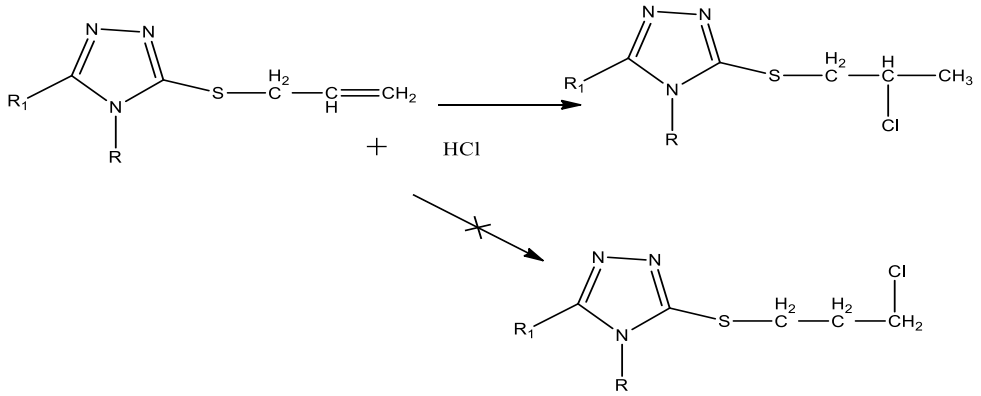
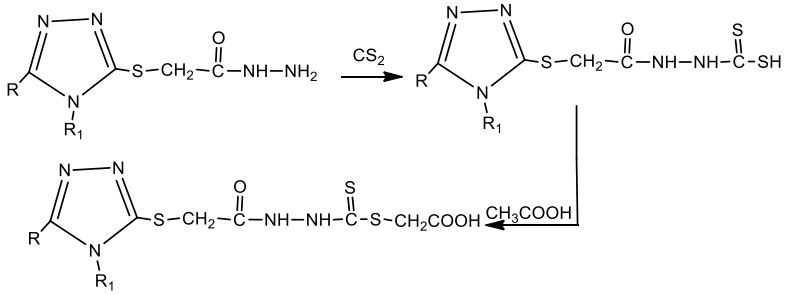


R= alk, Ar, R_1=Het

Fig 14: The synthesis of 3-(2-chloropropyl)thio-5-R_1-4-R-1,2,4-triazole

The team of domestic researchers successfully synthesized 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-2-[carboxymethylthio]carbonothioyl]hydrazinoacetic acids and their salts [13]. The preparation of 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-2-[carboxymethylthio]carbonothioyl]hydrazinoacetic acids was conducted in two stages. At first, 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-2-[carboxymethylthio]carbonothiones were obtained by adding carbon disulfide to hydrazides of 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]acetic acids; then, monochloroacetic acid in alkaline medium was added, which yielded the final acids (Fig. 15).



R= alk, Ar, R_1=Het

Fig 15: The synthesis of 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-2-[carboxymethylthio]carbonothioyl]hydrazinoacetic acids

The salts of 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-2-[carboxymethylthio]carbonothioyl]hydrazinoacetic acids with organic and inorganic bases were obtained using standard procedures [13].

The structures of the obtained compounds were confirmed with a complex investigation involving modern instrumental methods of analysis.

Authors [11, 12, 15] described methods of synthesis of 2-(4-R-5-R_1-4H-1,2,4-triazol-3-ylthio)acetic acids and their salts (Fig. 16). The reactions were conducted by adding monochloroacetic acid to the corresponding thiols in water or ethanol alkaline medium. The salts were obtained in terms of reactions of the corresponding acids with organic and inorganic bases. The structure was confirmed with elemental analysis, UV spectrometry, ^{1}H NMR spectroscopy, and mass-spectrometry. The compounds were separated with thin-layer chromatography.

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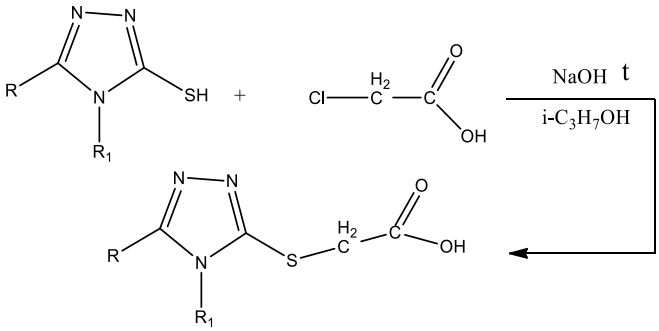
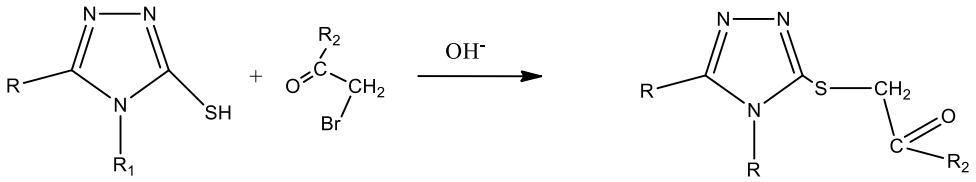


R= alk, Ar, R_1=Het

Fig 16: The synthesis of 2-(4-R-5-R_1-4H-1,2,4-triazol-3-ylthio)acetic acids

In the studies [21, 23], authors devised the preparation of 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-1-arylethanones. The reaction was conducted by adding of α-haloketones to the corresponding thiols in alkaline medium. The structures of the obtained compounds were confirmed with elemental analysis and spectrometry.

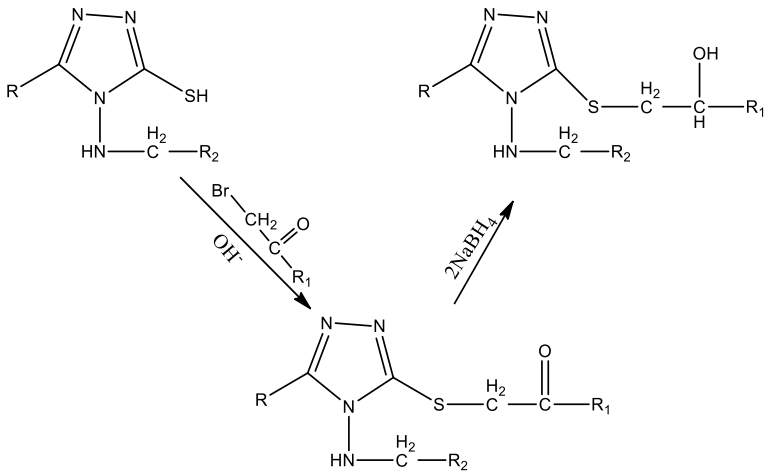


R= alk, Ar, R_1=Het, R_2=Ar.

Fig 17: The synthesis of 2-[5-R-4-R_1-1,2,4-triazol-3-ylthio]-1-arylethanones

Authors [14] continued searching for new 5-heteryl-4-(R-amino)-1,2,4-triazol-3-thiol derivatives. Researchers synthesized a range of 2-(4-(R-amino)-5-heteryl-4-H-1,2,4-triazol-3-ylthio)-1-(R_1)ethanones by adding α-haloketones to the corresponding thiols in alkaline medium (Fig. 18). In addition, researchers conducted a reduction of 1,2,4-triazol-3-ylthioethanones with sodium borohydride in ethanol.

The structure was confirmed with complex utilization of elemental analysis, ^{1}H NMR and IR spectroscopy.



R=Het, R_1= Ar, R_2 = Ar.

Fig 18: The synthesis of 2-(4-(R-amino)-5-heteryl-4-H-1,2,4-triazol-3-ylthio)-1-(R_1)ethanols

Studies [29-30] indicate that 1,2,4-triazole derivatives may exhibit a wide range of biological activity. There are substances with 1,2,4-triazole ring that found their application as drugs in veterinary and pharmaceutical practice [8].

Researches described antiviral activity of 1,2,4-triazole derivatives in the study [7]. The team was investigating antiviral activity of 2-[5-(furan-2-yl)-4-R-1,2,4-triazol-3-ylthio]acetate salts against complex viruses, namely the vesicular stomatitis virus, Indiana strain. Researchers found that the most active compound was piperidinium 2-[5-(furan-2-yl)-2H-1,2,4-triazol-3-ylthio]acetate. As a result, researchers concluded that the substance must be used during the treatment; otherwise, it could be ineffective in terms of preventive means.

Domestic researchers [6] studied antiviral activity of piperidinium 2-[5-(furan-2-yl)-4-phenyl-1,2,4-triazol-3-ylthio]acetate against the virus of chicken embryo. Having processed the data, it should be noted that the compound exhibits antiviral activity against the virus of infectious bronchitis and virus of infectious encephalomyelitis. Researches came up with the optimal concentration of the substance, concluding that the concentration of 0.01% affects both viruses.

A great majority of studies [1,2,4,5,19,24] were devoted to the research of antifatigue and actoprotector activity of 1,2,4-triazole derivatives.

Researchers [5,24] investigated antifatigue activity of alkyl-derivatives of 5-(furan-2-yl, 2-methylfuran-3-yl)-4-amino-1,2,4-triazol-3-thiones. Among these compounds, researchers suggest conducting a deeper study of 3-heptylthio-5-(furan-2-yl)-4-amino-1,2,4-triazole. It was determined that the increase of the carbon chain of the molecule enables a small activity.

Authors [2] researched actoprotector activity of N-R-3-alkythio-5-R_1-4H-1,2,4-triazol-4-amine derivatives. Forced swim test was used to evaluate pharmacological activity. Researchers studied a range of compounds and concluded that the compounds of research do not possess actoprotector activity. Among this class of structures, 3-(butylthio)-N-(4-chlorobenzyl)-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-amine is the most active.

As for actoprotector activity of 2-(4-R-3-(thiophen-2-yl)-4H-1,2,4-triazol-3-ylthio)acetate salts, authors [1] denoted that then tire class of these compounds exhibits actoprotector activity, except for piperidinium 2-(5-(thiophen-2-yl)-4H-1,2,4-triazol-3-ylthio)acetate. It was concluded that sodium 2-(4-methyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-ylthio)acetate andpiperidinium 2-(4-phenyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-ylthio)acetate are the most active.

Also, authors [4] studied acute toxicity of the most active compound, sodium 2-(4-methyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-ylthio)acetate. Acute toxicity was investigated using Prozorovsky-Belenky method. Researchers determined that the value of acute toxicity atintra-abdominal introduction is 3255.99 mg/kg, which tells that the substance is non-hazardous and safe for use at a single intra-abdominal administration. So, it is important that 1,2,4-triazole derivatives exhibit a relatively high spectrum of biological activity [32-36].

CONCLUSIONS

1. The literature review was held on the synthesis and biological activity of 5-heteryl-1,2,4-triazol-3-thiol derivatives.
2. Considering the reviewed data, it is safe to claim that 5-heteryl-1,2,4-triazol-3-thiol derivatives are the promising compounds for new and original drugs research.
3. There is practically no information on synthesis, physical, chemical, and biological properties of 4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole derivatives provided in technical data and patents. Hence, the study of these compounds is relevant and holds theoretical and practical significance.

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