ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

1,2,4-Triazole Derivatives with Halogen Substituted Fragments, Their Synthesis, Modification and Biological Properties: Review Article.

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ABSTRACT

Global achievements of scientists are engaged in the 1,2,4-triazole system simulation, studying various properties of the heterocycle and the formation on its base prospective "structures" can create favorable conditions for further search of new molecules with unique properties.The aim of the study was to analyze in detail and combine existing literary materials for the study of reactions associated with the formation and transformation of 1,2,4-triazole halogen derivatives, to study their physico-chemical and biological properties. Analyzing the studies results of physical and chemical properties of new halogen derivatives of 1,2,4-triazoles we should note the presence of original approaches for obtainment of condensed heterocyclic systems of imidazo[1,2-b][1,3]thiazolo[3,2-d][1 2,4]triazole. The above condensed system contains three angular fused heterocycles: imidazole, thiazole and 1,3-thiazole and 1,2,4-triazole. The original method of synthesis of 1-(2,4-difluorophenyl)-2-(1,2,4-triazoles-1-yl)-ethanone Chinese scientists offer. They explored the acylation reaction products of 1,2,4-triazoles using complex physical and chemical analytical approach (1H-NMR, 13C-NMR and LC-MS). Analysis of available publications undoubtedly proves the prospects of finding new biologically active compounds in some halogen derivatives of 1,2,4-triazoles using a wide variety of synthetic possibilities. The analysis of the literature identified several new compounds that have promising future as the original drugs and effective plant protection products.

Keywords: 1,2,4-triazoles, their halogen derivatives, physico-chemical, biological properties, transformation

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ISSN: 0975-8585

INTRODUCTION

In the pharmaceutical activities directly related to the search of bioactive compounds and their introduction into medical or veterinary practice, it is common that a successful selection of research object is a prerequisite for a positive final outcome to create original effective and low-toxic drugs. It should be noted today in the world there are many scientific "schools" that are engaged in solving problems by creating new bioactive molecules in different classes of organic compounds.

World achievements of scientists are engaged in the 1,2,4-triazole system simulation, studying various properties of the heterocycle and the formation on its base prospective "structures" can create favorable conditions for the further search for new molecules with a number of unique properties of 1,2,4-triazole derivatives.

We believe that an interesting from a scientific point of view is a combination of various atomic and molecular "fragments" of heterocyclic 1,2,4-triazoles in one molecule. Such groups may be interesting not only for synthetic chemists, but also for pharmacists, biologists, physiologists and others. The analysis of the literature convincingly demonstrates the urgency of studying the properties of compounds formed by such combination. At this point special attention deserve halogen derivatives of 1,2,4-triazoles. Such compounds are the subject of attention of various research activities. The systematization of information on research results halogen derivatives of 1,2,4-triazoles is absent.

The aim of the study was to analyze in detail and combine existing literature materials to study the reactions associated with the formation and transformation of 1,2,4-triazoles halogen derivatives, study their physico-chemical and biological properties.

In this research survey, systematic and content analysis for processing the literature for the last ten years were used.

DISCUSSION

Analyzing the studies results of physical and chemical properties of new 1,2,4-triazole halogen derivatives we should note the presence of original approaches for getting condensed heterocyclic systems of imidazo[1,2-b][1,3]thiazolo[3,2-d][1,2,4]triazole (Fig. 1).

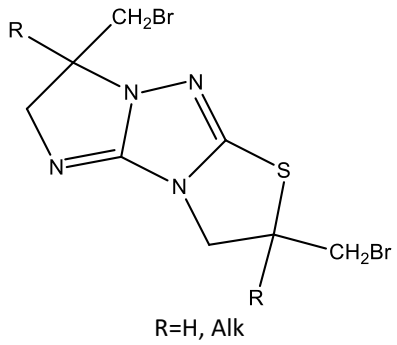

Fig 1: The general formula of imidazo[1,2-b][1,3]thiazolo[3,2-d][1,2,4]triazole derivatives

The above condensed system contains three angular fused heterocycles: imidazole, 1,3-thiazole and 1,2,4-triazole [1]. Synthesis of imidazo[1,2-b][1,3]thiazolo[3,2-d][1,2,4]triazoles was carried out by bromination of 5-N-(2-R-propenyl)-amino-4-(2-R-propenyl)-[1,2,4]triazole-3-thione in terms of 3-fold excess of bromine. Continuing analysis of the literature, our attention was drawn to the publication of Indian scientists to transformations among aminoderivatives of 4-amino-1,2,4-triazole-3-thiones with the remains of halogen (Fig. 2). With virtually target outputs a number of new imines was obtained [2].

ISSN: 0975-8585

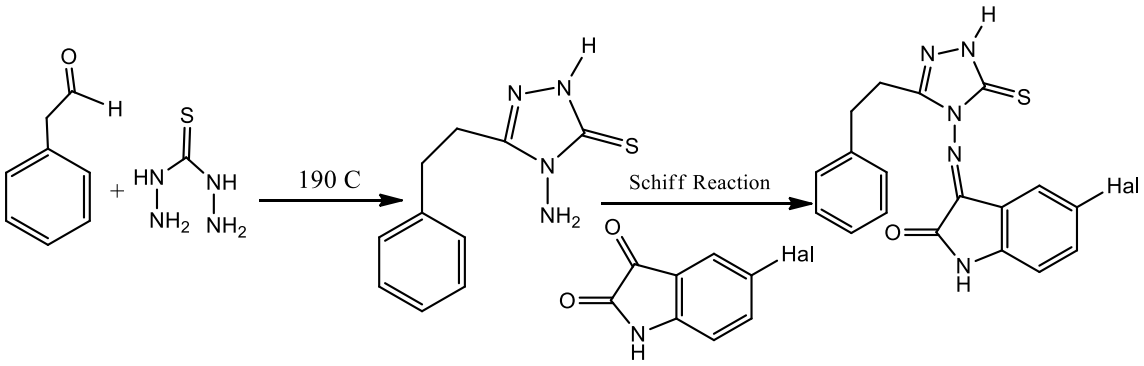

Fig 2: Some converting 4-amino-5-phenethyl-1,2,4-triazoles-3-thiones

The synthesis results of new 4-substituted 3-alkyl-4,5-dihydro-1-(chloro-4-fluorophenyl)-1,2,4-triazoles-5-one show the prospect of new antagonists of angiotensin AT1-receptor [3]. The original method of synthesis of 1-(2,4-difluorophenyl)-2-(1,2,4-triazoles-1-yl)-ethanone Chinese scientists offer [4]. They were able to explore the acylation reaction products of 1,2,4-triazoles using complex physical and chemical analytical approach (1H-NMR, 13C-NMR and LC-MS) (Fig. 3)

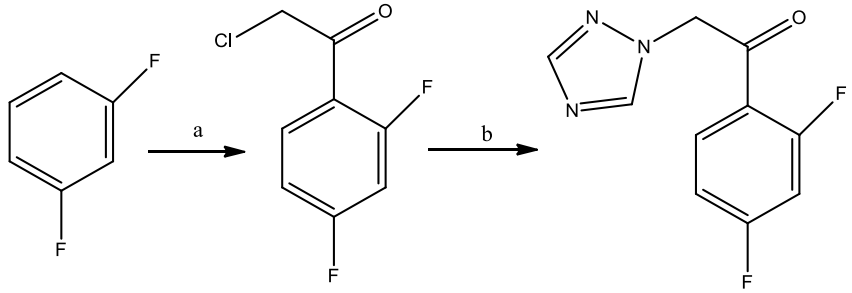

Fig 3: Synthesis of 1-(2,4-difluorophenyl)-2-(1,2,4-triazoles-1-yl)-ethanone

Noteworthy study of Turkish authors about a combination of indole structural fragments, 1,2,4-triazoles and 1,3-oxodiazole in one molecule [5]. The authors argued that high yields of reaction products are a series of imines. Another group of Chinese scientists studied the reaction of 1-(2,4-dichlorophenyl)-2-(1,2,4-triazoles-1-yl)-ethanone (Figure 4). The authors argue that the alkylation reaction takes place in the presence of dichloromethane [6].

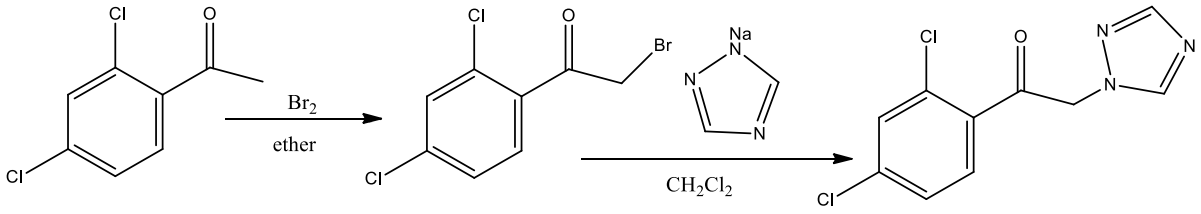

Fig 4: Synthesis of 1-(2,4-dichlorophenyl)-2-(1,2,4-triazoles-1-yl)-ethanone

Team of scientists from India proposed an original method of 3-methyl-5-(pyridine-4-yl)-1H-1,2,4-triazoles, which were subsequently subjected to transformation by the N1-atom heterocyclic system of 1,2,4-triazoles (Fig. 5).

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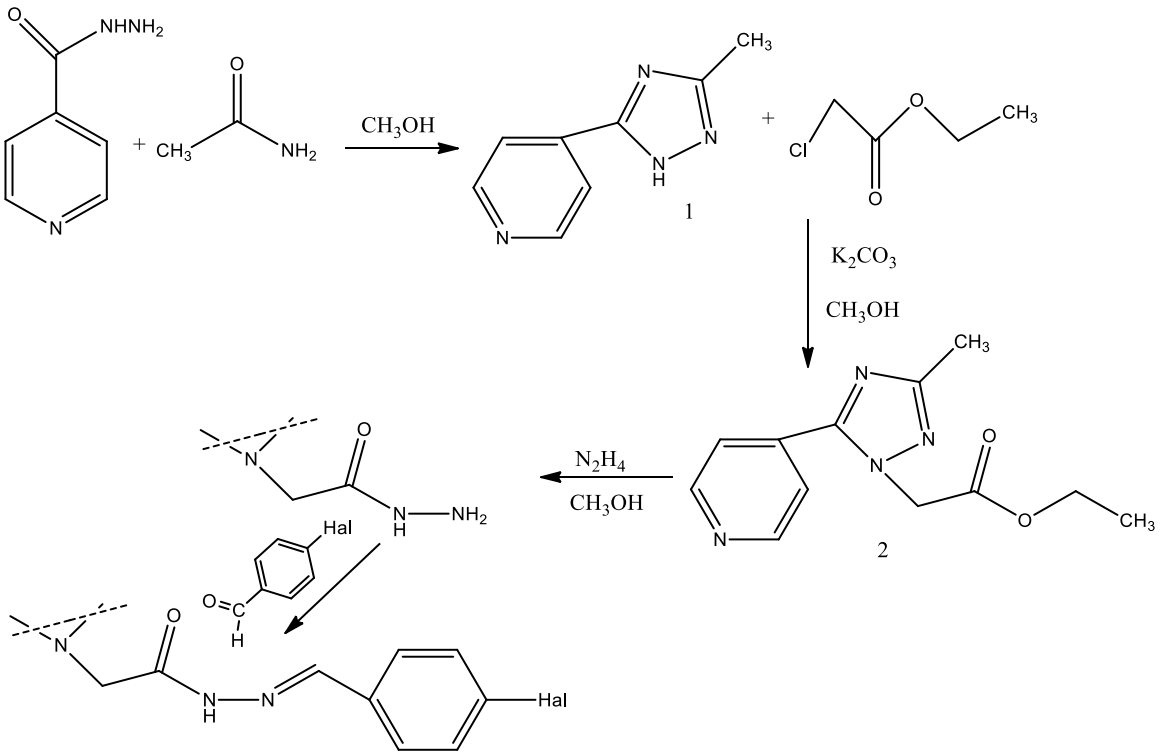

Fig 5: Synthesis of some imine-derivatives of 1,2,4-triazole

Scientists suggest to obtain the 3-methyl-5-(pyridine-4-yl)-1H-1,2,4-triazoles by reacting isonicotinic acid hydrazide of acetamide at 3 hour with stirring, followed by alkylation reaction by ethylchloroacetic acid [7].

Interesting results of 3-nitro-1,2,4-triazole transformations offer Belarusian researchers [8]. As alkylating agent they employ allyl bromide (Fig. 6).

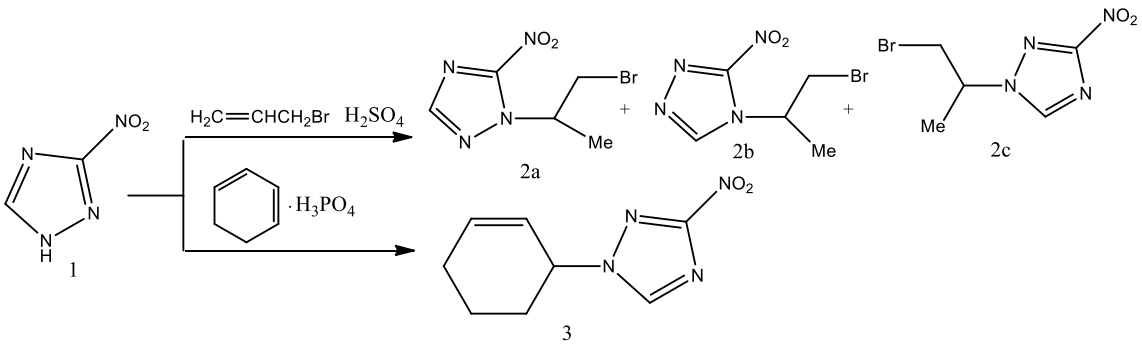

Fig 6: Alkylation of 3-nitro-1,2,4-triazoles allyl bromide and cyclohexa-1,3-diene

By the complex physical and chemical analysis methods authors showed that the interaction of 3-nitro-1,2,4-triazoles of allyl bromide formed by isomeric states (2a, 2b, 2c, Fig. 6). The staff of Chinese scientists studied a number of properties of 1-(4,5-dihydro-3-arylpyrazole-1-yl)-2-(1H-1,2,4-triazole-1-yl)-etanone [9]. The authors argued that the final products, namely 1-(4,5-dihydro-3-p-fluorophenylpyrazole-1-yl)-2-(1H-1,2,4-triazole-1-yl)-ethanone (a, Fig. 7) and 1-(3-p-chlorophenyl-4,5-dihydropyrazole-1-yl)-2-(1H-1,2,4-triazole-1-yl)-ethanone (b, Fig. 7) are the most promising in the biological aspect thanks to the halogen atoms in the molecules

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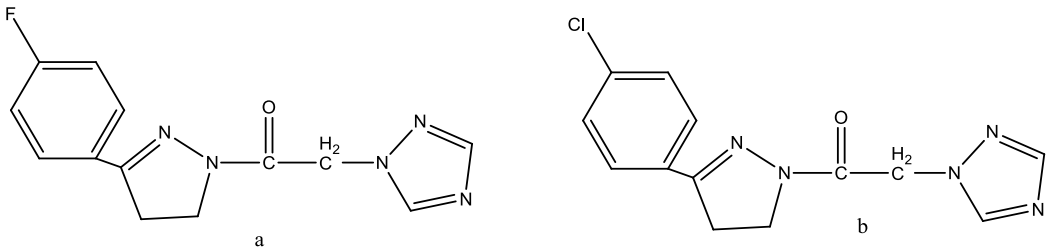

Fig 7: 1-(4,5-Dihydro-3-p-fluorophenylpyrazole-1-yl)-2-(1H-1,2,4-triazole-1-yl)-ethanone (a) and 1-(3-p-chlorophenyl-4,5-dihydropyrazole-1-yl)-2-(1H-1,2,4-triazoles-1-yl)-ethanone (b)

The original method of 3,5-substituted 1H-1,2,4-triazoles scientists from India offer. Continuing the method described previously [7], the authors used the hydrazide of halogenaromatic acid instead of hydrazide of isonicotinic acid [10] and on the acylation of 3,5-substituted 1H-1,2,4-triazoles they spent acetic acid anhydride in the presence of concentrated sulfuric acid.

There is no doubt in the new approach of national scientists to obtain 6-(4-chlorophenyl)-3-methyl-9-R-12N-benzo[4,5]furo[3,2-f][1,2,4]triazole[4,3b][1,2]diazepines [11]. They explored alternative way of benzo[4,5]furo[3,2-f][1,2,4]triazole[4,3b][1,2]diazepines, using as a starting material 1-(4-chlorophenyl)-8-methyl-3,5-dihydro-4H-benzo[4,5]furo[2,3-d][1,2]diazepin-4-one (Fig. 8).

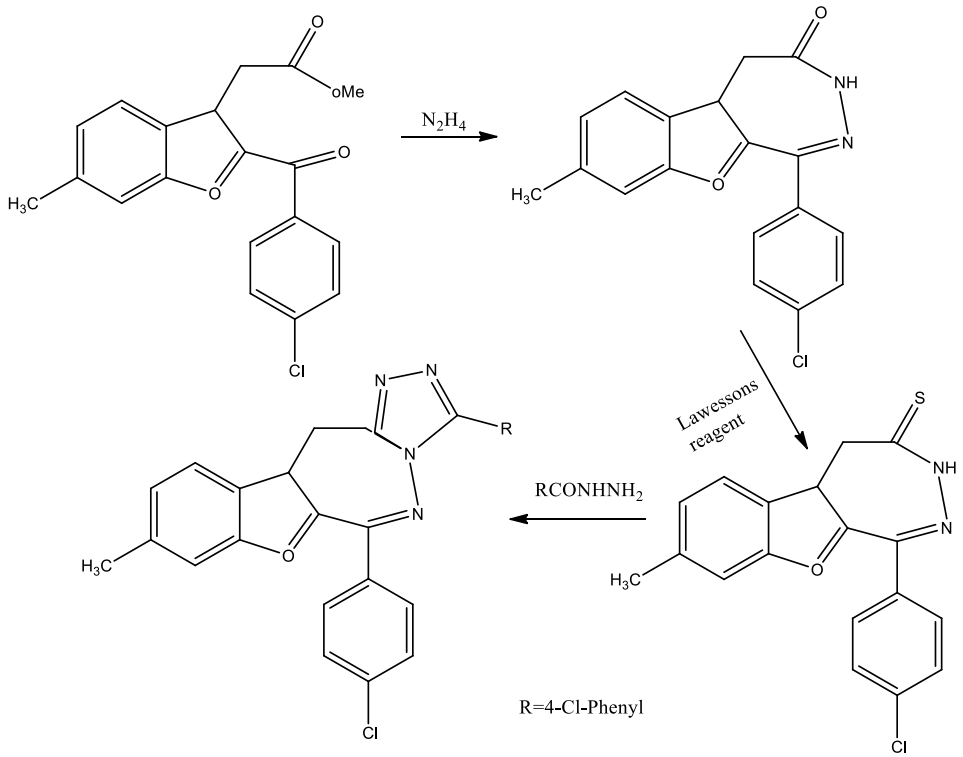

Fig 8: Synthesis of 6-(4-chlorophenyl)-3-methyl-9-R-12H-benzo-[4,5]-furo[3,2-e] [1,2,4] triazole [4,3-b] [1,2] diazepines

In this case the thermal cyclization of thione with hydrazide of 4-chlorophenilbenzoic acid was conducted in the presence of butanol. The output was 80-90%.

Domestic authors proposed optimal method of acylation of 1,3-azoles by the threefluoroacetic acid anhydride in the presence of triethylamine to produce 2-tryfluoracetyl-1,3-azole-ketones with acceptor groups in carbonyl carbon atom [12]. The process of formation of 1,1-dyhetaryl-2,2,2-tryfluorethanoles under acylation at some 1,3-azoles was studied and optimal conditions for purposeful synthesis of these compounds were found. The researchers found properties of electrophilic ketones dependent on the nature of heterocyclic substituent on the example of the formation of hydrates and hemiaminales.

ISSN: 0975-8585

Another group of local scientists investigated the methods of synthesis of 3-alkyl, aryl, heterylthio-5-(2-, 3-, 4-fluorophenyl)-4R1-1,2,4-triazoles, 5-(2-, 3-, 4-fluorophenyl)-4R1-1,2,4-triazole-3-thiols and products of their chemical reactions [13]. For the first time scientists held and investigated the reduction reaction of 2-(3-fluorophenyl)-5-ilidenthiazolo-[3,2-a]-1,2,4-triazole-6-(5H)-ones (Fig. 9).

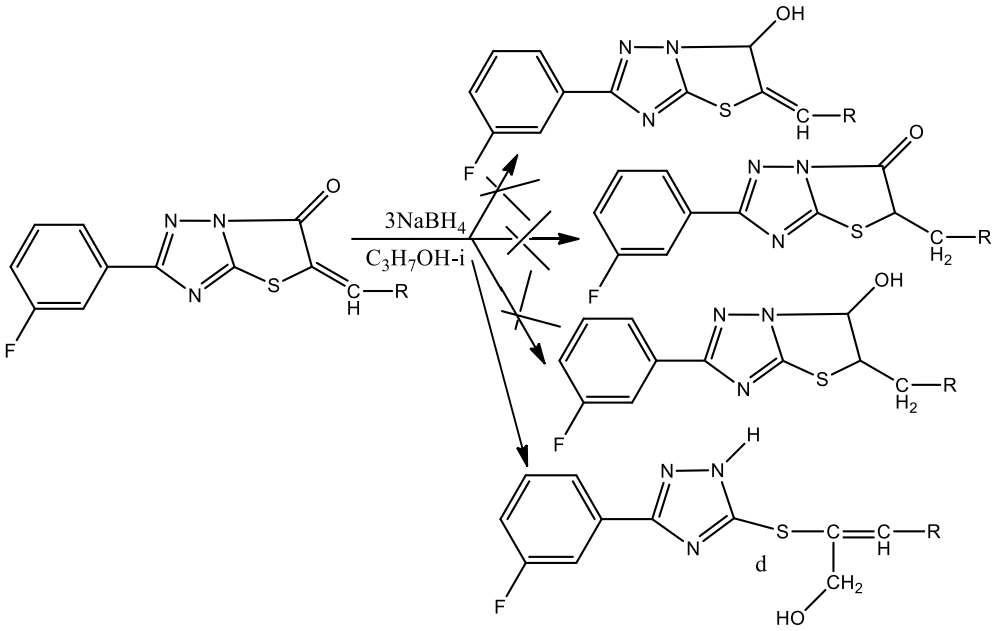

Fig 9: Restoring 5-benzyliden-2-(3-fluorophenyl)-triazole-[3,2-a]-1,2,4-triazoles-6-(5H)-ones

The feature of this process is that the reaction was carried out in the presence of excess sodium borohydride triple. The molecular structure of the reaction product is 3-(2-chloro-6-fluorophenyl)-2-((3-(3-fluorophenyl)-1,2,4-triazoles-5-yl)thio)prop-2-en-1-olu clearly demonstrated by X-ray analysis.

Noteworthy another synthetic method of 1,2,4-triazole halogenderivatives deserves the attention [14]. Domestic scientists emphasize that accession of the chloride ion to C2-atom of propyl residue takes place with the formation of individual compounds (Fig. 10).

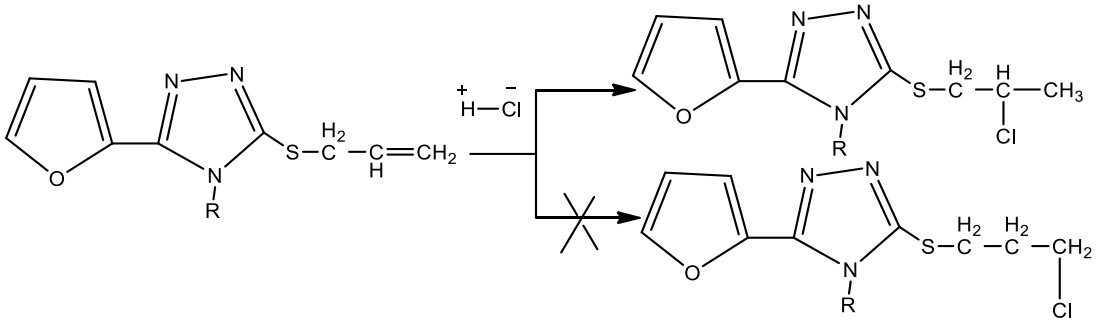

Fig 10: Interaction of aliltio-3,5-(furan-2-yl)-4R-1,2,4-triazoles of hydrogen chloride

Complex physical and chemical analysis methods confirmed that thye structure of the 3-(3-chloropropyl)-thio-5-(furan-2-yl)-4-(2-methylphenyl)-1,2,4-triazoles (Figure 10). The original method of sulfo-3,5-diamino-1,2,4-triazoles from "remains" of chloraromatic fragments offered russian inventors. [15]

Also interesting from our point of view is the method of 5,5-(1,4-phenylene)-bis-(4-(4-chlorophenyl))-4N-1,2,4-triazoles-3-thiol by Indian researchers [16]. Introduction in molecule of chlorine which enhances the antimicrobial activity (Fig. 11).

ISSN: 0975-8585

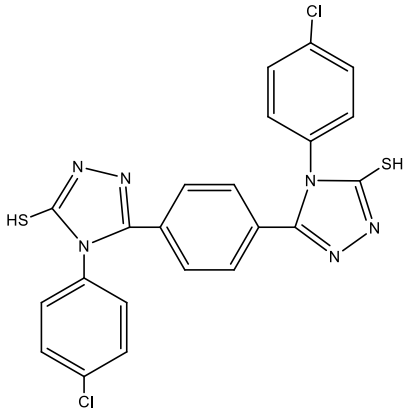

Fig 11: 5,5-(1,4-phenylene)-bis-(4-(4-chlorophenyl)-4N-1,2,4-triazole-3-thiol

The staff of the Chinese scholars studied in detail the formation erythro-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazole-1-yl)methyl]oxirane which exhibit very powerful antimicrobial properties [17] and inventors from India proved that in addition to antimicrobial activity of 3-(1,2,3-benzotriazolylmethyl)-4-(3-chloro-4-aryl-substituted-2-oxo-azetidine)-5-mercapto-1,2,4-triazoles the high antifungal activity was found [18]. The analogous biological effects have 1-[2-(2,4-dichlorophenyl)-4-alkoxymethyl-1,3-dioxolan-2-yl]-methyl-1H-1,2,4-triazoles [19] and substituted derivatives of bis[1,3,4]oxadiazol, bis[1,3,4]thiadiazol and bis[1,2,4]triazole with the structural fragments of halogen residues [20].

American inventors had patented a number of compounds which are derivatives of 1,2,4-triazole-3-thiols as inhibitors of matrix metaloprotein and TNF-α converting enzyme [21], which in the future can be used as a means to treat the osteoarthritis and rheumatoid arthritis. Chinese researchers had suggested the using of 5-n-butyl-4-(4-(2-(1H-tetrazol-5-yl)-1H-pyrrole-1-yl)phenylmethyl)-2,4-dihydro-2-(2, 6-dyhlorphenyl)-3N-1,2,4-triazole-3-one as inhibitor of angiotensin-converting enzyme [22] and diaryl-1,2,4-triazoles as a highly selective inhibitors of cyclooxygenase-2 for the treatment of inflammation [23].

The staff of American scientists patented a number of new derivatives of 1,2,4-triazoles and their tautomeric forms as potential antagonists of oxytocin, which can be used in the composition of medicines for the treatment of sexual dysfunction [24]. The original treatment of dementia with a 3-biphenyl-4-yl-4-(2-fluorophenyl)-5-isopropyl-4H-1,2,4-triazoles offer other American inventors [25].

The staff of German scientists patented in Ukraine several new derivatives of 1H-1,2,4-triazole-3-carboxamide with a trifluoromethyl fragments [26]. The authors argued that these compounds were the cannabinoid-CB1receptor ligands and may be effective in the treatment of disorders related to neurotransmission of cannabinoid-CB1 with different etiologies. Another group of German researchers has found an effective way to deal with the broad spectrum of activity against monocots and dicotyledonous plants with the use of N-(5,7-dimetoxy-(1,2,4)-triazole-(1,5-α)-pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-pyridin-3-sulfonamide [27]. The compound was effective herbicide that can be recommended for use in the spring in winter. An original way to combat pests and plant a new way to protect inventors patented a team [28]. As active ingredients authors proposed to use the 6-halogeno-(1,2,4-triazole)-(1,5-α)-pyrimidin. These derivatives were effective in the treatment of pets and their habitats, breeding sites, food, plants, seeds etc.

CONCLUSION

The analysis of available publications undoubtedly proves the prospects of finding new biologically active compounds in some halogen derivatives of 1,2,4-triazoles using a wide variety of synthetic possibilities. Scientists studied different types of biological properties of these compounds. The analysis of the literature identified several new compounds that have promising future as the original drugs and effective plant protection products.

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