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AN OVERVIEW ON 1,2,4-TRIAZOLE AND 1,3,4-THIADIAZOLE DERIVATIVES AS POTENTIAL ANESTHESIC AND ANTI-INFLAMMATORY AGENTS

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The aim. *The purpose of this review is to summarize data on the synthesis and structural modification of heterocyclic systems with triazole and thiadiazole fragments in molecules as promising objects in bioorganic and medicinal chemistry.*

Materials and methods. *The research based on bibliosemantic and analytical methods using bibliographic and abstract databases, as well as databases of chemical compounds.*

Results*. Modern medicinal chemistry faces many challenges, one of which is the determination of the activity and specificity of therapeutic agents. Recent scientific data showed that triazoles and/or thiadiazoles have broad spectrum of biological activities, in particular antimicrobial, antifungal, antiviral, anticancer and anticonvulsant. Synthetic research allows to propose a whole number of new molecular design directions of biological active triazole and/or thiadiazole derivatives, as well as to obtain directed library that include hundreds of new compounds. This review is an effort to summarize data of its analgesic and anti-inflammatory activity over the last decade. We summarized and analyzed the series of triazole and/or thiadiazole derivatives and provided data of their structure-activity relationship. For optimization and rational design of highly active molecules with optimal «drug-like» characteristics and discovering of possible mechanism of action SAR, QSAR analysis and molecular docking were summarized.*

Conclusions*. It has been shown that heterocyclic systems containing fragments of triazole and/or thiadiazole are a significant source of promising analgesic and/or anti-inflammatory agents. It has been established that the mentioned heterocyclic derivatives have a high selectivity of action, low toxicity and an effect commensurate with standard drugs*

Keywords*: heterocycles, triazoles, thiadiazoles, anti-inflammatory activity, analgetic activity, NSAIDs*

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1. Introduction

In recent years, heterocyclic compounds and their analogues are of considerable interest due to the wide range of their useful biological and pharmacological properties. Thus, different classes of heterocyclic systems underlie most existing drugs or compounds that are in the final stages of preclinical trials [1–5]. The particular interest in this context is the study of heterocyclic compounds based on azole core, which has significant synthetic and pharmacological potential [6–10]. The uniqueness of these heterocycle systems is based on easy functionalization with the possibility of obtaining various condensed [11–17] and non-condensed derivatives [18–23]. In addition, the use of modern approaches for studying this class heterocycles such as target-oriented [24–26] and diversity-oriented synthesis (DOS) approaches [27–30] are an opportunity to obtain combinatorial libraries to effectively searching new drugs or drug candidates.

The triazole core is present in various compounds characterized by pronounced antimicrobial [31–33], antifungal [32, 33], antiviral [34], anti-HIV-1 [35], antimycobacterial [31, 34], antihistamine [36], anticonvulsant [37–40], antitumor [33, 35], insecticidal [41], anxiolytic [42], analgesic [43] activities. On the other hand, thiadiazole derivatives are relevant for the searching agents with antifungal [44], antimicrobial [45, 46], antitumor [47], anticonvulsant [48], antiviral [46], antibacterial [44] activities. Triazoles and thiadiazoles exhibit a wide range of biological activity presented in various drugs, such as Trazodone (an antidepressant), Rizatriptan (an analgesic for treatment of headaches, including migraines), Hexaconazole (an antifungal agent) and Alprazolam (sedative and tranquilizer). The known modifications of the triazole or thiadizole ring have proven to be effective with greater efficiency and less toxicity. At the same time, the number of triazole and thiadiazole-base drugs currently used in the clinic as analgesics is quite small. These include Rizatriptan, which has been shown to be effective for headaches of various origins [49–54]. Given the abovementioned, triazole and thiadiazole derivatives are of interest for the search for anti-inflammatory drugs in view of both pharmacological potential and chemical novelty for modern medicinal chemistry and pharmacology.

The aim of the study was to analyze the literature data about the synthesis and biological activity evaluation of heterocyclic compounds with triazole and thiadiazole fragments in molecules.

2. Materials and methods

Bibliosemantic and analytical methods were used in the study. During the literature review were used also bibliographic and abstract databases (Pubmed), as well as databases of chemical compounds (PubChem, Reaxys and SciFinder).

3. Results and discussion

The potential nonsteroidal anti-inflammatory agents among triazolo-thiadiazole derivatives are of interest to many scientific groups [55]. Thus, *N*-[5-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-4-methyl-1,3-thiazol-2-yl]acetamide derivatives showed antiexudative activity comparable to reference drug diclofenac. Moreover, [1,2,4] triazolo[3,4-*b*][3,4-b][1,3,4]thiadiazine derivatives **1** obtained via condensation reaction of chloroacetic acid and α-haloketones also showed a significant antibacterial effect [43]. [2,1-*b*]Furan-2-yl-5-*H*-aryl-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole-6(5*H*)-thione **2** and [2,1-*b*]furan-2-yl-5,6-diaryl-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **3** derivatives possessed analgesic activity comparable to acetylsalicylic acid, under a single intragastric injection to nonlinear mice at a dose of 100 mg/kg in the model on acetic acid-induced writhing response in mice [56].

The authors [57] observed moderate antiexudative and significant antinociceptive activity of 3-β-[(*N*-benzenesulfonyl/tosyl)-4-phenylamino]ethyl-4-amino-5-mercapto-4(*H*)-1,2,4-triazoles **4**. Studied derivatives also showed a significant anti-exudative effect in the model of carrageenan edema in rats at the level of acetylsalicylic acid, as well as in the model of cotton granuloma. Moreover, the synthesized compounds did not have ulcerogenic action in experimental animals. The significant activity of these derivatives was demonstrated in the model of thermal nociceptive stimulation of tail flick, with 81.02–120.72 % inhibition compared with aspirin (49.39 % inhibition). The authors established the analgesic effect of target compounds related with a presence of biologically active sulfonamide fragment in the structure.

Synthesized 5-carbomethoxy-2-substituted-7*H*-1,2,4-triazolo[3,2-*b*]-1,3-thiazin-7-one derivatives **5** showed pronounced anti-inflammatory activity under oral administration in low doses (10 and 20 mg/kg) in models of carrageenan and serotonin edema which were equal or higher to diclofenac sodium. It should be noted that the anti-exudative activity correlated with the analgesic effect in the model of acetic acid-induced writhing response in mice. In addition, these biological effects were not accompanied by gastric lesions [58].

A pronounced antinociceptive effect was found for 3-(4-methylphenyl)-4-[3-(phenoxymethyl)-7*H*-1,2,4-triazolo[3,4-*b*][3,4-*b*][1,3,4]thiadiazine-6-yl]-1,2,3-oxadiazol-5-olates **6**, which exceed the activity of paracetamol [59] (Fig. 1).

Condensed 1,2,4-triazoles with a 2,4-dichlorophenoxyl moiety in molecules **7** showed anti-inflammatory activity under intragastrically administration in equal doses to indomethacin [60]. These compounds showed a dose-dependent anti-inflammatory effect in carrageenan and histamine edema models. Condensed derivatives with 2,4-dichlorophenoxyl group at position 6 showed the highest activity comparable to indomethacin, with 36–56 % inhibition of exudative inflammation.

3-(*N*-substituted carboxamidoethylthio)-4*H*-1,2,4-triazole derivatives **8** under administration intraperitoneally to rats at a dose of 40 mg/kg showed a significant antiexudative effect in the model of formalin edema with 25.92 %–44.44 % inhibition which exceeds reference drug diclofenac sodium (23.14 %). The anti-exudative effect of the studied compounds depends on the presence of chloro-, nitro-, methyl- or methoxy groups in the phenyl substituent. Several mentioned compounds also showed an antinociceptive effect on the hot plate model (up to 303.4 %), which exceeds the parameters of tramadol (169.4 %). In addition, the most active derivatives did not show anxiolytic activity [61].

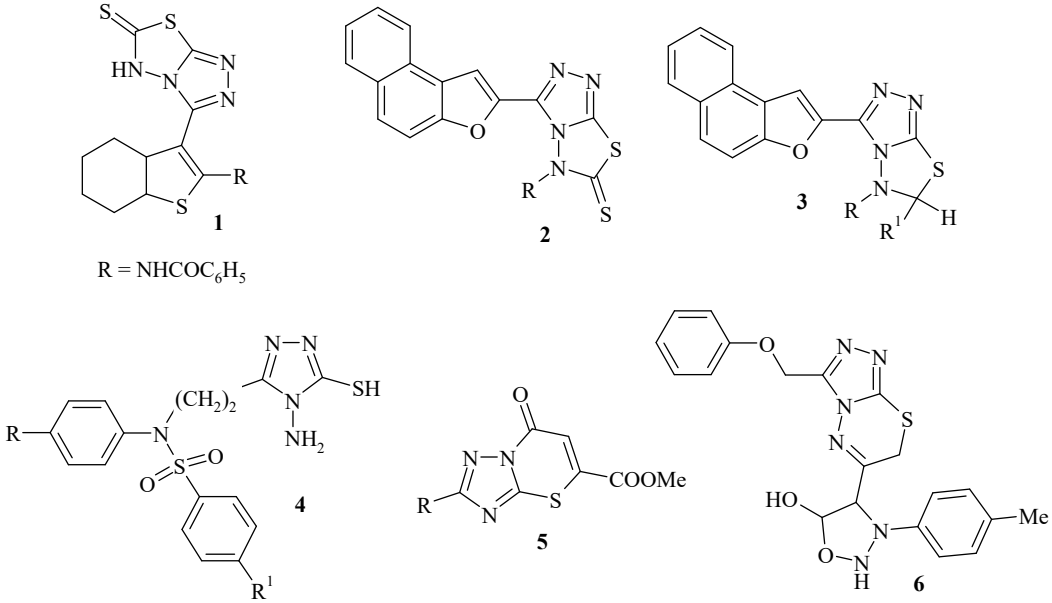

Fig. 1. Structures of derivatives 1–6

The authors [62] studied 1,3,4-thiadiazole and 1,2,4-triazole derivatives containing a phenylalanine moiety **9**. The studied derivatives had low toxicity (LD_{50} 1025–5010 mg/kg when administered intragastrically). When administered target derivatives at doses of 1/10 LD50 and 1/5 LD50 in the nystatin edema model, the compounds generally exeeded acetylsalicylic acid and phenylbutazone at the respective doses, but possess less activity than indomethacin.

Triazole-containing tetracyclic thienopyrimidines have proven to be promising as potential anti-inflammatory and analgesic agents [63]. The administration orally of mentioned compounds at doses of 10 mg/kg, predominate or are equivalent in analgesic and antiexudative activity diclofenac sodium in carrageenan edema (edema inhibition from –31.2 % to –56.1 %) and acetic acid-induced writhing response (degree of inhibition from 45.3 % – up to 71.7 %) models in mice. It worth mentioned that the tested compounds did not have ulcerogenic effect.

The authors [64] synthesized a series of 3-[2-(*N*-methylamino)phenyl]-6-[2-(2-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives **10** to assess their biological activity. Synthesized compounds were tested for anti-inflammatory activity in rats using carrageenan-induced paw edema model in rats. However, the tested compounds showed weak antiexudative activity than reference drug (diclofenac sodium). The evaluation their analgesic activity on hot-plate test led to identification the most active compound 3-[4-(*N*,*N*-dimethylamino)phenyl]-6-[2-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole, which was selected for further in-depth study.

In another study [65], the same authors studied triazolothiadiazole derivatives which contain an indole ring in structure. These derivatives show significant analgesic and anti-inflammatory activity, especially 3-(2-chloro-5-methoxyphenyl)-6-((5-methoxy-1*H*-indol-3-yl)methyl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole. The SAR-analysis showed that the introduction of electron donor groups (methyl, methoxyl) at position 5 of the indole ring leads to a decrease of anti-inflammatory and analgesic activity.

It is shown that the presence of a trichlorophenyl fragment in triazolothiadiazole and triazolothiadiazine core provides significant anti-inflammatory activity of tested compounds in the model of acute inflammation [66]. Derivative A-561 (6-(4-methoxyphenyl)-3-(2,3,5-trichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole) **11** showed the highest level of biological activity.

The authors [67] reported the synthesis of several triazole derivatives **12** and screening for their anti-inflammatory and analgesic activity. Among the fused derivatives, compounds with 3,4,5-trimethoxyphenyl and 4-fluorophenyl groups at position 6 of the basic cycle possessed the highest dose-dependent anti-inflammatory activity (Fig. 2). Thus, among the synthesized compounds 3-[2-(3,4,5-trimethoxyphenyl)ethyl]-6-(4-chlorophenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine showed the highest analgesic activity in the experiment, which was close to the effect of ketorolac. The SAR-analysis revealed that the presence of methoxy groups is favourable on the presence of analgesic activity.

Synthesized 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives were evaluated for anti-inflammatory activity in the model of carrageenan and formalin edema. The studied derivatives showed a pronounced anti-exudative effect. In particular, 3-(phenoxymethyl)-6-(3-oxo-3-phenylpropyl)-[1,2,4]triazolo[3,4][1,3,4]thiadiazoles possess prominent anti-inflammatory activity comparable to reference drug indomethacin. The SAR-analysis showed that the replacement of 3-oxo-3-phenylpropyl group in the C-6 position by other groups led to decreasing of anti-inflammatory activity. In addition, the synthesized compounds exhibited the higher level of antiexudative activity than phenoxyacetic and salicylic acid derivatives [68]. The study of analgesic activity on acetic acid-induced writhing response in mice model was shown that synthesized compounds which include 3-oxo-3-phenylpropyl group in the C-3 position of the triazolothiadiazole ring showed high level of analgesic activity comparable to standard drug (acetylsalicylic acid).

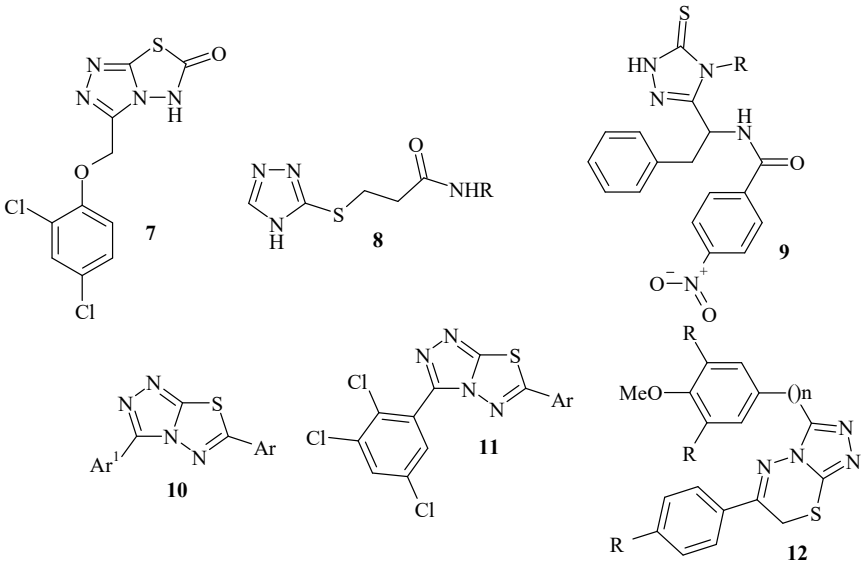

Fig. 2. Structures of derivatives 7–12

The authors [69] reported *in vitro* and *in vivo* screening for the anti-inflammatory activity of a series of pyridine-substituted triazoles and thiadiazoles **13** on carrageenan-induced paw edema model. *In vivo* experiments were performed on albino rats using indomethacin as a reference drug. 3,6-Di(pyridin-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole showed maximum anti-inflammatory activity.

Authors [70] synthesized and evaluated biological activity of 3,6-disubstituted-1,2,4-triazolothiadiazole derivatives which contain apyrazole fragment in structure. The screening results showed that 3-propyl-6-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **14** po-

sessed significant antiexudative activity on carrageenan-induced paw edema and serotonin edema models comparable to reference drug diclofenac sodium.

The authors [71] reported synthesis of several triazolothiadiazole derivatives **15** that showed significant analgesic activity in a model of visceral pain caused by intra-abdominal acetic acid in mice (modified by R. Koster, 1959). The results showed that the highest analgesic activity showed 5-methoxy-2-(3-((5,6,7,8-tetrahydro-naphthalen-2-yloxy)methyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizin-6-yl)phenol, with antinociceptive effect higher than acetylsalicylic acid. It worth mentioned that, the presence of hydroxyl and methoxy groups in the phenyl ring at position 6 may cause good analgesic activity.

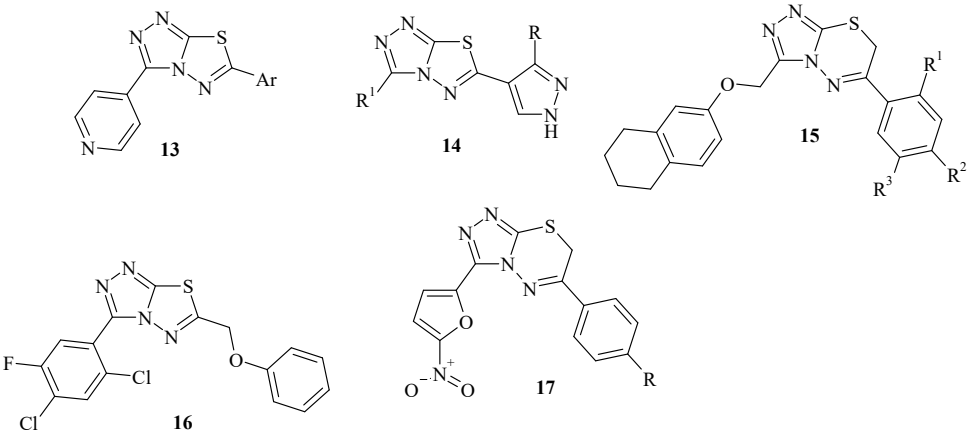

Fig. 3. Structures of derivatives 13–17

Interesting data are given by the authors [72], who report the study of the activity of numerous triazole and thiadiazole derivatives **16**. The synthesized compounds were studied for analgesic activity in the hot plate model. The screening results led identification of active compounds, namely 6-(3-chloro-4-fluorophenyl)-3-(2,4-dichloro-5-fluorophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole and 3-(2,4-dichloro-5-fluorophenyl)-6-[(4-pephenoxy)methyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole. The analgesic activity of these derivatives depends on the presence of halogen substituent (chlorine and fluorine) on both aryl rings in positions 3 and 6.

The results of a study of recently synthesized derivatives of triazolethiadiazole and triazolothiadiazines **17**, including 3-nitronaphtho[2,1-*b*]furan moiety, showed a significant antinociceptive effect of these heterocyclic compounds [73] (Fig. 3). The activity of the synthesized derivatives was comparable to the standard drug (tramadol). In addition, triazolethiadiazole and triazolothiadiazine derivatives possess other types of biological activities, namely anticancer [74–76], antileishmanial [77] and antimicrobial [78–83].

It should be noted that molecular docking studies against COX-2 [84–87], 15-LOX [88], p38 α MAP kinase [89, 90] and TNF-α [91] biotargets of triazole and thiadiazole derivatives are correlated with experimental data confirming the significant analgesic and anti-inflammatory potential of mentioned compounds.

4. Conclusion

We reviewed data on the anti-inflammatory and analgesic activity of compounds containing triazole and/or thiadiazole fragment in molecules. Data analysis showed that these derivatives are characterized by significant antinociceptive and antiexudative effects, which are often accompanied by low toxicity, lack of ulcerogenic action, which reveal the significant interest to pharmacy and medicine. The activity profile of these derivatives is based on the nature of the substituent of the basic triazole and/or thiadiazole core. The use of the obtained literature data and their systematic analysis could be promising for the rational design of potential biologically active molecules and further study of the pharmacological effect of mentioned derivatives.

Conflict of interests

The authors declare there is no conflict of interests.

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