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Mini-review

Synthetic approaches, structure activity relationship and biological applications for pharmacologically attractive pyrazole/pyrazoline–thiazolidine-based hybrids

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Abstract

The features of the chemistry of 4-thiazolidinone and pyrazole/pyrazolines as pharmacologically attractive scaffolds were described in a number of reviews in which the main approaches to the synthesis of mentioned heterocycles and their biological activity were analyzed. However, the pyrazole/pyrazoline–thiazolidine-based hybrids as biologically active compounds is poorly discussed in the context of pharmacophore hybrid approach. Therefore, the purpose of this review is to summarize the data about the synthesis and modification of heterocyclic systems with thiazolidine and pyrazoline or pyrazole fragments in molecules as promising objects of modern bioorganic and medicinal chemistry. The description of biological activity was focused on SAR analysis and mechanistic insights of mentioned hybrids.

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1. Introduction

Pharmacophore hybrid approach is a current concept in drug design and development to produce molecules with improved affinity and efficacy. There are some reviews dealing with the concept of molecular hybridization and the promises/challenges associated with these hybrid molecules along with recent advances on anticancer hybrids \cite{1-3}. Various heteroaryl based hybrids in particular isatin and coumarins \cite{3} or indoline-thiazolidinones \cite{4} have been recently reviewed as conjugates with remarkable inhibitory potential.

Design of new drug-like small molecules based on the pharmacologically attractive scaffolds of thiazolidine (4-thiazolidinone) \cite{5-10} and pyrazole or pyrazoline \cite{11-15} is a reasonable and promising direction in modern medicinal chemistry. The chemical approaches for the synthesis of thiazolidinone- and pyrazole-based derivatives and their pharmacological activity were described in a numerous reviews \cite{5-12}. However, the pyrazole/pyrazoline–thiazolidine-based conjugates as biologically active compounds are poorly reviewed in the context of pharmacophore hybrid approach.

The recent synthetic studies of pyrazole–thiazolidines and related hybrids and biological investigations for their antitumor, antimicrobial, antiviral, antiparasitic, anti-inflammatory activities allowed to identify the promising drug-like compounds. Thus, the pyrazole–thiazolidinones/thiazoles have been patented as inhibitors of necroptosis \cite{16}, VHR protein tyrosine phosphatase inhibitors \cite{17}, Pin1-modulating compounds \cite{18}, compounds for modulating RNA-binding proteins \cite{19} and activators of pro-apoptotic BAX \cite{20}. In addition, the pyrazole–thiazolidinone hybrids have been studied for their possibility to inhibit the TNF-α–TNFRc1 interaction \cite{21}, as inhibitors of histone acetyltransferases \cite{22} and inhibitors of COX \cite{31,39} and ADAMTS-5 enzymes \cite{83}. Therefore, the purpose of this review is to summarize the data about the synthesis and biological activity of heterocyclic systems with thiazolidine and pyrazole/pyrazoline fragments in molecules. The most promising pyrazole–thiazolidinone/thiazole hybrids and target heterocycles that have been reviewed as fragments of hybrid molecules are depicted in Fig. 1.

The reviewed hybrids were classified as 2-, 3- and 5-pyrazole/pyrazoline-substituted thiazolidines based on linkage of target heterocyclic cores. The basic approaches for the synthesis of...
mentioned derivatives provide a combination of two “small” molecules in aminolysis reactions, acylation and Knoevenagel procedure or heterocyclization of monocyclic compounds via the [2+3]-cyclization reaction yielding the series of non-condensed bicyclic systems.

2. Synthetic approaches for 4-thiazolidinone-based hybrids with pyrazole/pyrazoline fragments in position 2

Detailed biological activity evaluation of pyrazoline–thiazolidine conjugates 1.2–1.7 and pyrazoline–thiazole 1.8, 1.9 (Fig. 2), synthesized via the [2+3]-cyclocondensation of 4,5-dihydropyrazole-1-carboxylic acids 1.1 as S,N-binucleophiles in reactions with equivalents of dielectrophilic synthon [C2]2+, allowed to identify compounds with antimicrobial [23–28], antiviral [29,30], anti-inflammatory [31], antitumor [32–35] and insecticidal [36] activities. For synthesis of target derivatives α-halogenocarboxylic acids [31,33] and their ethyl esters [23–29,35,36], maleic anhydride [30], maleimides [30,38], β-aroylacrylic acids [30], dimethyl acetylenedicarboxylate [37], bromoacetophenones [23,24,28,29,35] and ethyl 4-chloroacetooacetate [35] were used as equivalents of dielectrophilic synthon [C2]2+.

Three-component one-pot reaction that includes [2+3]-cyclocondensation of 4,5-dihydropyrazole-1-carboxylic acids 1.1 with chloroacetic acid and the further Knoevenagel reaction with aromatic aldehydes [33,34] and isatin derivatives [32] is an effective approach for design of new anticancer agents among the pyrazoline–thiazolidiones 1.10, 1.11 (Fig. 3).

The reaction between pyrazolyl-imines [39,40] or pyrazolyl-hydrazones [41] and thioglycolic acid or its esters is widely used approach for the synthesis of 4-thiazolidinone conjugates 1.12, 1.13

Fig. 1. Heterocycles for pyrazole/pyrazoline–thiazole/thiazolidine hybridization and the most promising conjugates.

Fig. 2. Synthesis of pyrazoline–thiazolidinones via [2+3]-cyclization reactions.
with pyrazole moiety in position 2. A. Khodairy proposed a synthesis of 2-substituted 4-thiazolidinone with benzoypyran [2,3-c] pyrazol-3-one fragment 1.14, using N-cyanoacetyl-benzopyranopyrazoline [42] as a starting compound (Fig. 4).

Another direction for synthesis of pyrazole-substituted thiazolidine 1.16 (Fig. 5) was realized by the creation of pyrazole moiety via the reaction between 5-fluoro-2-hydrazino-4-hydroxy-4,5-bis(trifluoromethyl)-1,3-thiazoline 1.15 with acetoacetone [43,44].

A broad group of pyrazole–thiazolidinone derivatives exemplified by 2-imino-4-thiazolidinones (pseudothiohydantoin) 1.18, 1.19 were synthesized via [2+3]-cyclocondensation of pyrazole substituted asymmetric bis-thioureas 1.17 as S,N-binucleophiles with some equivalents of dielectrophilic synthons [C2]2+ (ethyl 2-chloroacetate [45,46], dimethyl acetylenedicarboxylate [47]). Simultaneously, bioisosteric pyrazolyl-2-iminothiazolidines 1.20 [46] were obtained by reaction of thioureas 1.17 with α-bromoaacetophenone (Fig. 6).

Aiming to search for new anticancer or antimicrobial compounds among pyrazole–thiazolidinone conjugates the pyrazole-sulfonylethiourea 1.21 were used as starting materials. The reaction between compounds 1.21 and ethyl 2-chloroacetate or α-bromoaacetophenone resulted in formation of the corresponding pyrazole–thiazolidinones 1.22 and pyrazole–thiazolidines 1.23 with sulfonylimine linker group [48–53] (Fig. 7).

Another approach for the synthesis of pyrazole derivatives of pseudothiohydantoin 1.26 was suggested by B. Insuasty et al. [54]. The synthesis of target compounds was carried out via aminolysis of 5-arylidene-2-thioxo-4-thiazolidinones (5-arylidenerhodanines) 1.24 by 4,5-diaminopyrazoles 1.25 (Fig. 8).

A row of 2-pyrazolyl-hydrazide–thiazolidinones 1.28–1.30 was synthesized via [2+3]-cyclocondensation of thiosemicarbazones 1.27 with α-halogenoarboxylic acids derivatives or maleic anhydride [55–60]. The pyrazole with bioisosteric 2-thiohydantoin 1.31 [61] and thiazolidine 1.32 [55–60] fragments were obtained by reaction of thiosemicarbazones 1.27 with chloroacetic acid in pyridine or α-bromoacetophenone. However, the reaction of thiosemicarbazones 1.27 with acetic anhydride or iron chloride was accompanied by the formation of pyrazole–thiadiazole derivatives 1.33, 1.34 [56] (Fig. 9).

Pyrazole-substituted thiosemicarbazides 1.35 were used for synthesis of the pyrazole–thiazolidinones 1.36 with carboxydrazide linker group [62,63]. The three-component one-pot reaction between thiosemicarbazides 1.35, chloroacetic acid and aromatic aldehydes accompanied by formation of the corresponding 5-arylidene-4-thiazolidinones 1.37 [63,64]. The modification of 1.35 in sulfuric acid medium gave pyrazole–thiadiazole 1.38 [64]. The reaction of compounds 1.35 with α-bromoaacetophenones was accompanied by the formation of corresponding pyrazole-thiazolidine conjugates 1.39 [62–64] (Fig. 10).

3. The main methods for synthesis of 4-thiazolidinones with pyrazole/pyrazoline moiety in position 3

Synthesis of 2-diazole-substituted 4-thiazolidinones was achieved via the [2+3]-cyclocondensation of the pyrazole-based asymmetric thioureas 1.17 as S,N-binucleophiles (see Fig. 6). At the same time, the numerous papers represent the data about obtaining of 4-thiazolidinones with diazole moiety in 3 position (compound 2.1, Fig. 11), in particular via the reaction of thioureas with ethylchloroacetate [65].

The dithiocarbamate method of 2-thioxo-4-thiazolidinones (rhodanines) synthesis is a convenient and often used variant of the synthesis of 4-thiazolidinone derivatives based on the [2+3]-cyclocondensation [5]. R.M. Mohareb et al. had successfully applied the dithiocarbamate method for the synthesis of 3-(pyrazol-5-yl)-2-thioxo-4-thiazolidinone via two-stage process based on the reaction between 3-phenyl-5-aminopyrazole 2.2 and carbon disulfide in an alkaline medium and subsequent cyclization with

Fig. 3. Three-component one-pot reactions in synthesis of 2-pyrazolinyl-4-thiazolidinones.

Fig. 4. Thioglycolic acid reagent in thiazolidinone ring-formation reactions.
ethyl 2-bromoacetate [66]. The presence of the methylene group in the position 5 of thiazolidine cycle allowed the authors to carry out the structural modification of pyrazole–thiazolidinone 2.3 in the Knoevenagel reaction (ethanol medium, catalyst – piperidine) and diazotization to get the 5-substituted derivatives 2.4, 2.5.

Starting from rhodanine 2.3 the alternative methods for the synthesis of condensed pyrano[2,3-d]thiazole system 2.6 with pyrazole moiety in position 3 were proposed, namely the reaction of 5-arylidenetherodanines 2.5 with malononitrile or by heterocyclization of compound 2.3 with benzylidenemalononitrile. Pyrazole–thiazolidinone 2.3 in the presence of hydrazine hydrate undergoes ring transformation with obtaining of the pyrazole-triazole 2.7 (Fig. 12).

Various 4-thiazolidinones were synthesized by reaction of α-mercaptocarboxylic acids (especially thioglycolic acid) with isothiocyanates (R–N=C=S). Thus, a pyrazole–thiazolidinone 2.8 with phenyl sulfonamide linker group was obtained based on the mentioned approach [67]. There were described the synthesis of 3-pyrazole-substituted or polyheterocyclic derivatives of 4-thiazolidinones 2.9, 2.10 based on the reaction between thioglycolic acid and corresponding imines and methylidenehydrazides or three-component reaction involving thioglycolic acid, aromatic aldehydes and heterocyclic amines containing diazole fragment [68–72]. The reaction of isatin with heterocyclic amines led to Schiff’s bases which were further reacted with thioglycolic acid to form 3-diazole-substituted indoline-spirothiazolidinones 2.11 [73,74] (Fig. 13).

The reaction between trithiocarbonyl diglycolic acid and amines in alcohol or alcohol–water medium (Holmberg synthesis) is a convenient and effective method for synthesis of 3-substituted rhodanines, especially based on the aromatic amines and carboxylic acid hydrazides [5]. The mentioned reaction was used by Augustin M. et al. for synthesis of rhodanine 2.12 with benzopyrazole fragment in position 3 [75] (Fig. 14).
The method for synthesis of pyrazole–thiazolidinone 2.15 (Fig. 15) with acetamide linker group was proposed based on the reaction of 5-arylidenehydrazine-3-acetic acid 2.13 and 5-aminopyrazole 2.14 in DMF in the presence of HATU (1-[bis(di- 

![Fig. 9. Synthesis of pyrazole derivatives with thiazolidinone, imidazolidine and thiazoline fragments in molecules.](image)

Semantically, the reaction can be described as follows:

1. **Synthesis of structurally related azolidine–pyrazolines** 2.16, 2.17 was proposed based on N-alkylation reaction of potassium salts of 2,4-thiazolidinedione, hydantoin and their 5-arylidene derivatives, obtained in situ (Fig. 16). 2-Chloro-1-(3,5-diarylpyrazolin-1-yl)-ethanones were successfully used as alkylation agents [77].

4. **The main approaches to the synthesis of 4-thiazolidinones with pyrazole/pyrazoline moiety in position 5**

   One of the main approaches for the synthesis of 5-pyrazole/pyrazoline substituted 4-thiazolidinones is based on Knoevenagel reaction of 4-thiazolidinones [5]. A numerous 1-, 3- and 5-substituted pyrazole-4-carbaldehydes were used as carbonyl compounds and allowed to obtain a series of new 2,4-thiazolidinediones [78–81], rhodanines [82–86] and 2-imino-4-thiazolidinones with pyrazole moiety (compounds 3.1) [87–89]. The synthesis of pyrazolone–thiazolidinones 3.2 was conducted by reaction of 3-arylrhodanines with 4-acetyl-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one [90]. Position 5 of thiazolidine cycle was
successfully modified in diazo coupling reaction [91] using pyrazolyl diazonium chloride yielding compound 3.3 (Fig. 17).

The synthesis of pyrazoline–indoline–thiazolidinone conjugates 3.5, 3.6 was realized by the Knoevenagel reaction of pyrazoline–isatines 3.4 with 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinone and 2-amino-4-thiazolidinone in the acetic acid medium and in the presence of sodium acetate [92] (Fig. 18).

The synthesis of pyrazolone–thiazolidinones 3.7 (Fig. 19) was achieved based on the reaction between isonitrrosorhodanines and 5-methyl-2,4-dihydropyrazol-3-one using piperidine as basic catalyst [93].

Magdy Ahmed Ibrahim et al. investigated a modification of 5-[4-oxo-4H-chromen-3-ylmethylene]-1,3-thiazolidin-2,4-dione 3.8 in particular in the ring-transformation reactions of chromene cycle with hydrazine hydrate and phenylhydrazine. These reactions
allowed to obtain the corresponding pyrazole-thiazolidinones 3.9 [94]. Using hydrazine hydrate the structure of final compounds depended on the reaction medium. Thus, 1N-non-substituted pyrazoles were obtained in alcohol medium and in the presence of sodium ethylate, while 1N-acetylderivatives were formed in acetic acid. The reaction of the compound 3.8 and 1-phenylpyrazolidin-
3.5-dione in the presence of sodium ethylate led to formation of polyheterocyclic system 3.10 (Fig. 20).

Synthesis of 5-pyrazolyl-4-thiazolidinones with ethylene linker group 3.11 was performed via the [2 + 3]-cyclocondensation reaction of thiourea with γ-pyrazolyl-α-chlorobutanoates [95] (see Fig. 21).

Pharmacologically attractive 5-(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)rhodanines 3.12 (Fig. 22) were synthesized following hetero-cyclization of 2-thiazolidinyl-3-oxobutanoates with phenylhydrazine or conjugation of 4-bromopyrazol-5-ones to 3-arylhodanines [96].

The group of pyrazoline–thiazolidinones 3.13 was obtained by reaction of 5-bromo-2,4-thiazolidindione with 3,5-diarylpyrazolines (Fig. 25). 5-Pyrazoline substituted 4-thioxo-1,4-yl)rhodanines 3.14 (Fig. 22) were synthesized following hetero-cyclization of 2-thiazolidinyl-3-oxobutanoates with phenylhydrazine or conjugation of 4-bromopyrazol-5-ones to 3-arylhodanines [96]. The following approach to the synthesis of pyr-azolone–thiazolidinone conjugates 3.16 with carbonyl methylidene linker group was based on the acylation reaction of 3,5-diarylpyrazolines in alcohol medium (Fig. 23). The synthesized compounds were modified in position 3 of thiazolidine cycle by Mannich reaction with secondary cyclic amines and alkylation re-actions forming 3.14, 3.15 [97].

To explore the structure-antitrypanosomal activity relationship the pyrazoline–thiazolidinone conjugates 3.18 were synthesized through the reaction of the 5-ethoxymethylidenerhodanines with 3,5-diarylpyrazolines (Fig. 24). The further reaction of substances 3.16 with chloroacetamides via N-alkylation reaction led to derivatives 3.17 [97].

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The SAR study revealed that: (1) potent anti-cancer activity of tested compounds depended on the presence of a combination of three heterocycles in one molecule, thus the pyrz-azoline–thiazolidinone–isatin conjugates were more active in comparison with pyrazoline–thiazolidinone or pyrazole-indoline-2-one systems; (2) attachment of halogen (Br or Cl) to 5-position of isatin scaffold allowed to gain one log unit of activity (GI50 level), in comparison with 5-unsubstituted isatin analogs; (3) introduction of a methyl group or CH2COOH group at 1-position of the pyrazoline cycle, (2) introduction of p-OH group in 5-benzylidene fragment enhanced potency, and (3) the positional isomers, namely 2-pyrazoline 4.2 and 4-pyrazoline 4.3 substituted thiazolones are promising compounds for further optimization (Fig. 27).

Novel pyrazoline–thiazolidinone–isatin 4.4 and pyrazole-indoline-2-one 4.5 conjugates were designed as potential anti-cancer agents (Fig. 28). The most effective anticancer compound 4.6 was found to be active with a mean GI50 and TGI values of 0.071 μM and 0.76 μM, respectively and demonstrated the highest anti-proliferative influence on the non-small cell lung cancer cell line HOP-92 (GI50 < 0.01 μM), colon cancer line HCT-116 (GI50 = 0.018 μM), CNS cancer cell line SNB-75 (GI50 = 0.0159 μM), ovarian cancer cell line NC/ADR-RES (GI50 = 0.0169 μM) and renal cancer cell line RXF 393 (GI50 = 0.0197 μM). The SAR study revealed that: (1) potent anti-cancer activity of tested compounds depended on the presence of a combination of three heterocycles in one molecule, thus the pyrazoline–thiazolidinone–isatin conjugates were more active in comparison with pyrazoline–thiazolidinone or pyrazole-indoline-2-one systems; (2) attachment of halogen (Br or Cl) to 5-position of isatin scaffold allowed to gain one log unit of activity (GI50 level), in comparison with 5-unsubstituted isatin analogs; (3) introduction of a methyl group or CH2COOH group at 1-position of isatin fragment led to the loss of activity; (4) the nature of a substituent in the 5-aryl fragment also had an influence on the antitumor activity. Therefore, the introduction of electron-withdrawing group – 4-chlorine improved the antiproliferative activity in comparison with electron-donor 2-OH, 4-OMe and 4-NMe2 groups. This would indicate that decreased of electron density on 5-aryl moiety is important for the inhibitory activity; and (5) substitution of the phenyl fragment in 3 position of pyrazoline cycle on naphthalene-2-yl substituent did not have significant influence on antitumor activity, but introduction of the 4-methoxyphenyl group in the mentioned position limited this effect [32].
Y. Rajendra Prasad et al. synthesized a series of pyrazoline-thiazoles 4.7, 4.8, and examined their antitumor activity in vitro on tumor lines: Hela (human cervix carcinoma cell line), A549 (human lung adenocarcinoma cell line), MCF-7 (human breast adenocarcinoma cell line), A2780 (human ovarian cancer cell line) and BGC-823 (human gastric cancer cell line), using the MTT
method. As a result of studies two hit-compounds 4.10 and 4.11 were selected. SAR analysis showed that the determining factor for expression of antitumor activity is the structure of the substituent in the 4 position of thiazole (Fig. 29). A modification of the ester group into hydrazide and, subsequently, a hydrazone gave the potentiation of antitumor properties. At the same time, pyrazoline-thiazolidinones 4.9 had no significant cytotoxicity [35].

The series of pyrazoline–thiazolidine-based compounds were tested for antitumor activity according to standard NCI protocol and 4-thiazolidinone derivatives with pyrazoline fragment 4.12, 4.14, 4.17 showed moderate cytostatic effect. The group of publications includes the synthesis of these pyrazoline–thiazolidinones 4.12, 4.14, 4.17 and pyrazoline–thiazolidines 4.13, 4.15, 4.16, 4.18 with diversity of substitution in pyrazole core. The analysis of mentioned results demonstrates that the modification of pyrazoline fragment is not crucial to the implementation of antineoplastic action (Fig. 30). This statement is evidenced by the level of efficiency of compounds 4.12–4.18 with moderate rates of effective
Magdy I. El-Zahar et al. synthesized a group of benzofuran–pyrazole with various heterocycles, including thiazole (4.19) and thiazolidine (4.20) fragments for screening of antitumor activity on lines: HEPG2 (liver carcinoma cell line) and HELA (cervix carcinoma cell line). Interestingly, each of these compounds showed selective effect on one of the lines similar to 5-fluorouracil (Fig. 31).

Synthesis and study of antitumor activity of pyrazole-thiazolidinone on lung cancer MCF-7 line were conducted by Arun M. Isloor et al. Among the studied conjugates the compound 4.21 was the most active with the effective concentration IC_{50} = 22 μM. The presence of o-tolyl fragment was most favorable for the anticancer effect, while substitution with napthyl ring caused complete loss of activity (Fig. 32).

An important achievement in the study of anticancer pyrazole-thiazolidinone hybrid compounds is the establishing of the necrosis inhibition for pseudothiohydantoin derivatives with pyrazole moiety in 5 position (Fig. 33). Among these derivatives a potential inhibitor Necrostatin-7 (Nec-7) was identified with the activity index of 10.6 μM. Further studies aiming to optimize of Nec-7 molecule, were focused on the modification of thiazole fragment, replacement of substituents in the phenyl ring and replacement of pyrazole cycle by other heterocycles. It was established that the replacement of thiazole fragment by the 1,3,4-thiadiazole led to the complete loss of activity. The introduction of the methyl group in...
the 4 position of thiazole caused a slight gain of inhibitory action, while presence of methyl in the 5 position of thiazole had a negative effect. The most effective direction for modification of Nec-7 was the replacement of fluorine atom in the 4 position of benzene core. Thus, the introduction of morpholine (4.22), phenol (4.23) and phenyl sulphonic (4.24) fragments allowed to get 3–7 fold potentiation in comparison to Nec-7. In general, it should be noted that the presence of the substituent in the 4 position and its nature was crucial for the implementation of necroptosis inhibitory activity, because the change of a fluorine atom position was accompanied by loss of activity. The authors synthesized a group of related compounds with aromatic heterocycles (triazole and isoxazole) to establish the impact of pyrazole cycle for activity. This modification resulted in the loss of inhibitory activity, which confirmed the importance of pyrazole moiety in the analogs Nec-7 [87].

The study of antitumor activity for pyrazole-rhodanines allowed to identify the compound 4.25, which proved effective inhibitory effect on the most of the 60 tumor lines at micromolar concentrations according to NCI protocol (Fig. 34). The substance 4.25 was characterized by a selective effect on leukemia and lung cancer cell lines – especially on HOP-92 (lung cancer) with the values of effective concentration and cytotoxicity GI_{50} = 0.62 μM and LC_{50} > 100 μM, respectively [82].

Manal Sarkis et al. carried out the synthesis of new bis-thiazolone derivatives as potential inhibitors of CDC25V phosphatase (specified enzyme involved in cell cycle progression and unregulated tumor development). Aiming to investigate the selectivity, the affinity of the compounds was studied to PTP1B (Protein Tyrosine Phosphatase 1B) and VHR (Vaccinia virus H1 Related – a dual-specificity phosphatase). Overall 31 compounds from bis-thiazolidinone group were synthesized and most of them displayed inhibitory activity with micromolar IC_{50} values lower than the corresponding monomers. Mentioned group of the compounds included the thiazolidinone–indazole conjugate 4.26 (Fig. 35). It was established that the replacement of a 4-hydroxyphenoxy fragment with indazole was accompanied by selective inhibition of CDC25B phosphatase and loss of PTP1B inhibitory activity (abolished PTP1B inhibition) [99].

Screening of in vitro antitumor activity for 5-pyrazoline substituted 4-thiazolidinones (compounds 4.27 and 4.28) was carried out within the DTP NCI [77,97]. Overall tested substances
had a moderate activity, but two compounds were identified with selective effect on leukemia cell lines with effective concentration \( GI_{50} \) 2.12 - 4.58 \( \mu M \) (4.29) and 1.64 - 3.20 \( \mu M \) (4.30). SAR analysis showed that the introduction of the linker group between heterocycles promoted the potentiation of antitumor activity, however, modification of 3N-position of thiazolidinone cycle via Mannich reaction and alkylation was not effective approach to optimization of hit-compounds (Fig. 36).

5.2. Antimicrobial and antifungal activity of pyrazoline–thiazolidinones

The search for new antimicrobial and antifungal agents among pyrazoline–thiazolidinone related conjugates is a promising direction for biological testing of mentioned compounds. Mervat M. El-Enany et al. synthesized the group of 4-thiazolidinones and thiazoles with pyrazoline fragment in 2 position and studied their antimicrobial activity against Gram-positive bacteria (Staphylococcus aureus ATCC 29213, Bacillus subtilis ATCC 6633, Bacillus megaterium ATCC 9885, Sarcina lutea), gram-negative bacteria (Klebsiella pneumonia ATCC13883, P. aeruginosa ATCC27953, E. coli ATCC 25922) and fungi (Saccharomyces cerevisiae and C. albicans NRRLY-477) compared with Ciprofloxacin and Ketoconazole [23]. Among the tested thiazole–pyrazolines compound 4.33 showed the highest activity for strain P. aeruginosa (MIC = 8.25 \( \mu g/mL \)), which was twice higher than for Ciprofloxacin. Activity of 4.34 appeared commensurate with the drug for bacteria S. aureus and B. subtilis (MIC = 8.25 \( \mu g/mL \)). At the same time 4.35 showed a high antifungal activity (MIC = 8.25 \( \mu g/mL \)). It should be noted that the replacement of thiazole fragment with the 4-thiazolidinone was accompanied by the loss of antimicrobial activity against most types of bacteria and fungi, but compound 4.36 showed the highest activity in B. megaterium and E. coli, which were much less sensitive to the action of thiazole–pyrazolines (Fig. 37). Study of antimicrobial activity for structurally related quinolines–pyrazoline–thiazolidones 4.37 against strains E. coli (MTCC 443), P. aeruginosa (MTCC 1688), S. aureus (MTCC 96), Streptococcus pyogenes (MTCC 442) and antifungal effect on C. albicans (MTCC 442) showed that the introduction of the linker group between heterocycles promoted the potentiation of antitumor activity.

Fig. 34. Selective antitumor activity of pyrazole-rhodanine 4.25.

Fig. 35. Bis-thiazolone with indazole fragment as potential inhibitor of CDC25V phosphatase.

Fig. 36. Antitumor activity of 4-thiazolidinones with pyrazolines in 5 position.
227). Aspergillus niger (MTCC 282) and Aspergillus clavatus (MTCC 1323) evidenced of their minor or moderate activity against most types of microorganisms with MIC values range = 50–500 μg/mL [25]. However, among the above groups of compounds 4.38 could be selected, which showed 2–8 times higher bactericidal activity in experiment than Ampicillin and was twice active than Crisefulvin on fungi. The mentioned compound showed the highest activity with the value of MIC 12.5 μg/mL to P. aeruginosa (Fig. 37).

C.S. Reddy et al. performed the synthesis and study of antimicrobial activity of thiazolidinone–pyrazoles 4.39 against the B. subtilis, S. aureus, E. coli and S. pyogenes. It was established the moderate effect of mentioned compounds (MIC = 6.25–50 μg/mL) (Fig. 38). The introduction of chlorine, nitro or hydroxyl groups in the para-position of the benzene ring resulted in 2–4 fold potentiation of activity in comparison to 3-phenyl-4-thiazolidinones. However, replacement of the phenyl moiety to pyridine (4.40) or pyrimidine was particularly effective, which allowed to get 4–8 fold enhance of efficiency [100].

The pyrazole–thiazolidinones 4.41 or pyrazole–thiazoles 4.42, coupled by hydrazone linker group were investigated as promising agents with antimicrobial and antifungal activity. It was found that the compound 4.41b (R = Me) showed comparable activity (MIC = 25 μg/mL) with Ampicillin against E. coli, and the compound 4.41c (R = Cl) appeared to be the most active on C. albicans (MIC = 12.5 μg/mL) (Fig. 39). Overall, pyrazole-thiazolidinones 4.41 had higher activity than related pyrazole-thiazoles 4.42 [60]. Adnan A. Bekhit et al. synthesized the pyrazoline–thiazoles and thiazolidinones with sulfanilamide group. Among the studied pyrazole-thiazolidinones 4.43 and pyrazole–thiazoles 4.44 the compounds 4.43b (R = Me) and 4.44a (R = H) (Fig. 39) were most effective against E. coli (MIC = 25 μg/mL) [56]. The study of wide range of antimicrobial and antifungal activities of new benzofuranyl–pyrazoles with thiazolidinone fragment was conducted by Bakr F. Abdel-Wahab et al. The compound 4.45 showed activity against C. albicans and B. subtilis, and thiazole-derivative 4.46 was effective against the E. coli [62] (Fig. 40). To continue the research of pyrazole derivatives with different heterocycles, authors conducted the synthesis of new derivatives of pyrazole with thiophene fragment 4.47–4.49, including pyrazole-thiazolidine 4.50 (Fig. 40) and offered a wide range of biological studies, including the evaluation of antimicrobial activity against the following microorganisms: S. aureus ATCC 29213, B. subtilis ATCC6633, Salmonella typhi, Enterobacter Cloaca ATCC3047, K. pneumoniae ATCC13883, P. aeroginosa ATCC27953, E. coli ATCC 25922, Enterococcus faecalis ATCC29212, Mycobacterium phlei, S. cervisiae and C. albicans NRRL Y-477. Among the tested compounds 4.47 and 4.49 showed high/good or moderate efficiency against all strains of microorganisms. While compound 4.48 had proved to be the most effective on E. faecalis (MIC = 83.3 μg/mL), compound 4.50 was effective bactericidal agent on the strain S. aureus (MIC = 20.8 μg/mL) and showed significant antifungal effect on S. cervisia (MIC = 41.6 μg/mL) [58].

Evaluation of antimicrobial activity for thiazolidines with 5-pyrazolone fragment 4.51–4.53 (Fig. 41) revealed their effectiveness on B. subtilis NCTC 10400, S. aureus ATCC 25923, E. coli ATCC 25922, P. aeroginosa ATCC 10415) and fungi C. albicans TMRU 3669, A. niger ATCC 6265 [57].

An antimicrobial screening was carried out for 3-pyrazolinyl-4-thiazolidinones against gram-positive bacteria S. aureus MTCC096, B. subtilis MTCC 441 and Staphylococcus epidermidis MTCC435, gram-negative bacteria E. coli MTCC 443, P. aeroginosa MTCC 424, S. typhi MTCC 733 and K. pneumoniae MTCC 432, and antifungal effect was studied on A. niger MTCC 282, Aspergillus flavigus MTCC 343, Aspergillus flavus MTCC 277 and C. albicans MTCC 227. In general the tested compounds (Fig. 42) showed promising antimicrobial activity. However, it could be emphasized that the bis-spiroindolones 4.55 showed better growth inhibition compared with compounds 4.54 [101].

S.S. Reddy et al. proposed the synthesis of pyrazole-pyrimidine–thiazolidinones 4.56 (Fig. 43) and the study of their

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![Fig. 37. Pyrazoline–thiazolidinone hybrids with antimicrobial activity.](image-url)

![Fig. 38. SAR analysis of antimicrobial pyrazole–thiazolidinone hybrids.](image-url)
antimicrobial (B. subtilis MTCC 441, Bacillus sphaericus MTCC 11, S. aureus MTCC 96, P. aeruginosa MTCC 741, Klebsiella aerogenes MTCC 39 and Chromobacterium violaceum MTCC 2625) and antifungal (C. albicans ATCC 10231, Aspergillus fumigatus HIC 6094, Trichophyton rubrum IFO 9185 and Trichophyton mentagrophytes IFO 40996) activities. Despite the wide range of antimicrobial research, none of the tested compounds was more active than Penicillin (MIC = 1.56–12.5 μg/mL). The range value of the minimum inhibitory concentration was 13–30 μg/mL. However, it should be noted an antifungal activity of pyrazole-pyrimidine–thiazolidinones 4.56.

The compounds with furane and 4-dimethylaminophenyl-groups in position 2 of thiazolidinone showed a higher or comparable efficacy (MIC = 14–22 μg/mL) to Fluconazole [72].

Among 5-pyrazolyl-4-thiazolidinones the compounds 4.57 (Fig. 44) were investigated for their antimicrobial activity. The most effective pyrazole-thiazolidinones included the 4-Br-phenyl or thiophene fragments in molecules and showed 2–4 times higher efficiency (MIC = 16–31 μg/mL) in comparison with other derivatives [80]. The moderate antimicrobial activity towards E. coli and S. aureus was identified for 3N-glycoside substituted 2-thioxo-
4-thiazolidinone derivatives \textsuperscript{4.58} (Fig. 44). The \( p \)-bromophenyl substituted derivative showed the highest efficiency against \textit{E. coli} (MIC = 143 \( \mu \)g/mL) but was 3 times less active than tetracycline (MIC = 39 \( \mu \)g/mL) \cite{84}.

However, the most promising group of antimicrobial agents is 5-pyrazolylrhodanines \textsuperscript{4.59} \textsuperscript{e} \textsuperscript{4.63} \cite{85,86,102,103}. Antimicrobial activity of these substances was studied against methicillin- (MRSA) and quinolone-resistant (QRSA) \textit{S. aureus}. Compounds \textsuperscript{4.59} \textsuperscript{e} \textsuperscript{4.61} exhibited stronger activity than the standard drugs, norfloxacin and oxacillin, with MIC values of 1–2 mg/mL. SAR analysis for pyrazole-rhodanine derivatives \textsuperscript{4.62} \textsuperscript{e} \textsuperscript{4.63} revealed the importance of aryl moiety presence in the pyrazole ring for expression of antimicrobial action and a number of substituents that considerably increased effectiveness were identified (Fig. 45).

5.3. Antiviral and antiparasitic activity of pyrazole–thiazolidinone hybrids

The search for new chemotherapeutic agents among pyrazole–thiazolidinones is not limited by anticancer and antimicrobial studies. The evaluation of antiviral and antiparasitic activities for mentioned hybrid compounds allowed identifying promising hit-compounds and conducting SAR analysis. Osama I. El-Sabbagh proposed the synthesis of a group of pyrazoline–thiazolidinones \textsuperscript{4.64} and structurally related pyrazoline–thiazoles \textsuperscript{4.65} (Fig. 46) and performed a study of a wide range of antiviral activity. It should be noted that described compounds showed selective activity. However, one derivative (\( Ar = 4-\text{Me}-\text{C}_6\text{H}_4 \)) among compounds \textsuperscript{4.64} had moderate efficacy against \textit{herpes simplex virus type 1}, \textit{herpes simplex virus type 2}, \textit{vaccinia virus}, \textit{vesicular stomatitis virus} and \textit{thymidine kinase-deficient herpes simplex virus type 1} with value of the effective concentration of 4 \( \mu \)g/mL and cytotoxicity value 20 \( \mu \)g/mL (SI = 5) \cite{29}.

Study of thiazolidinones with sulfonamide fragment against the hepatitis C virus, conducted by Yili Ding et al. allowed to identify a number of promising antiviral agents \cite{104}. Among the studied 4-thiazolidinones the pyrazole derivative \textsuperscript{4.66} (Fig. 46) showed moderate effectiveness (IC\textsubscript{50} = 10 \( \mu \)g/mL and EC\textsubscript{50} = 70 \( \mu \)g/mL and cytotoxicity index CC\textsubscript{50} = 90 \( \mu \)g/mL).

5-Pyrazoline substituted 4-thiazolidinones (Fig. 47) were studied for their antiviral activity against \textit{SARS coronavirus} (SARS CoV) and \textit{influenza} types A and B viruses (Flu A, Flu B), as well as anti-trypansomal effect against \textit{Trypanosoma brucei brucei} (Tbb) and \textit{Trypanosoma brucei gambiense} (Tbg). Overall compounds were characterized by the similar values of anti-influenza viruses’ activity and cytotoxicity with selectivity indexes 1.0 to 2.1. Compound \textsuperscript{4.68} had moderate activity against duck strain of influenza A with 50% effective concentration (EC\textsubscript{50}) 21.78 \( \mu \)M and selectivity index
16.3. In general, tested compounds had no antiviral activity against SARS CoV [97]. The screening was conducted for compounds (Fig. 45) against Trypanosoma brucei brucei (Tbb) and Trypanosoma brucei gambiense (Tbg). The results showed moderate antitrypanosomal activity of compounds 4.67, 4.69, and 4.70 against both strains of tested parasites (activity indexes IC\(_{50}\) (Tbb) = 5.43–13.87 μM and IC\(_{50}\) (Tbg) = 2.53–6.66 μM) [97].

Aiming to investigate the trypanocidal activity for pyrazoline-thiazolidinone conjugates the synthesis of new 5-(pyrazolin-1-ylmethylene)-4-thiazolidinones was carried out (Fig. 48). Target heterocycles were branched by the methylidene or oxoethylamino-methylidene linker groups. The results of screening against Trypanosoma brucei gambiense allowed to identify 5 compounds with sufficient antitrypanosomal activity (IC\(_{50}\) ≤ 1.2 μM) and moderate or low cytotoxicity (CC\(_{50}\) = 13.6 – 184.3 μM) towards myoblast derived cell line (L-6). Compounds 4.71 (IC\(_{50}\) = 0.6 μM, CC\(_{50}\) = 175.2 μM, SI = 292) and 4.72 (IC\(_{50}\) = 0.7 μM, CC\(_{50}\) = 40 μM, SI = 57) were significantly more effective than Nifurtimox (IC\(_{50}\) = 4.4 μM, 78.2 μM = CC\(_{50}\), SI = 17.8). SAR analysis has been directed on substitution of pyrazoline core and modification of N3-thiazolidinone position (4.73), elongation of linker group (4.74) and rhodanine-isorhodanine isomerism (4.75) [98].

The study of antiparasitic activity for pyrazoline-thiazolidinone 4.76 (Fig. 49) was carried out towards Trypanosoma cruzi, Trypanosoma b. rhodesiense, Leishmania donovani and Plasmodium falciparum. The results indicated a moderate inhibitory effect on Trypanosoma b. rhodesiense (IC\(_{50}\) = 12 μg/mL) and L. donovani (IC\(_{50}\) > 30 μg/mL) and a higher influence on P. falciparum (IC\(_{50}\) > 5 μg/mL) with cytotoxicity index CC\(_{50}\) > 90 μg/mL [36].

5.4. Design of new anti-inflammatory agents among pyrazole-thiazolidinones

The promising direction for pharmacological investigation of...
pyrazole–thiazolidinones is the search for new anti-inflammatory agents considering their structural relationship with a known NSAIDs COX-2 inhibitor – celecoxib. Magda N.A. Nasr and Shehta A. Said studied a group of pyrazoline–thiazolidines/ thiazoles \( \text{IC}_{50} = 0.5 \text{µM} \) for COX-2) with the best selective index (SI = 84.8), which effectiveness was similar to that of celecoxib. SAR analysis (Fig. 51) of the results showed the dependence of COX-2 inhibition on the nature of aryl substituents in the 3 (A-ring) and 5 (B-ring) pyrazoline positions (structure 4.81). Thus, compounds with electron-donor substituents (methyl group) in the para- and meta-positions of the A-ring had better inhibitory effect compared with chlorine. The nature of the substituent in the para-position of the B-cycle also had a significant impact on the inhibitory activity of COX-2 in the order of: \( H > Br > Cl > F \) (for \( R^1 = 3,4-\text{Me}_2, 4.81 \)); \( H > Me > OMe \) (for \( R^1 = 3,4-\text{Cl}_2, 4.81 \)) [31].

To continue the development of structural analogues of Celecoxib, Adnan A. Bekhit et al. synthesized the series of pyrazoline–thiazolidines \( \text{IC}_{50} = 0.5 \text{µM} \) for COX-2) with anti-inflammatory activity screening using cotton pellet-induced granuloma and carrageenan-induced rat paw edema bioassays. The highly active compounds were tested for their ability to inhibit COX-1/COX-2 as well as ulcerogenic effect and acute toxicity. The first phase of the study (cotton pellet induced granuloma bioassay) allowed to...
establish that all compounds possessed anti-inflammatory activity with 
ED\textsubscript{50} = 7.86–28.42 μM and the thiazolidine carboxylic acid 
derivatives (compounds 4.83 – ED\textsubscript{50} = 9.74–11.86 μM, compounds 
4.84 – ED\textsubscript{50} = 7.86–8.11 μM) showed better efficiency than Celecoxib 
(ED\textsubscript{50} = 16.74 μM) and commensurable with Indomethacin 
(ED\textsubscript{50} = 9.64 μM). Further studies of highly active compounds (4.83 
and 4.84) allowed to identify their ability to selective inhibition of 
COX 2 (IC\textsubscript{50} = 0.38–0.94 μM) and reaffirmed their low ulcerogenic 
action and acute toxicity [39].

Adam M. Gilbert et al. synthesized a series of 5-
pyrazolymethylidene-2-thioxo-4-thiazolidinones 4.87 (Fig. 53) as 
potential inhibitors of ADAMTS-5 (a disintegrin and metalloproteinase 
with thrombospondin motifs 5) with significant anti-
inflammatory activity. Highly active compound 4.88 was identified 
with the inhibition of ADAMTS-5 IC\textsubscript{50} = 1.1 μM, that demonstrated a 
strong selectivity (SI > 40) compared to the inhibition of ADAMTS- 
4. Structural modification of substituents in the pyrazole moiety 
allowed to establish the main structural criteria to increase the 
inhibitory effect [83].

Amal M. Youssef et al. carried out the synthesis of 5-((1,3-ary1-
1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones as potential 
anti-inflammatory and neuroprotective agents [79]. The studies 
conducted in vitro and in vivo allowed to identify a group of highly 
active anti-inflammatory compounds with a low ulcerogenic 
impact and satisfactory toxicometry parameters. Based on in vitro 
experiments four compounds (4.89) were selected for in vivo 
studies according to screening protocols: the formalin-induced 
paw edema and turpentine oil-induced granuloma pouch bio-
assays. It was established that the tested compounds showed activity 
comparable to Celecoxib at a concentration of 20 mg/kg. The 
troduction of benzyl moiety in position 3 of thiazolidinone was 
accompanied by the loss of anti-inflammatory activity (Fig. 54).

6. Conclusions

This review article presents the rational approaches to the 
design of chemotherapeutic agents based on molecular hybridization 
of pharmacologically attractive thiazolidine and pyrazole/ 
pyrazolone heterocycles. Based on linkage of target heterocyclic 
cores the reviewed hybrids were classified as 2-, 3- and 5-pyrazole/ 
pyrazoline-substituted thiazolidines. The basic approaches for the 
synthesis of pyrazole-thiazolidinones have been provided by a 
combination of two “small” molecules via aminolysis, acylation 
reactions and Knoevenagel procedure or heterocyclization of 
monocyclic compounds via the [2+3]-cyclization reaction yielding 
the series of non-condensed bicyclic systems. The review of bio-
logical applications was focused on SAR analysis and mechanistic 
insights of thiazolidine–pyrazole hybrids. Molecular hybridization 
as a tool of medicinal chemistry has been successfully used for 
design of biologically active conjugates with antitumor activity, 
including inhibition of necroptosis, CDC25V phosphatase, TNF-
α–TNFRc1 interaction or activation of pro-apoptotic BAX, antimi-
crobial, antifungal, antiviral and antiparasitic applications, as well 
as anti-inflammatory properties as inhibitors of COX or ADAMTS-5 
enzymes.

Abbreviations

ADAMTS a disintegrin and metalloproteinase with 
thrombospondin motifs
BAX Bcl-2–associated X protein
CC\textsubscript{50} half maximal cytotoxic concentration
CDC25V dual-specificity phosphatase, the “cdc” in name refers to 
“cell division cycle”
DCC dicyclohexylcarbodiimide
DTP Development Therapeutics Program
ED\textsubscript{50} half maximal effective dose
EC\textsubscript{50} half maximal effective concentration
IC\textsubscript{50} half maximal inhibitory concentration

Fig. 52. Pyrazole-thiazolidine hybrids as COX-2 inhibitors.

Fig. 53. ADAMTS-5 inhibitors among pyrazole-thiazolidinone hybrids.

Fig. 54. Pyrazole–thiazolidinones with anti-inflammatory activity.
drug concentration resulting in a 50% reduction in the net protein increase in control cells during the drug incubation

HATU 1-(bis(dimethylamino)methylene)-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

MIC minimal inhibitory concentration

MRSA methicillin-resistant Staphylococcus aureus

MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

NCI National Cancer Institute

PIN1 peptidyl-prolyl cis-trans isomerase NIMA-interacting 1

PTP1B protein tyrosine phosphatase 1B

QRSA quinolone-resistant Staphylococcus aureus

SAR structure-activity relationships

SARS severe acute respiratory syndrome

SARS severe acute respiratory syndrome

SI selectivity index

Tb Tryppanosoma brucei brucei

Tbg Tryppanosoma brucei gambiense

TGI drug concentration resulting in total growth inhibition

TNF-α tumor necrosis factor alpha

TNFR1 type-1 tumor necrosis factor receptor

VHR Vaccinia virus H1 Related – a dual-specificity phosphatase

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