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Mini-review

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

Dmytro Havrylyuk^{a, b}, Olexandra Roman^a, Roman Lesyk^{a, *}^a Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, 69 Pekarska Street, Lviv, 79010, Ukraine^b Department of Chemistry, University of Kentucky, 505 Rose Street, Lexington, KY 40506, United States

ARTICLE INFO

Article history:

Received 12 December 2015

Received in revised form

10 February 2016

Accepted 11 February 2016

Available online 16 February 2016

Keywords:

Synthesis

Biological activity

Pyrazole

Pyrazoline

Thiazolidine

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 anti-cancer hybrids [1–3]. Various heteroaryl based hybrids in particular isatin and coumarins [3] or indoline–thiazolidinones [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) [5–10] and pyrazole or pyrazoline [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 [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 [16], VHR protein tyrosine phosphatase inhibitors [17], Pin1-modulating compounds [18], compounds for modulating RNA-binding proteins [19] and activators of pro-apoptotic BAX [20]. In addition, the pyrazole–thiazolidinone hybrids have been studied for their possibility to inhibit the TNF- α –TNFRc1 interaction [21], as inhibitors of histone acetyltransferases [22] and inhibitors of COX [31,39] and ADAMTS-5 enzymes [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

* Corresponding author.

E-mail addresses: dr_r_lesyk@org.lviv.net, roman.lesyk@gmail.com (R. Lesyk).

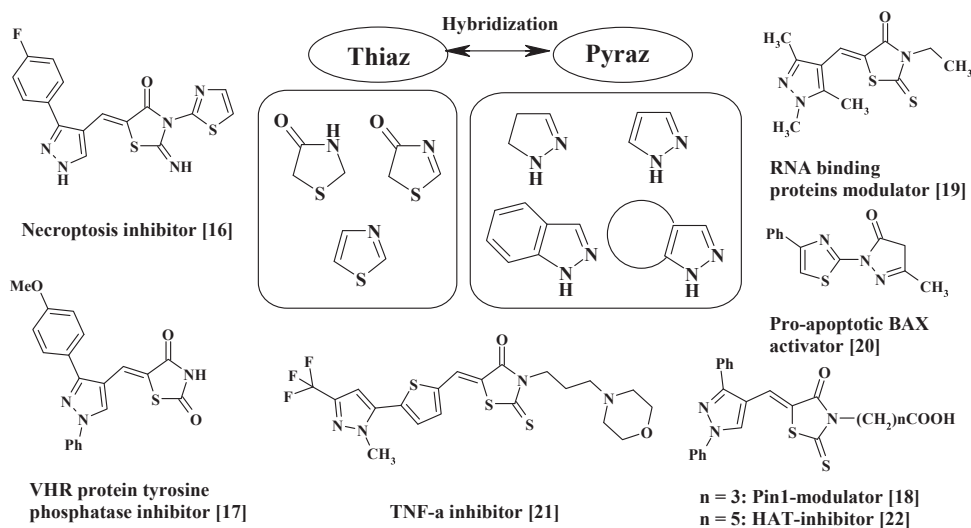


Fig. 1. Heterocycles for pyrazole/pyrazoline–thiazole/thiazolidine hybridization and the most promising conjugates.

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–thiazolidinone conjugates **1.2–1.7** and pyrazoline–thiazoles **1.8, 1.9** (Fig. 2), synthesized via the [2+3]-cyclocondensation of 4,5-dihydropyrazole-1-carbothioamides **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-chloroacetoacetate [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-carbothioamides **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–thiazolidinones **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**

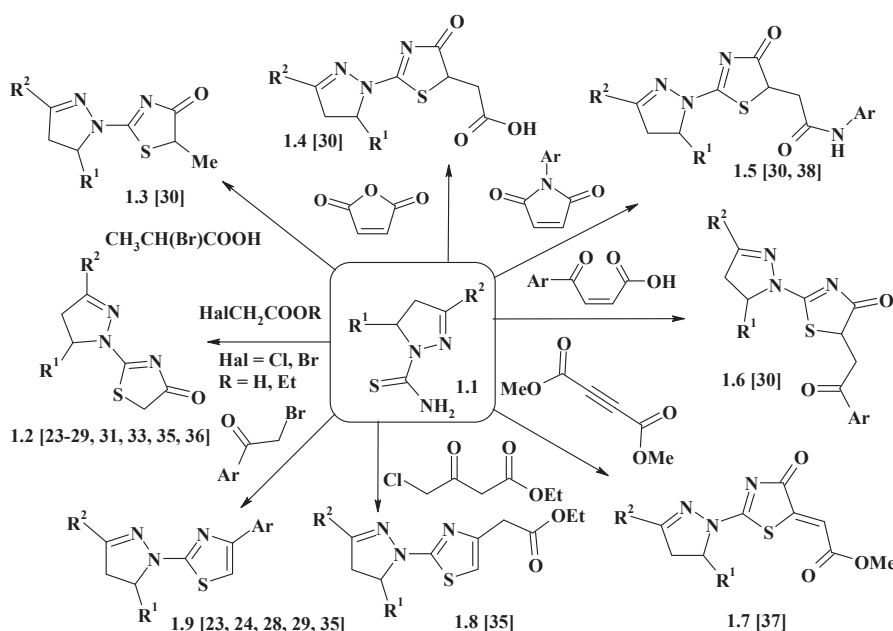


Fig. 2. Synthesis of pyrazoline–thiazolidinones via [2+3]-cyclization reactions.

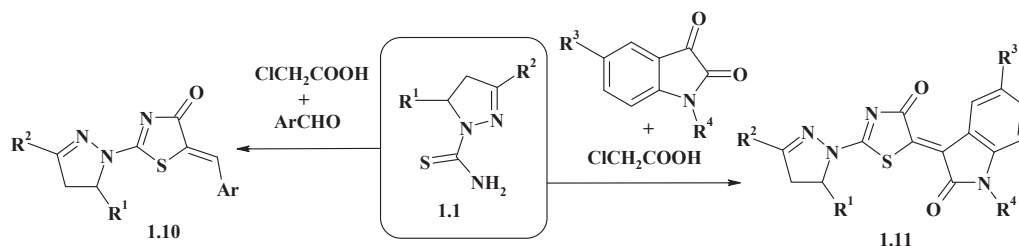


Fig. 3. Three-component one-pot reactions in synthesis of 2-pyrazolyl-4-thiazolidinones.

with pyrazole moiety in position 2. A. Khodairy proposed a synthesis of 2-substituted 4-thiazolidinone with benzopyrano[2,3-c]pyrazol-3-one fragment **1.14**, using *N*-cyanoacetyl-benzopyranopyrazolone [42] as a starting compound (Fig. 4).

Another direction for synthesis of pyrazole-substituted thiazolidinone **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-thiazolidinone **1.15** with acetoacetone [43,44].

A broad group of pyrazole–thiazolidinone derivatives exemplified by 2-imino-4-thiazolidinones (pseudothiohydantoines) **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 synthon $[C2]^{2+}$ (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 -bromoacetophenones (Fig. 6).

Aiming to search for new anticancer or antimicrobial compounds among pyrazole–thiazolidinone conjugates the pyrazole-sulfonyl-thioureas **1.21** were used as starting materials. The reaction between compounds **1.21** and ethyl 2-chloroacetate or α -bromoacetophenone 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-hydrazone–thiazolidinones **1.28–1.30** was synthesized via [2+3]-cyclocondensation of thiosemicarbazones **1.27** with α -halogenocarboxylic 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 carbonyl 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 -bromoacetophenones 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

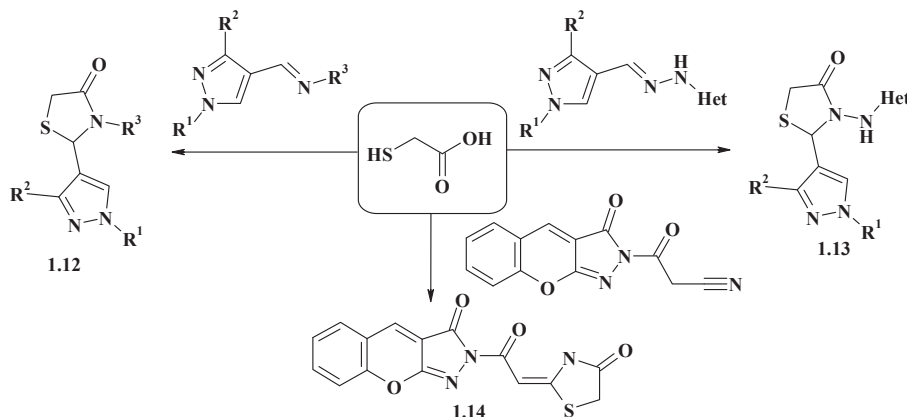


Fig. 4. Thioglycolic acid reagent in thiazolidinone ring-formation reactions.

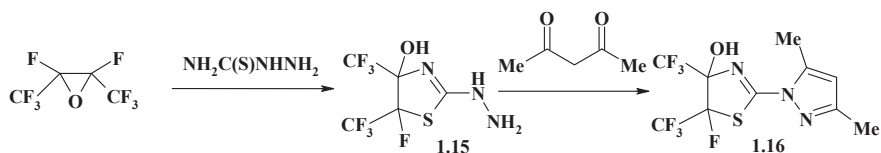


Fig. 5. Example of pyrazole formation in the synthesis of pyrazole-thiazolines.

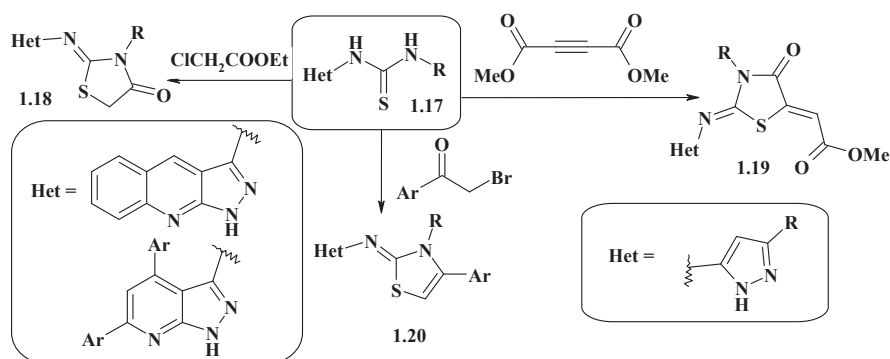


Fig. 6. Synthesis of pyrazole-thiazolidinones with imine linker group.

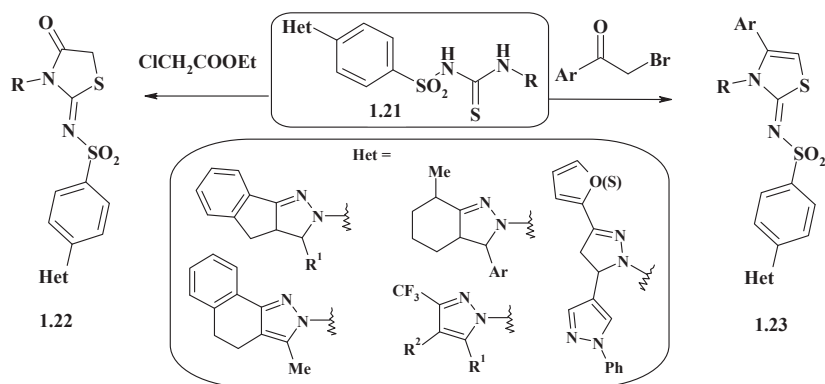


Fig. 7. Synthesis of diazole-thiazolidinones/thiazolidines with sulfonylimine linker group.

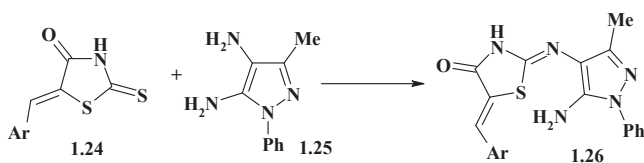


Fig. 8. Aminolysis reaction in synthesis of pyrazole-thiazolidinones.

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-arylidenerhodanines **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 methylenedihydrazides 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).

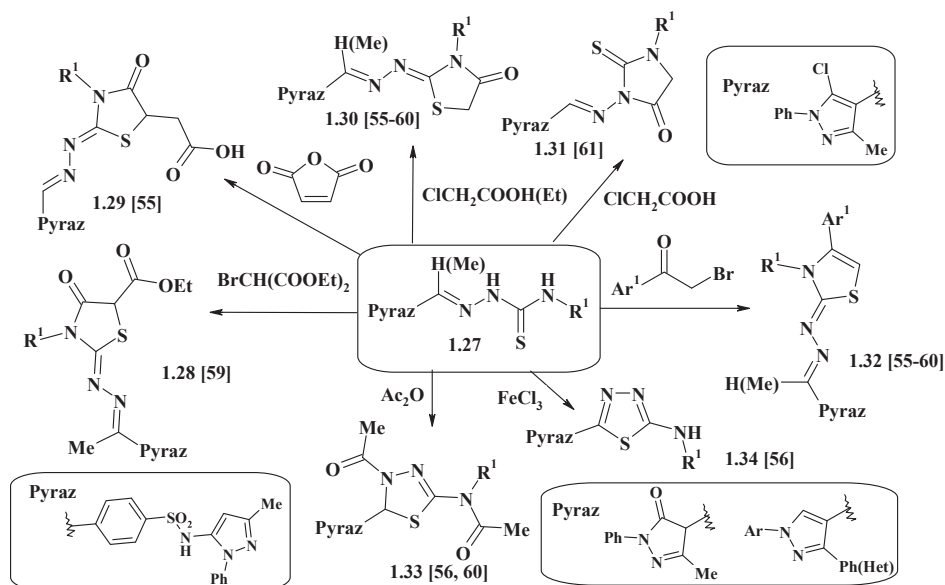


Fig. 9. Synthesis of pyrazole derivatives with thiazolidinone, imidazolidine and thiazoline fragments in molecules.

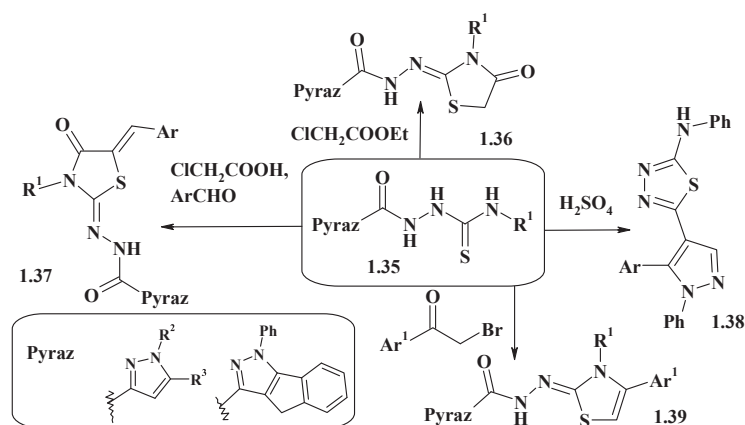


Fig. 10. Pyrazole-substituted thiosemicarbazides in synthesis of pyrazole–thiazole hybrids.

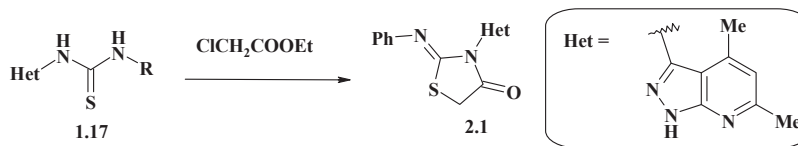


Fig. 11. Synthesis of 3-diazole-substituted 4-thiazolidinones.

The method for synthesis of pyrazole–thiazolidinone **2.15** (Fig. 15) with acetamide linker group was proposed based on the reaction of 5-arylidenerhodanine-3-acetic acid **2.13** and 5-aminopyrazole **2.14** in DMF in the presence of HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) [76].

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 alkylating 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 pyrazole–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

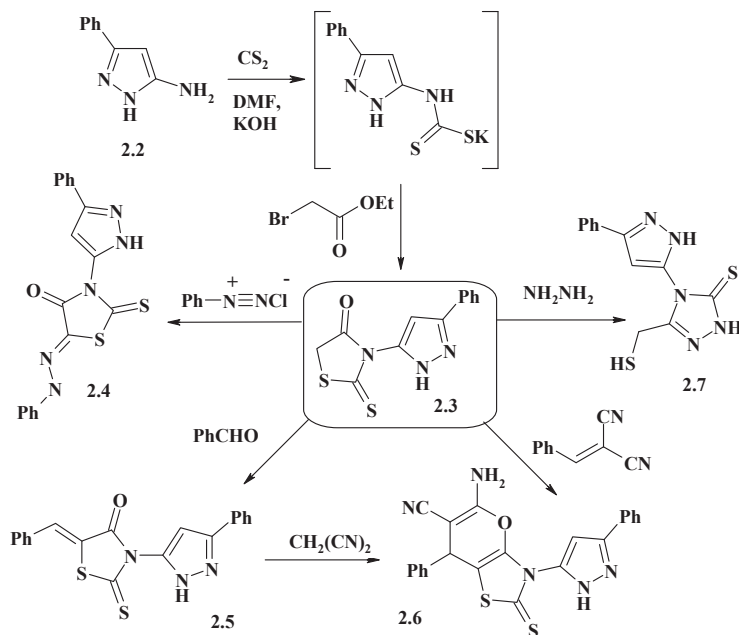


Fig. 12. Synthesis and modification of 3-pyrazole-substituted rhodanines.

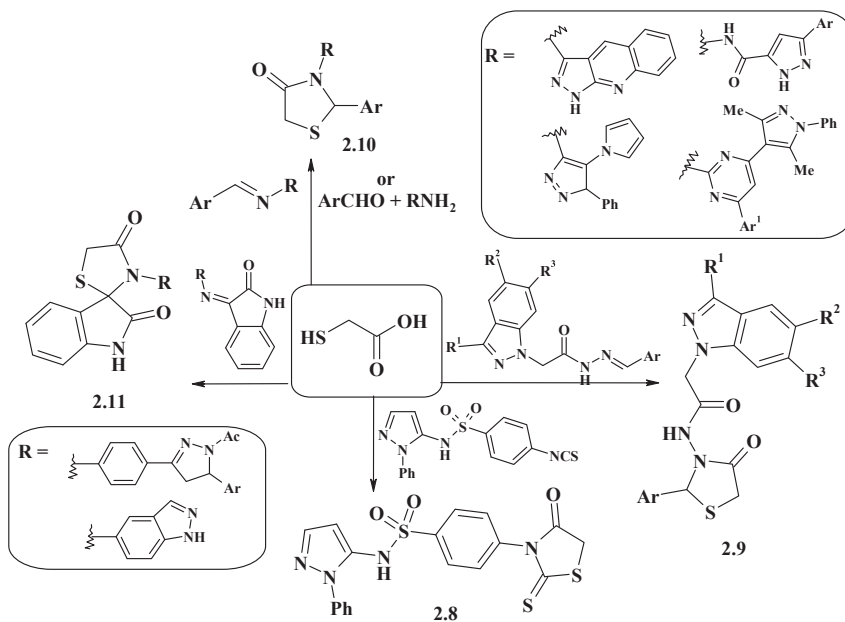


Fig. 13. α -Mercaptocarboxylic acids reagent in the synthesis of 3-substituted thiazolidinones.

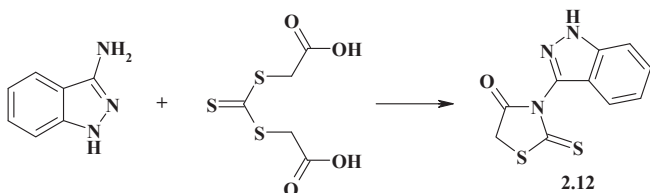


Fig. 14. Holmberg synthesis for benzopyrazole-rhodanine.

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 isonitrosorhodanines 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-4*H*-chromen-3-yl)methylene]-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

successfully modified in diazo coupling reaction [91] using pyrazolyl diazonium chloride yielding compound **3.3** (Fig. 17).

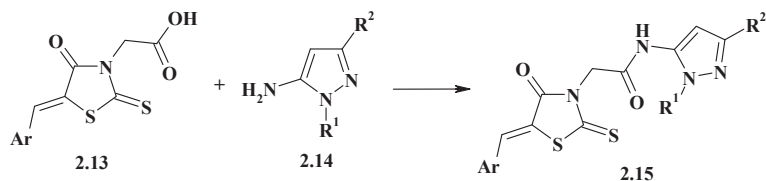


Fig. 15. Synthesis of pyrazole–thiazolidinone conjugates via acylation reaction.

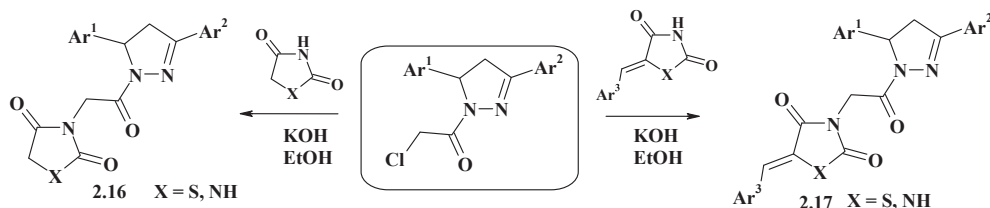


Fig. 16. Synthesis of pyrazoline–azolidinone conjugates via alkylation reaction.

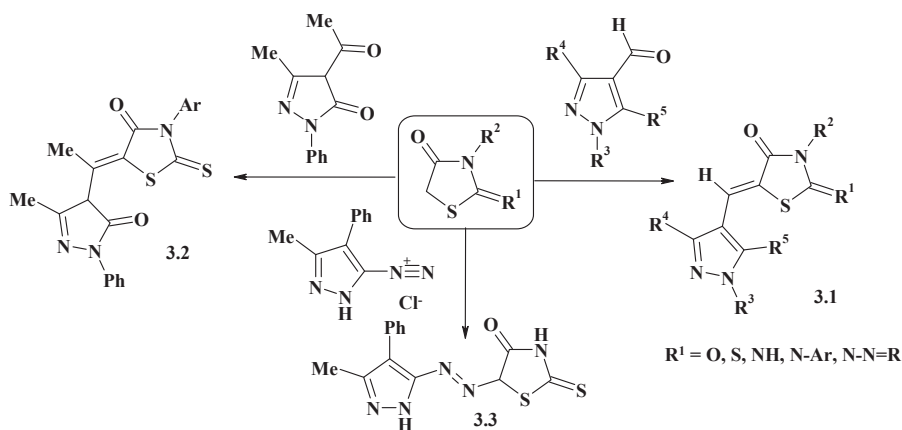


Fig. 17. Knoevenagel and diazo coupling reactions for synthesis of pyrazole–thiazolidinones.

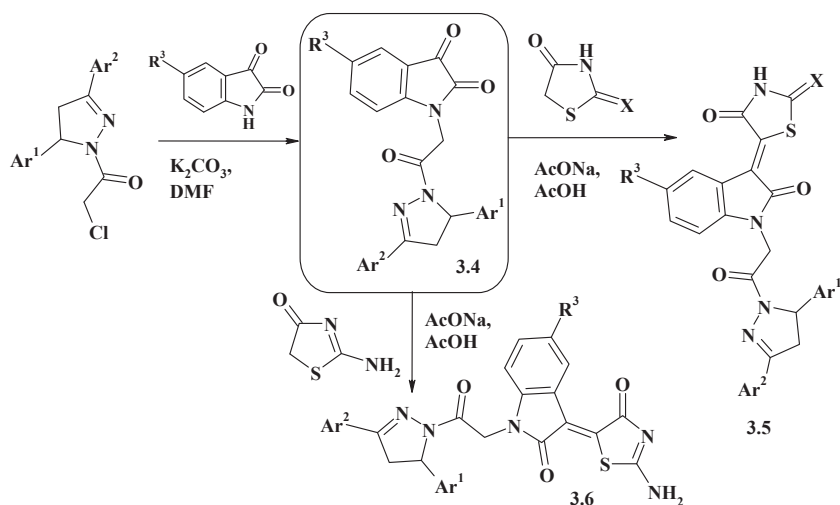


Fig. 18. Synthesis of pyrazoline–indoline–thiazolidinone conjugates.

allowed to obtain the corresponding pyrazole-thiazolidinones **3.9** [94]. Using hydrazine hydrate the structure of final compounds depended on the reaction medium. Thus, 1*N*-non-substituted

pyrazoles were obtained in alcohol medium and in the presence of sodium ethylate, while 1*N*-acetyl derivatives were formed in acetic acid. The reaction of the compound **3.8** and 1-phenylpyrazolidin-

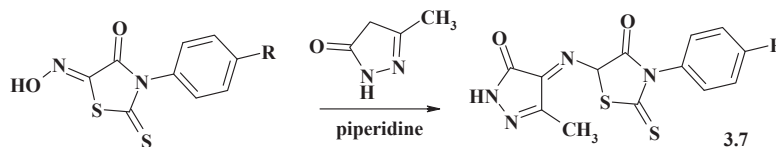


Fig. 19. Synthesis of pyrazolone–thiazolidinone conjugates.

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 heterocyclization of 2-thiazolidinyl-3-oxobutanoates with phenylhydrazine or conjugation of 4-bromopyrazolon-5-ones to 3-arylrhodanines [96].

The group of pyrazolone–thiazolidinones **3.13** was obtained by reaction of 5-bromo-2,4-thiazolidindione with 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 reactions forming **3.14**, **3.15** [97].

The following approach to the synthesis of pyrazolone–thiazolidinone conjugates **3.16** with carbonyl methylene linker group was based on the acylation reaction of 3,5-diarylpyrazolines (Fig. 24). The further reaction of substances **3.16** with chloroacetamides via *N*-alkylation reaction led to derivatives **3.17** [97].

To explore the structure–antitrypanosomal activity relationship the pyrazolone–thiazolidinone conjugates **3.18** were synthesized through the reaction of the 5-ethoxymethylidenerhodanines with 3,5-diarylpyrazolines (Fig. 25). 5-Pyrazolone substituted 4-thioxo-2-thiazolidinones **3.19** were obtained under the same conditions [98].

To continue the above mentioned study, 5-pyrazolone derivatives of 4-thiazolidinone **3.21** with oxoethylamino-methylene linker group were synthesized by modification of rhodanine-5-carboxylic acid **3.20** in the reaction with pyrazolines and in the presence of DCC (dicyclohexylcarbodiimide) [98] (Fig. 26).

5. Biological activity of pyrazole-thiazolidinones derivatives and related heterocyclic hybrids

5.1. Antitumor activity of pyrazole/pyrazolone-thiazolidinone hybrids

Antitumor activity evaluation is promising for the thiazolidinones with pyrazolone fragment. The *in vitro* anticancer activity of

thiazolidinones with pyrazolone cycle in position 2 (**4.2**) or 4 (**4.3**) of thiazolidine was tested by the National Cancer Institute (NCI) and most of them displayed anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines. The most efficient anticancer compound **4.1** was found to be active with selective influence on colon cancer cell lines, especially on HT 29 ($\text{lgGI}_{50} = -6.37$) [33]. The SAR study revealed that: (1) anticancer activity of compounds is sensitive to the nature of substituent in position 5 of thiazolone cycle, (2) introduction of *p*-OH group in 5-benzylidene fragment enhanced potency, and (3) the positional isomers, namely 2-pyrazolone (**4.2**) and 4-pyrazolone (**4.3**) substituted thiazolones are promising compounds for further optimization (Fig. 27).

Novel pyrazolone–thiazolidinone–isatin **4.4** and pyrazole-indoline-2-one **4.5** conjugates were designed as potential anticancer agents (Fig. 28). The most effective anticancer compound **4.6** was found to be active with a mean GI_{50} and TGI values of 0.071 μM and 0.76 μM , respectively and demonstrated the highest antiproliferative influence on the non-small cell lung cancer cell line HOP-92 ($\text{GI}_{50} < 0.01 \mu\text{M}$), colon cancer line HCT-116 ($\text{GI}_{50} = 0.018 \mu\text{M}$), CNS cancer cell line SNB-75 ($\text{GI}_{50} = 0.0159 \mu\text{M}$), ovarian cancer cell line NCI/ADR-RES ($\text{GI}_{50} = 0.0169 \mu\text{M}$) and renal cancer cell line RXF 393 ($\text{GI}_{50} = 0.0197 \mu\text{M}$). The SAR study revealed that: (1) potent anticancer activity of tested compounds depended on the presence of a combination of three heterocycles in one molecule, thus the pyrazolone–thiazolidinone–isatin conjugates were more active in comparison with pyrazolone–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 (GI_{50} level), in comparison with 5-unsubstituted isatin analogs; (3) introduction of a methyl group or CH_2COOH group at 1*N*-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 pyrazolone 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].

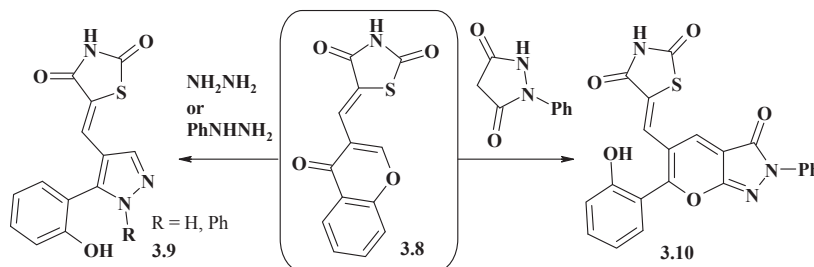


Fig. 20. Chromene ring-transformation reactions in synthesis of thiazolidinone–diazole hybrids.

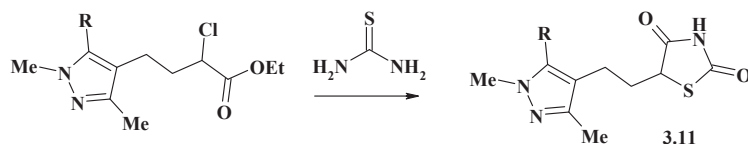


Fig. 21. Synthesis of 5-pyrazole-substituted thiazolidinones via [2+3]-cyclocondensation.

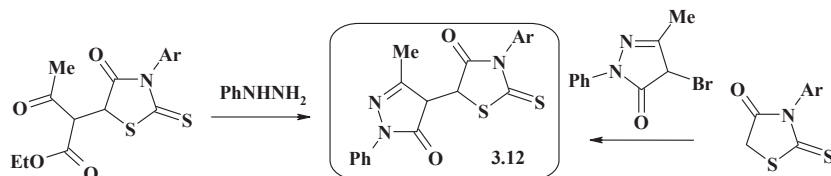


Fig. 22. Alternative approaches for the synthesis of thiazolidinone–pyrazolones.

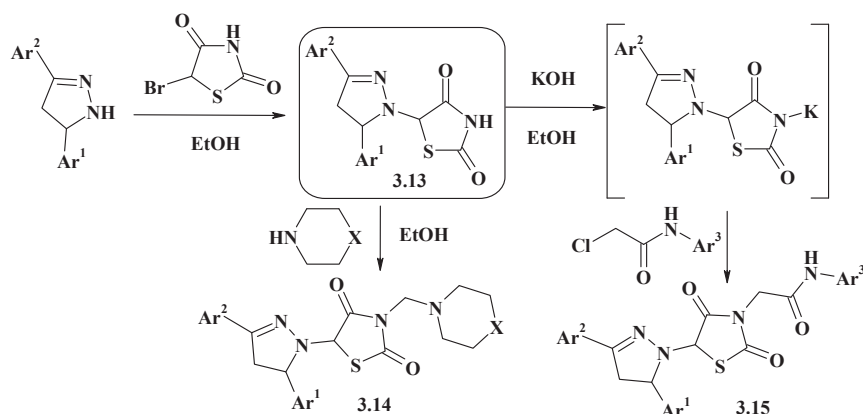


Fig. 23. Synthesis and modification of pyrazoline–thiazolidinones.

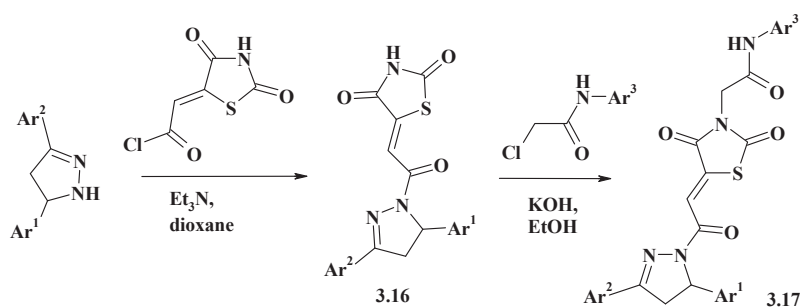


Fig. 24. Synthesis and alkylation of thiazolidinone–pyrazolines 3.16.

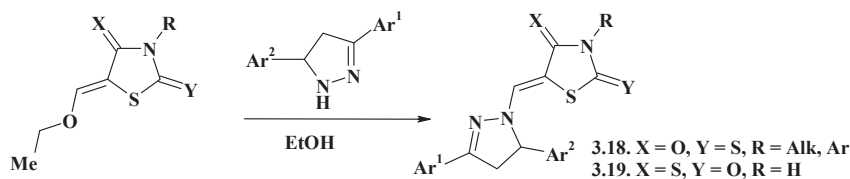


Fig. 25. Synthesis of 5-pyrazoline substituted thiazolidinones.

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

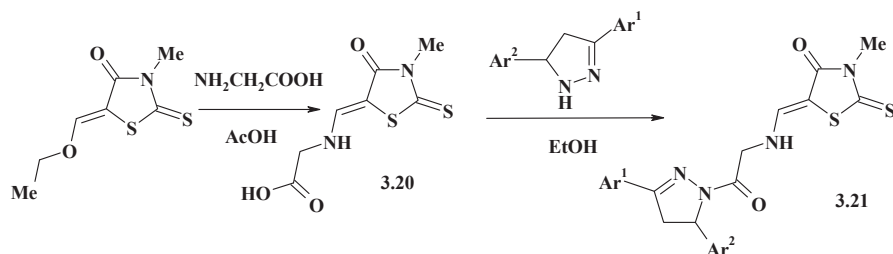


Fig. 26. Synthesis of pyrazoline–rhodanine conjugates with oxoethylamino–methylene linker group.

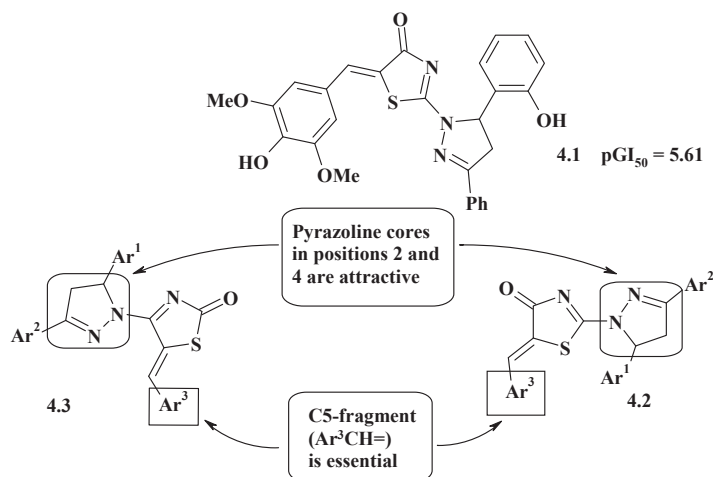


Fig. 27. Antitumor activity for pyrazoline–thiazolidinone based hybrids.

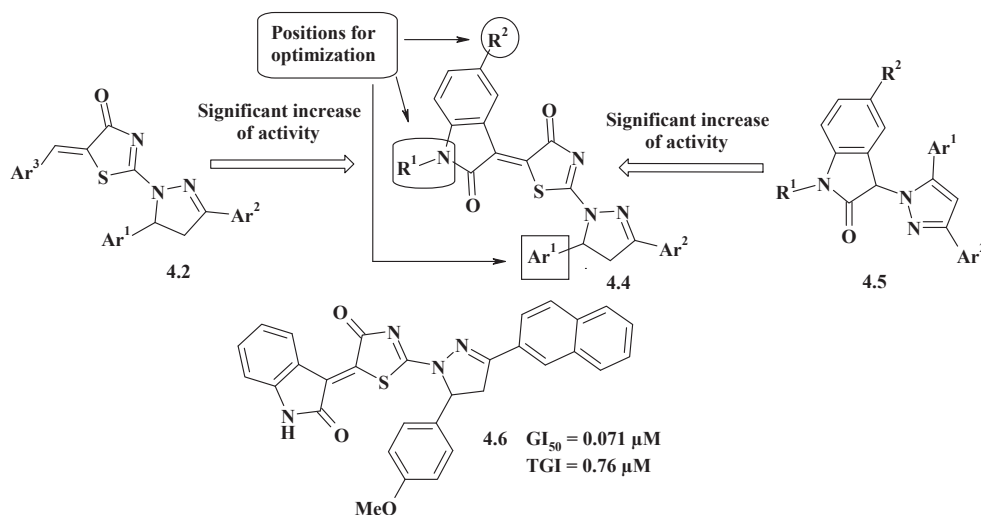


Fig. 28. Isatin-based conjugates with antitumor activity.

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–thiazolidinone-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–thiazolidinones **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

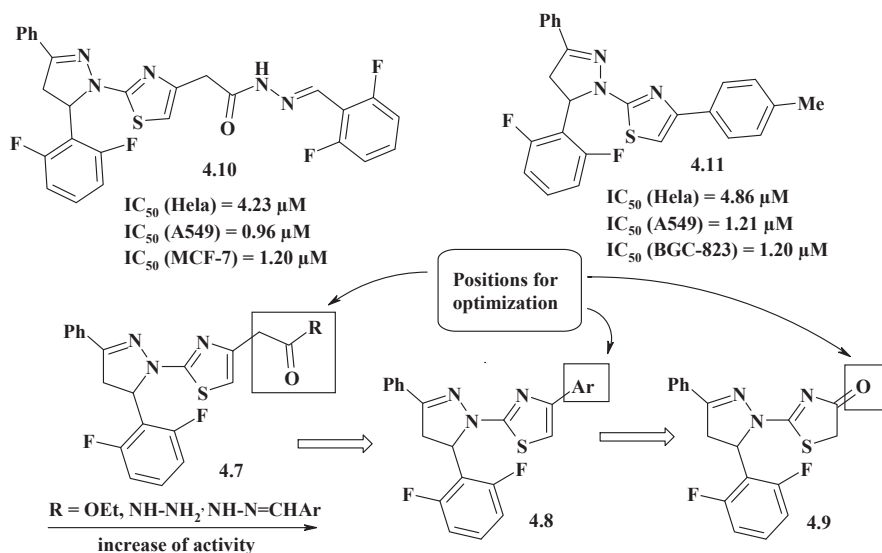


Fig. 29. Thiazole–pyrazoline hybrids with antitumor activity.

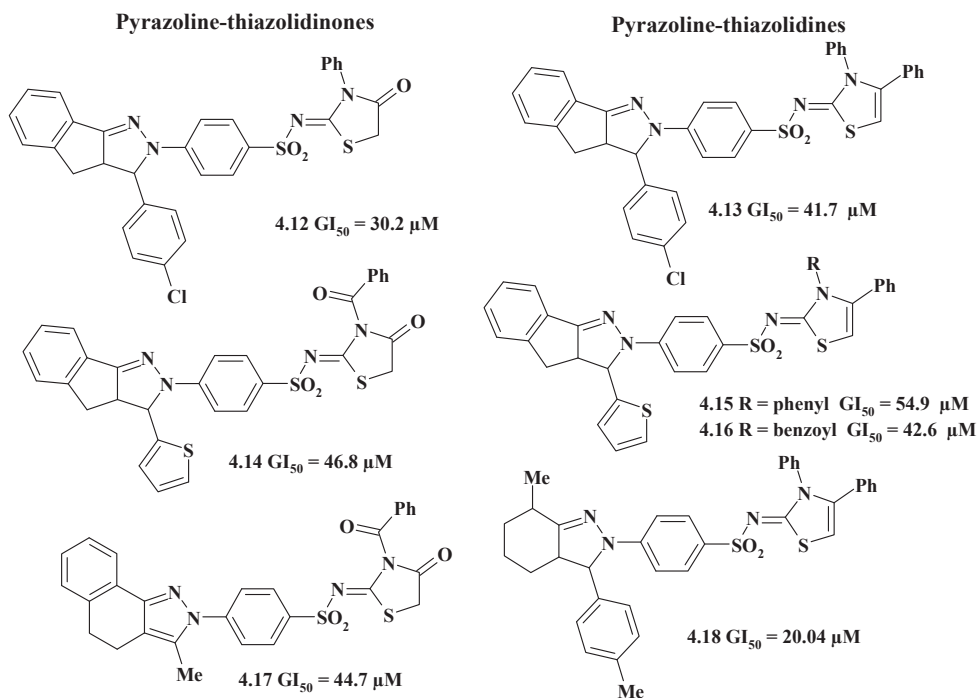


Fig. 30. Antitumor thiazolidinone/thiazole derivatives with pyrazoline moiety in 2 position.

concentration [48–51].

Magdy I. El-Zahar et al. [55] synthesized a group of benzofuran–pyrazoles 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–triazoles on lung cancer MCF-7 line were conducted by Arun M. Isloor et al. [40]. Among the studied conjugates the compound 4.21 was the most active with the effective concentration $IC_{50} = 22 \mu$ g/mL. The presence of *o*-tolyl fragment was most

favorable for the anticancer effect, while substitution with naphthyl 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 necroptosis 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 μ M. 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

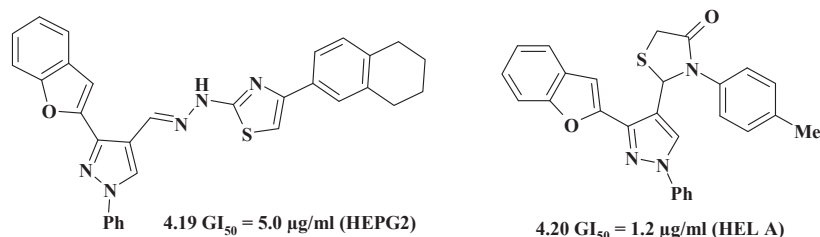


Fig. 31. Antitumor azolidine-pyrazolines with thiazolidinone/thiazole fragments.

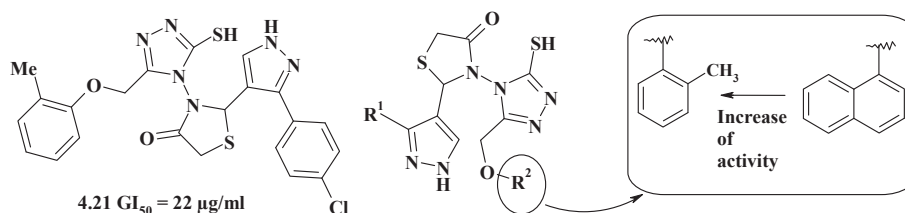


Fig. 32. Antitumor activity of pyrazole-thiazolidinone-triazoles on lung cancer.

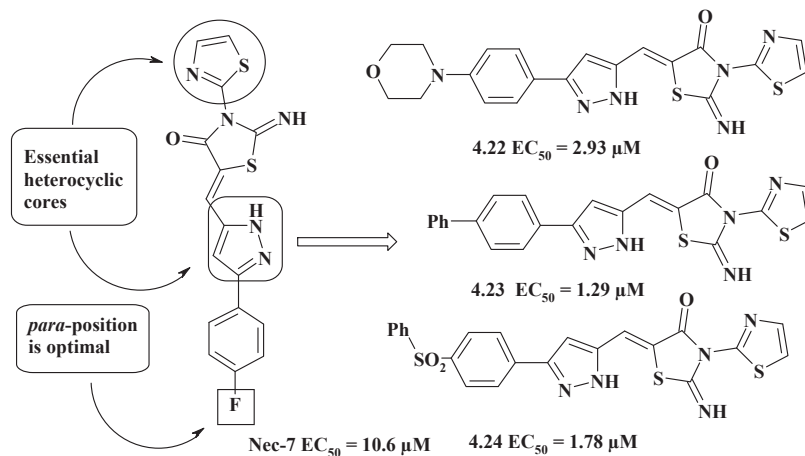


Fig. 33. 5-Pyrazoline-substituted pseudothiohydantoines as promising necroptosis inhibitors.

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 sulphanic (**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 $GI_{50} = 0.62 \mu\text{M}$ and $LC_{50} > 100 \mu\text{M}$, 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-hydroxyphenyl 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

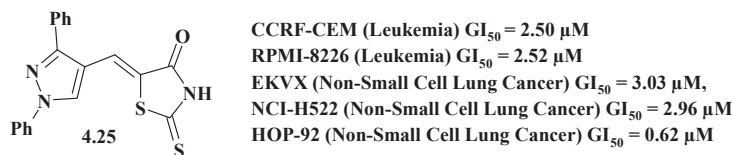


Fig. 34. Selective antitumor activity of pyrazole-rhodanine **4.25**.

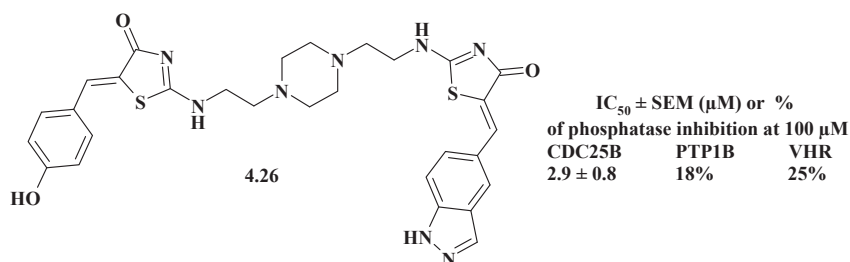


Fig. 35. Bis-thiazolone with indazole fragment as potential inhibitor of CDC25V phosphatase.

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 μM (**4.29**) and 1.64–3.20 μM (**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 (*Staphylococcus aureus*, *Bacillus subtilis*), gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and fungi *Candida albicans* [24]. However, the compound **4.31** was inactive to any of the microorganisms, while activity of **4.32** on *B. subtilis* appeared commensurate with Amoxicillin and Propenicillin (Fig. 37). The research of Bakr F.

Abdel-Wahab et al. was more successful. The authors synthesized a group of triazole–pyrazoline–thiazoles and corresponding 4-thiazolidinones and studied their activity against gram-positive bacteria (*S. aureus* ATCC 29213, *B. subtilis* ATCC6633, *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* NRRL Y-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 $\mu\text{g}/\text{mL}$), 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 $\mu\text{g}/\text{mL}$). At the same time **4.35** showed a high antifungal activity (MIC = 8.25 $\mu\text{g}/\text{mL}$). 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 quinoline–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

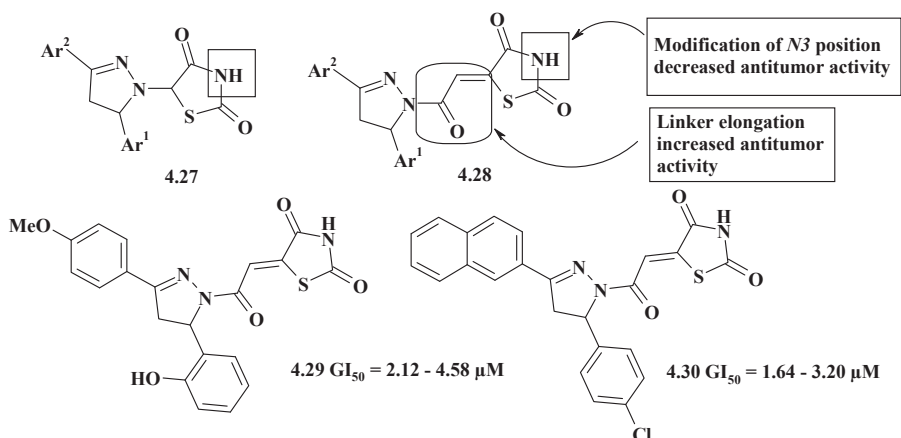


Fig. 36. Antitumor activity of 4-thiazolidinones with pyrazolines in 5 position.

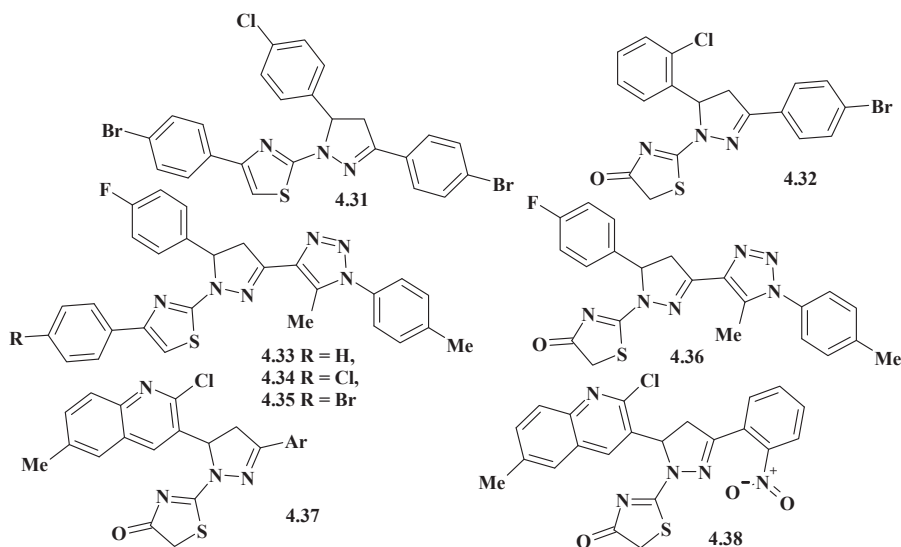


Fig. 37. Pyrazoline–thiazolidinone hybrids with antimicrobial activity.

227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) evidenced of their minor or moderate activity on most types of microorganisms with MIC values range = 50–500 $\mu\text{g}/\text{mL}$ [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 Griseofulvin on fungi. The mentioned compound showed the highest activity with the value of MIC 12.5 $\mu\text{g}/\text{mL}$ 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 $\mu\text{g}/\text{mL}$) (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 $\mu\text{g}/\text{mL}$) with Ampicillin against *E. coli*, and the compound **4.41c** (R = Cl) appeared to be the most active on *C. albicans* (MIC = 12.5 $\mu\text{g}/\text{mL}$) (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 $\mu\text{g}/\text{mL}$) [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. aeruginosa* ATCC27953, *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC29212, *Mycobacterium phlei*, *S. cerevisiae* 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 $\mu\text{g}/\text{mL}$), compound **4.50** was effective bactericidal agent on the strain *S. aureus* (MIC = 20.8 $\mu\text{g}/\text{mL}$) and showed significant antifungal effect on *S. cerevisiae* (MIC = 41.6 $\mu\text{g}/\text{mL}$) [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. aeruginosa* 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. aeruginosa* MTCC 424, *S. typhi* MTCC 733 and *K. pneumoniae* MTCC 432, and antifungal effect was studied on *A. niger* MTCC 282, *Aspergillus fumigatus* 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

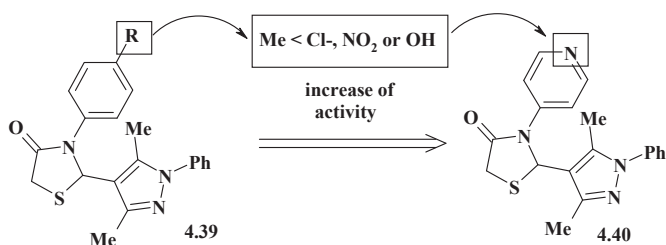


Fig. 38. SAR analysis of antimicrobial pyrazole–thiazolidinone hybrids.

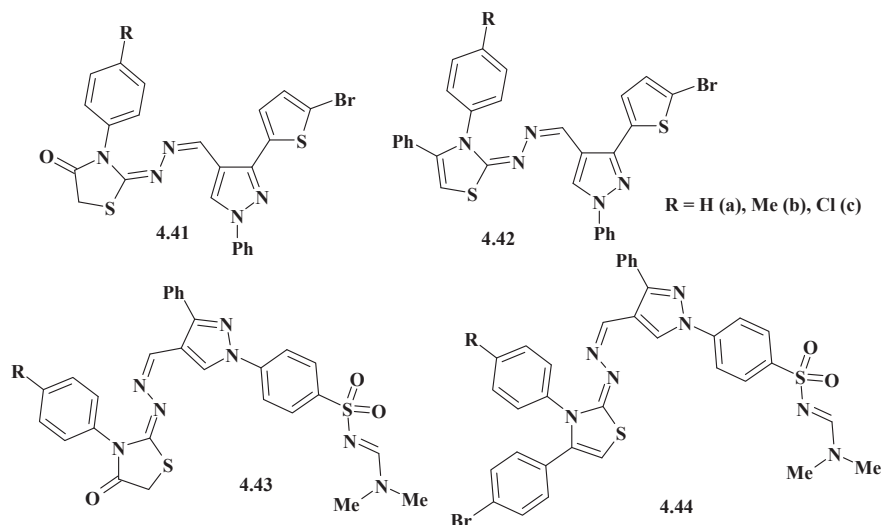


Fig. 39. Antimicrobial and antifungal pyrazole–thiazolidinones/thiazoles, coupled by hydrazone linker group.

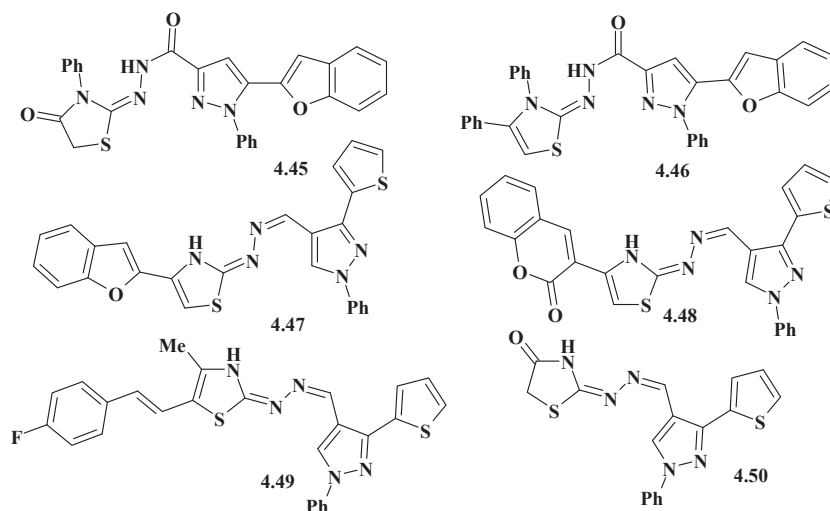


Fig. 40. Antimicrobial and antifungal activity for polyheterocyclic systems based on pyrazole–thiazolidinones/thiazoles.

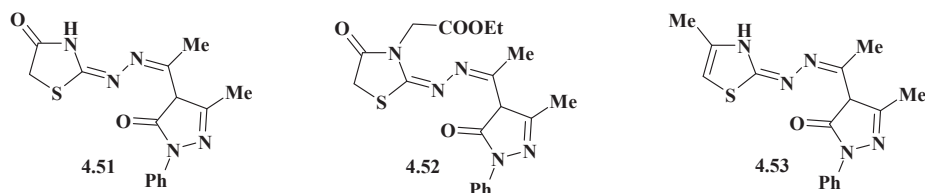


Fig. 41. Antimicrobial thiazolidines/thiazoles with 5-pyrazolone fragment.

antimicrobial (*B. subtilis* MTCC 441, *Bacillus sphaericus* MTCC 11, *S. aureus* MTCC 96, *P. aeruginosa* MTCC 741, *Klobsinella 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 3*N*-glycoside substituted 2-thioxo-

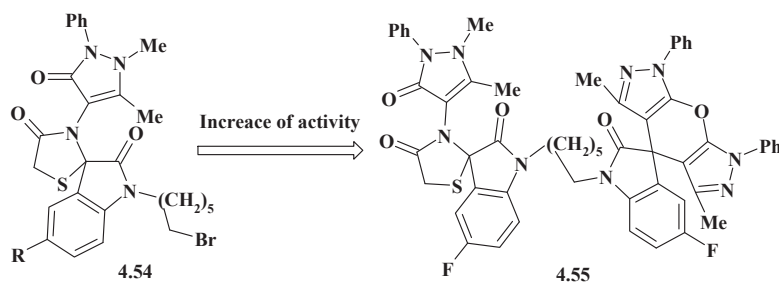


Fig. 42. 3-Pyrazolinyl-4-thiazolidinones with antimicrobial activity.

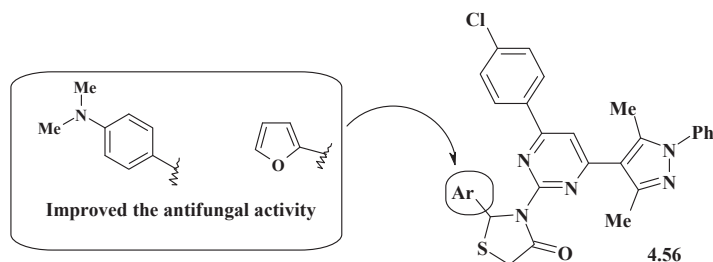


Fig. 43. Pyrazole-pyrimidine-thiazolidinones as promising antimicrobial agents.

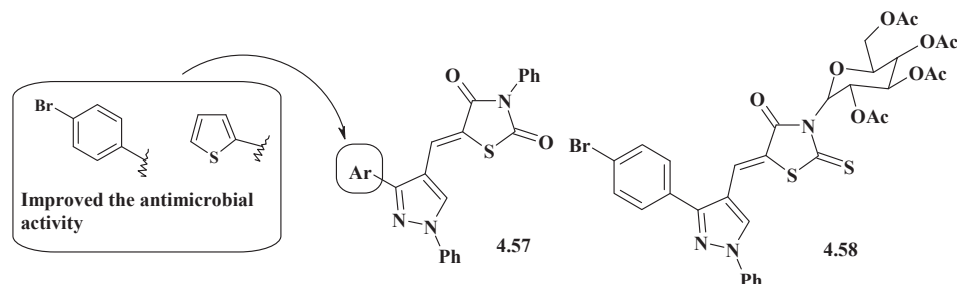


Fig. 44. Antimicrobial activity of 4-thiazolidinones with pyrazole in 5 position.

4-thiazolidinone derivatives **4.58** (Fig. 44). The *p*-bromophenyl substituted derivative showed the highest efficiency against *E. coli* (MIC = 143 $\mu\text{g/mL}$) but was 3 times less active than tetracycline (MIC = 39 $\mu\text{g/mL}$) [84].

However, the most promising group of antimicrobial agents is 5-pyrazolylrhodanines **4.59–4.63** [85,86,102,103]. Antimicrobial activity of these substances was studied against methicillin- (MRSA) and quinolone-resistant (QRSA) *S. aureus*. Compounds **4.59–4.61** exhibited stronger activity than the standard drugs, norfloxacin and oxacillin, with MIC values of 1–2 mg/mL. SAR analysis for pyrazole-rhodanine derivatives **4.62, 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 pyrazole-thiazolidinones

4.64 and structurally related pyrazole-thiazoles **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-Me-C₆H₄) among compounds **4.64** had moderate efficacy against *herpes simplex virus type 1*, *herpes simplex virus type 2*, *vaccinia virus*, *vesicular stomatitis virus* and *thymidine kinase-deficient herpes simplex virus type 1* with value of the effective concentration of 4 $\mu\text{g/mL}$ and cytotoxicity value 20 $\mu\text{g/mL}$ (SI = 5) [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 [104]. Among the studied 4-thiazolidinones the pyrazole derivative **4.66** (Fig. 46) showed moderate effectiveness (IC₅₀ = 10 $\mu\text{g/mL}$ and EC₅₀ = 70 $\mu\text{g/mL}$ and cytotoxicity index CC₅₀ = 90 $\mu\text{g/mL}$).

5-Pyrazole substituted 4-thiazolidinones (Fig. 47) were studied for their antiviral activity against *SARS coronavirus* (SARS CoV) and *influenza* types A and B viruses (Flu A, Flu B), as well as anti-trypanosomal effect against *Trypanosoma brucei brucei* (Tbb) and *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 **4.68** had moderate activity against duck strain of influenza A with 50% effective concentration (EC₅₀) 21.78 μM and selectivity index

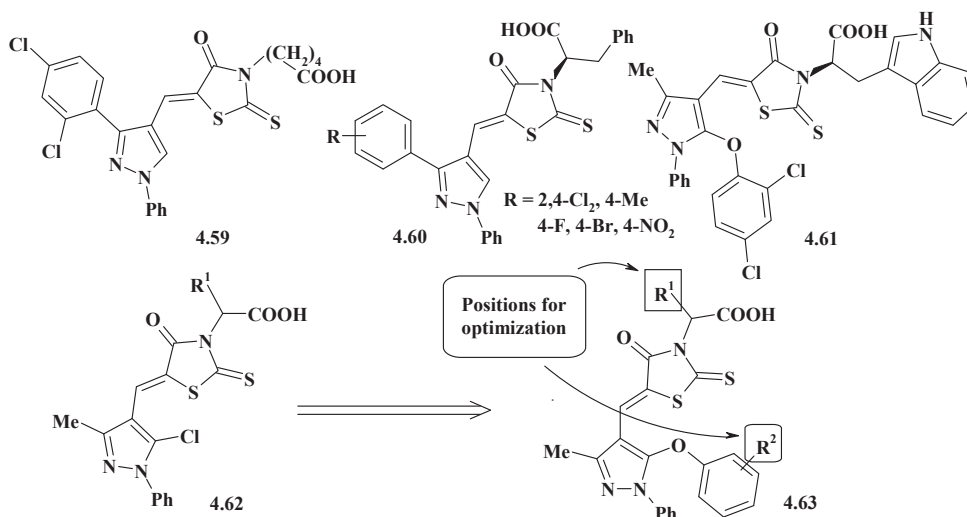


Fig. 45. Structure-antimicrobial activity relationship for pyrazole–rhodanine derivatives.

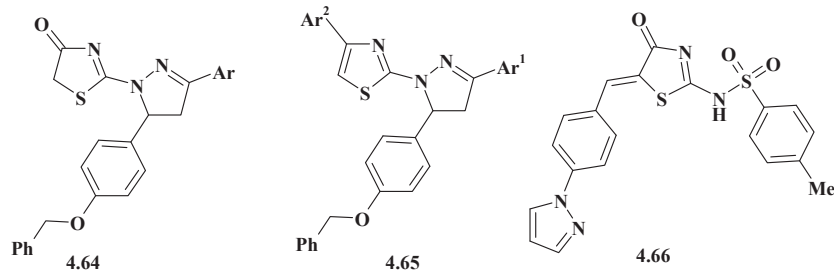


Fig. 46. Pyrazole/pyrazolines–thiazolidinone/thiazoles with antiviral activity.

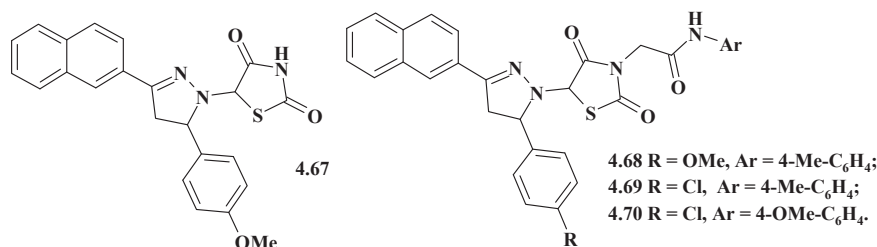


Fig. 47. Antiviral and antitrypanosomal 5-pyrazoline substituted 4-thiazolidinones.

(SI) > 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 μ M and IC_{50} (Tbg) = 2.53–6.66 μ M) [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 ($IC_{50} \leq 1.2$ μ M) and moderate or low cytotoxicity ($CC_{50} = 13.6$ – 184.3 μ M) towards myoblast derived cell line (L-6). Compounds **4.71** ($IC_{50} = 0.6$ μ M, $CC_{50} = 175.2$ μ M, SI = 292) and **4.72** ($IC_{50} = 0.7$ μ M,

$CC_{50} = 40$ μ M, SI = 57) were significantly more effective than Nifurtimox ($IC_{50} = 4.4$ μ M, 78.2 μ M = 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* ($IC_{50} = 12$ μ g/mL) and *L. donovani* ($IC_{50} > 30$ μ g/mL) and a higher influence on *P. falciparum* ($IC_{50} > 5$ μ g/mL) with cytotoxicity index $CC_{50} > 90$ μ g/mL [36].

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

The promising direction for pharmacological investigation of

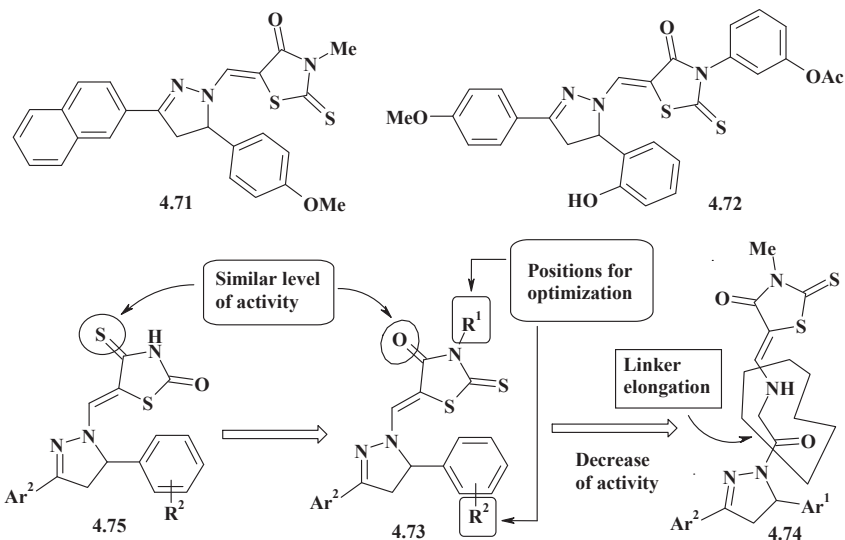


Fig. 48. SAR for trypanocidal 5-(pyrazolin-1-ylmethylene)-4-thiazolidinones.

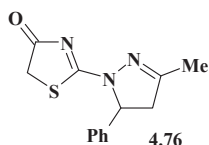


Fig. 49. Pyrazoline–thiazolidinone hybrid with antiparasitic activity.

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–thiazolidine/thiazoles **4.79**, **4.80** and thiazolidine/thiazole derivatives with hexahydroindazole fragment **4.77**, **4.78** and carried out *in vivo* research on carrageenin induced paw edema at dose of 100 mg/kg using ketoprofen as a reference standard [105]. Results showed that pyrazoline–thiazoles/thiazolidinones **4.79**, **4.80** possessed the better anti-inflammatory activity (percentage reduction of paw edema from control group was 17–50, and ketoprofen efficiency – 63%) compared with hexahydroindazole **4.77**, **4.78** analogues. Comparing the effectiveness of thiazole derivatives (**4.78**, **4.80**) with thiazolidinones (**4.77**, **4.79**) it could be concluded the higher activity of pyrazoline–thiazole hybrids (39–50%) (Fig. 50).

Detailed study of pyrazoline–thiazolidinones as potential COX-1 and COX-2 inhibitors allowed to identify highly active compound **4.82** ($IC_{50} = 0.5 \mu\text{M}$ 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 pyrazole–thiazolidines **4.83**–**4.86** (Fig. 52) for 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

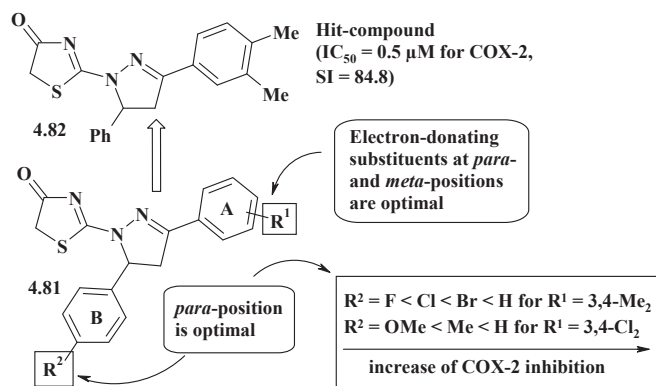


Fig. 51. Pyrazoline–thiazolidinone hybrids as COX-2 inhibitors.

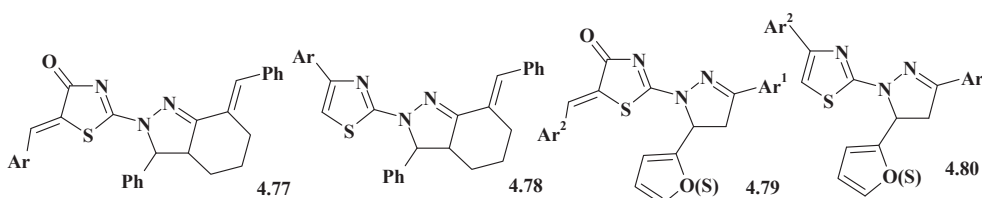


Fig. 50. Thiazolidinones and thiazoles with pyrazoline fragments as anti-inflammatory agents.

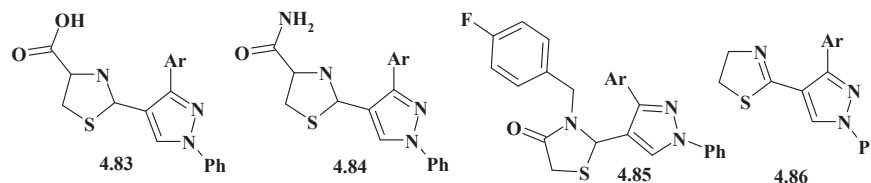


Fig. 52. Pyrazole-thiazolidine hybrids as COX-2 inhibitors.

establish that all compounds possessed anti-inflammatory activity with $ED_{50} = 7.86\text{--}28.42\ \mu\text{M}$ and the thiazolidine carboxylic acid derivatives (compounds **4.83** – $ED_{50} = 9.74\text{--}11.86\ \mu\text{M}$, compounds **4.84** – $ED_{50} = 7.86\text{--}8.11\ \mu\text{M}$) showed better efficiency than Celecoxib ($ED_{50} = 16.74\ \mu\text{M}$) and commensurable with Indomethacin ($ED_{50} = 9.64\ \mu\text{M}$). Further studies of highly active compounds (**4.83** and **4.84**) allowed to identify their ability to selective inhibition of COX 2 ($IC_{50} = 0.38\text{--}0.94\ \mu\text{M}$) and reaffirmed their low ulcerogenic action and acute toxicity [39].

Adam M. Gilbert et al. synthesized a series of 5-pyrazolylmethylene-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 $IC_{50} = 1.1\ \mu\text{M}$, 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-aryl-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 bioassays. It was established that the tested compounds showed activity comparable to Celecoxib at a concentration of 20 mg/kg. The introduction 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/pyrazoline 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

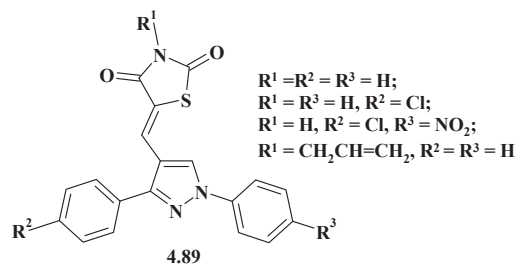


Fig. 54. Pyrazole-thiazolidinones with anti-inflammatory activity.

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 biological 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, antimicrobial, 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 ₅₀	half maximal cytotoxic concentration
CDC25V	dual-specificity phosphatase, the “cdc” in name refers to “cell division cycle”
DCC	dicyclohexylcarbodiimide
DTP	Development Therapeutics Program
EC ₅₀	half maximal effective concentration
ED ₅₀	half maximal effective dose
IC ₅₀	half maximal inhibitory concentration

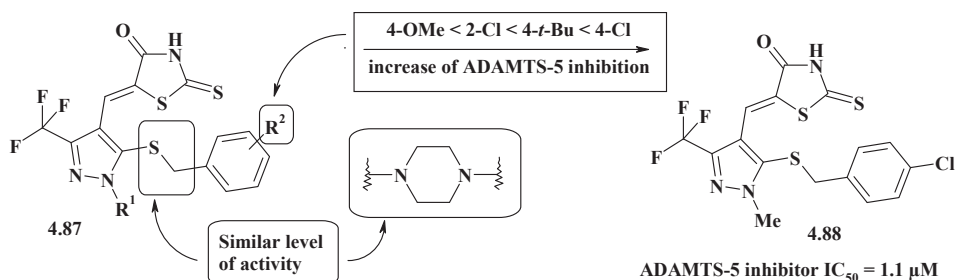


Fig. 53. ADAMTS-5 inhibitors among pyrazole-thiazolidinone hybrids.

GI ₅₀	drug concentration resulting in a 50% reduction in the net protein increase in control cells during the drug incubation
HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
MIC	minimal inhibitory concentration
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCI	National Cancer Institute
PIN1	peptidyl-prolyl <i>cis</i> - <i>trans</i> isomerase NIMA-interacting 1
PTP1B	protein tyrosine phosphatase 1B
QRSA	quinolone-resistant <i>Staphylococcus aureus</i>
SAR	structure-activity relationships
SARS	severe acute respiratory syndrome
SI	selectivity index
Tbb	<i>Trypanosoma brucei brucei</i>
Tbg	<i>Trypanosoma brucei gambiense</i>
TGI	drug concentration resulting in total growth inhibition
TNF- α	tumor necrosis factor alpha
TNFRc1	type-1 tumor necrosis factor receptor
VHR	Vaccinia virus H1 Related – a dual-specificity phosphatase

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