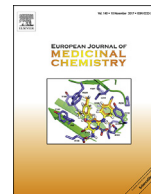




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## Review article

## 5-Ene-4-thiazolidinones – An efficient tool in medicinal chemistry



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## ABSTRACT

The presented review is an attempt to summarize a huge volume of data on 5-ene-4-thiazolidinones being a widely studied class of small molecules used in modern organic and medicinal chemistry. The manuscript covers approaches to the synthesis of 5-ene-4-thiazolidinone derivatives: modification of the C5 position of the basic core; synthesis of the target compounds in the one-pot or multistage reactions or transformation of other related heterocycles. The most prominent pharmacological profiles of 5-ene derivatives of different 4-thiazolidinone subtypes belonging to hit-, lead-compounds, drug-candidates and drugs as well as the most studied targets have been discussed. Currently target compounds (especially 5-en-rhodanines) are assigned as frequent hitters or pan-assay interference compounds (PAINS) within high-throughput screening campaigns. Nevertheless, the crucial impact of the presence/nature of C5 substituent (namely 5-ene) on the pharmacological effects of 5-ene-4-thiazolidinones was confirmed by the numerous listed findings from the original articles. The main directions for active 5-ene-4-thiazolidinones optimization have been shown: *i*) complication of the fragment in the C5 position; *ii*) introduction of the substituents in the N3 position (especially fragments with carboxylic group or its derivatives); *iii*) annealing in complex heterocyclic systems; *iv*) combination with other pharmacologically attractive fragments within hybrid pharmacophore approach. Moreover, the utilization of 5-ene-4-thiazolidinones in the synthesis of complex compounds with potent pharmacological application is described. The chemical transformations cover mainly the reactions which involve the exocyclic double bond in C5 position of the main core and correspond to the abovementioned direction of the 5-ene-4-thiazolidinone modification.

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## 1. Introduction

4-Thiazolidinones and related heterocyclic based compounds have been extensively explored as the source of antiinflammatory, antitumor, antimicrobial, antidiabetic, antibacterial agents. The findings in the medicinal chemistry and pharmacology of 4-thiazolidinones have significantly increased since [1–3] 60<sup>s</sup> being reflected in the rapid growth of the number of scientific papers [4], numerous reviews and patents covering various 4-thiazolidinone derivatives [5–10]. The papers are dedicated to the selected 4-thiazolidinones subtypes, namely 2-(imino)amino-4-thiazolidinones [11], 4-thiazolidinones with the exocyclic C=C double bond at the C(2)-position etc [12]. This proves that 4-thiazolidinones belong to the privileged scaffolds in the modern medicinal chemistry [4,13,14]. Combination of several reaction centers in the structure of 4-thiazolidinone derivatives makes them an effective tool for the rational diversity oriented synthesis or privileged substructure-based diversity oriented synthesis [15–17] for the new lead-compounds creation.

Major achievements in the 4-thiazolidinone field are related to the 2,4-thiazolidinedione, rhodanine (2-thioxo-4-thiazolidinone), 2-alkyl(aryl)-substituted, and 2-R-amino(imino)-substituted 4-thiazolidinone subtypes as sources of antimicrobial, antidiabetic, anti-inflammatory and anticancer lead-compounds and drug-candidates [7,10,11]. This is largely due to the investigation and introduction into the medical practice the antidiabetic drugs: glitazones (peroxisome proliferator-activated receptor- $\gamma$  (PPAR) agonists, e.g. Rosiglitazone, Troglitazone, Pioglitazone, etc.) [18,19] and aldose reductase inhibitor Epalrestat [20], and the simplicity in the synthesis of abovementioned compounds. Very less attention has been paid to the 4-thio- and 4-amino(imino)-derivatives (isorhodanine (4-thioxo-2-thiazolidinone), thiorhodanine (2,4-thiazolidinedithione), and especially 4-amino(imino)-2-thiazolidinone derivatives) [21–25].

Despite foregoing, among all 4-thiazolidinone subtypes 5 substituted thiazolidinones, namely 5-ene (5-ylidene) derivatives are of special interest in the context of chemical features and pharmacological profiles [6,8,26,27].

In this manuscript we tried to present the powerful pharmacological and chemical potential of 5-ene-4-thiazolidinones. Pursuing this goal we had not divided thiazolidinones according to the nature of their substituents (e.g. derivatives of 2,4-thiazolidinedione, rhodanine etc.) (Fig. 1).

The arguments in this favour were the following: *i*) large number of reviews is devoted to the selected thiazolidinones subtypes; *ii*) generally 5-ene-derivatives of different thiazolidinone cores are characterized by the same pharmacological profiles (see below) as well as the similar synthetic protocols.

## 2. Synthesis of 5-ene-4-thiazolidinones

The methods used for the synthesis of 4-thiazolidinones and their derivatives depend undoubtedly on the nature of thiazolidinone subtypes and are well represented in numerous reviews and original articles (see above) [28]. Presented retro-synthetic

approach (Fig. 2) shows wide range of synthetic routes for thiazolidine ring formation based on various condensation reactions that successfully have been employed for the 4-thiazolidinones synthesis [1–3,6].

These approaches are also speculatively attractive for the synthesis of 5-thiazolidinones as positional isomers of mentioned structures and they are rarely represented [30]. The most prominent and referred protocol for their synthesis is the cyclocondensation of reactants bearing the N=C=S fragment with  $\alpha$ -halocarbonyl compounds. But, in most cases, mentioned protocol leads to the formation of 4-thiazolidinones only [31].

However, the protocols for synthesis of 5-ene derivatives of 4-thiazolidinones are often similar and can be divided into the next groups: *i*) modification of the C5 position of the basic core; *ii*) synthesis of the target compounds in the one-pot or multistage reactions (simultaneous formation of the core heterocycle and C5 exocyclic double bond); *iii*) transformation of thiazolidine derivatives or other related heterocycles in the recyclization reactions.

### 2.1. Modification of the C5 position of the thiazolidinone core

*Knoevenagel condensation.* One of the most prominent and referred protocols for 5-ene-4-thiazolidinones synthesis is the Knoevenagel condensation of thiazolidinone core and oxo-compound (Scheme 1). The methylene carbon atom at the C5-position possesses nucleophilic activity and can attack an electrophilic center affording the target ene-derivatives. The different aldehydes, ketones, and heterocycles (e.g. isatins, anhydrides of pyridine-3,4-dicarboxylic and phthalic acids etc.) [27,32–38] have been used as oxo compounds. Acetic acid or its anhydride and sodium acetate; ethanol and ammonium acetate or piperidine [39]; toluene and ammonia acetate [33,40,41]; isopropanol and potassium *tert*-butylate [42,43]; toluene and *L*-proline [44]; dimethylformamide and sodium acetate; ethanol and monoethanolamine as well as the solid carriers and phasetransfer catalysts etc. [45,46] have been widely used as the medium and catalysts in this reaction. The reaction performance was also described in the medium of the aldehyde or ketone (without solvent addition) [21], polyethyleneglycol-300 [47] or based on the green chemistry approach. Moreover, performance of such condensation in aqueous solutions [48]; usage of atypical agents as well as ionic liquids [49]; the soluble polymer-supported synthesis [50] have also been investigated. Microwave assistant organic synthesis approach was also successfully employed [51,52].

The utilization of the aromatic aldehydes leads to maximal yields of the target compounds, unlike aliphatic aldehydes and especially ketones [38,53]. The reactivity of 4-thiazolidinones differs also and depends on the main core's substituents (2,4-thiazolidinedione, rhodanine etc.) [27,43,43]: rhodanines react easier than 2-amino(imino)-4-thiazolidinone, 2,4-thiazolidinone etc; 2-R-substituted-4-thiazolidinones are characterized by the lower reactivity levels. When aldehydes are utilized the preferred (and mostly only one) product had been reported to have the Z geometry based on NMR and X-ray study regardless of the thiazolidinone subtypes [53–55]. Knoevenagel condensation between

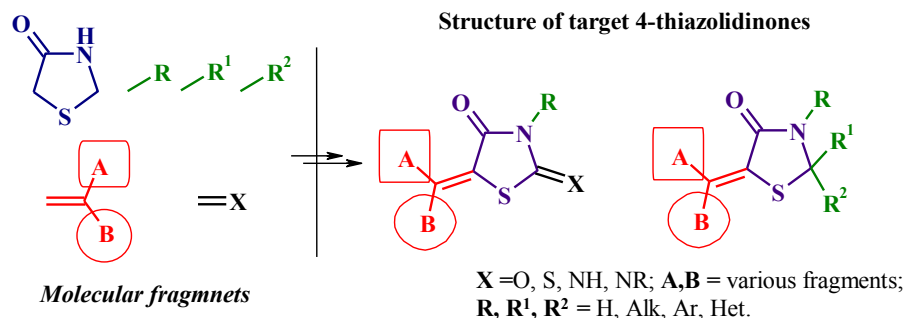


Fig. 1. Structure of the target 5-ene-4-thiazolidinones.

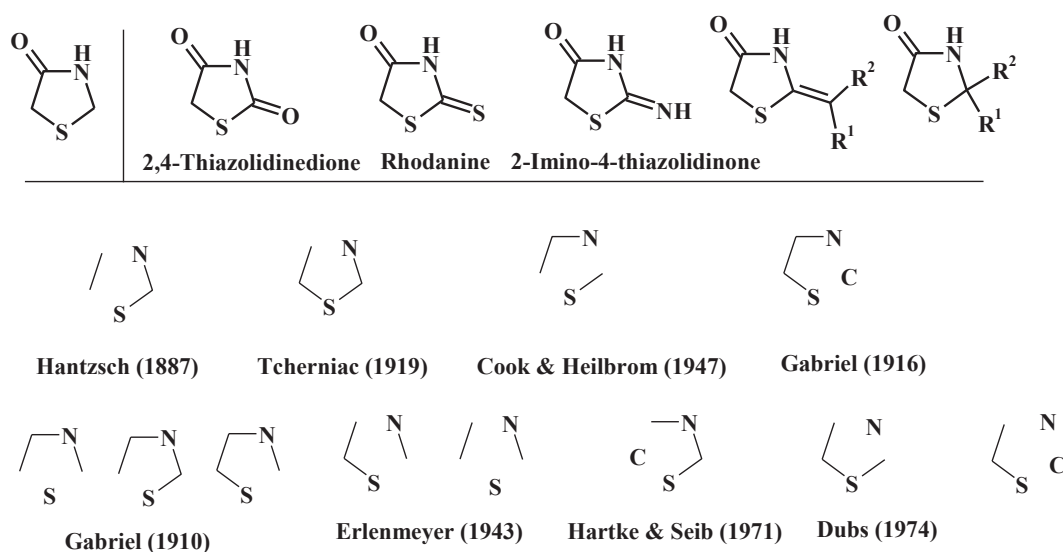
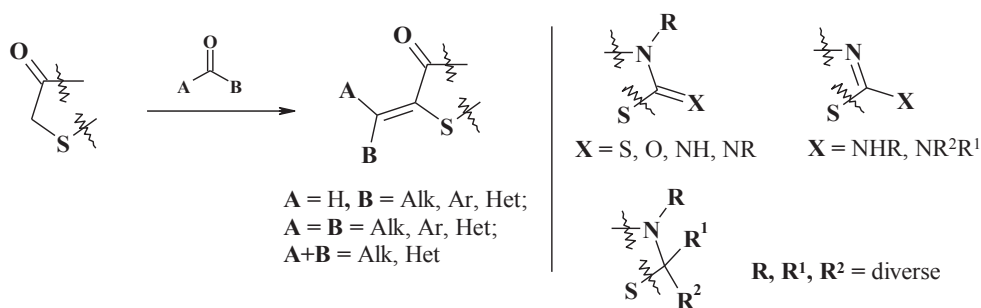


Fig. 2. Retro-synthetic approach to the 4-thiazolidinone scaffold formation, adapted from Ref. [29].



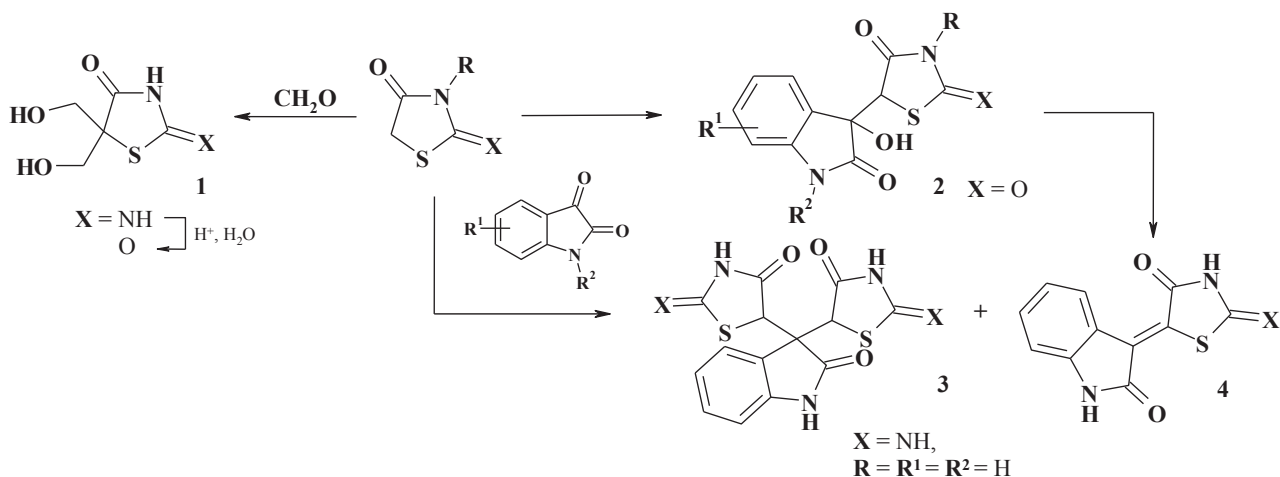
Scheme 1. General scheme of Knoevenagel condensation of 4-thiazolidinones.

4-thiazolidinones and ketones generally leads to the mixtures of *Z*- and *E*-isomers. The use of the dicarbonyl compounds in this reaction leads to the formation of unfused heterocycles with two thiazolidinone fragments in molecule [36,56–58].

Despite the simplicity of such condensation, the formation of other products have been reported also [59]. For instance, thiopyrano[2,3-*d*][1,3]thiazoles were obtained from highly reactive 4-thioxo-thiazolidin(thi)one-2 and ketones (in ethanol in the presence of monoethanolamine) [21]. The condensation of 2-imino-4-thiazolidinone and formaldehyde in water (pH-9, triethylamine) leads to the formation of 5,5-bishydroxymethyl-2-imino-4-thiazolidinone (1) [37,60]. The uncatalyzed reaction in water with

C–C bond-formation was reported to be thiazolidinedione-isatin conjugates' (2) synthetic protocol. The formation of the products was found to be thermodynamically controlled [59,61] and further heating leads to dehydration and double bond formation at C5 position of thiazolidinone core (Scheme 2).

The reaction of pseudothiohydantoin (2-imino-4-thiazolidinone) and isatin (molar ratio 2:1) was carried out in absolute ethanol under reflux affording not only target 5-ene-4-thiazolidinone (4) but also spiro-isatin conjugate (45%) 3 [57]. Based on the Knoevenagel condensation the efficient method for 5-ethoxy-4-thiazolidinones synthesis (5) using triethylorthoformate was described [32,62–66], the latter (5) can be easily converted



**Scheme 2.** Variety of products of condensation reactions.

into the appropriate amines (**6**) (Scheme 3).

Knoevenagel condensation often may be a stage in the tandem and/or domino reactions whilst the corresponding 5-ene-thiazolidinones appear as intermediates in the synthesis of fused thiazolidinone-based heterocycles (see below) [67–69] or simple molecules of other thiazolidinone subtypes. For example, an efficient approach to the 5-ene-2-amino-4-thiazolidinones obtaining via sulfur/nitrogen displacement [70] was the base for the development of multicomponent reactions involving Knoevenagel condensation [71]. The one-pot reaction of isatin derivatives, rhodanine and secondary amines (magnesium oxide nanoparticles used as heterogeneous catalyst, water medium, r.t.) is an efficient green approach to the preparation of novel isatin-thiazolidinone based conjugates (**7**) [72] (Scheme 4).

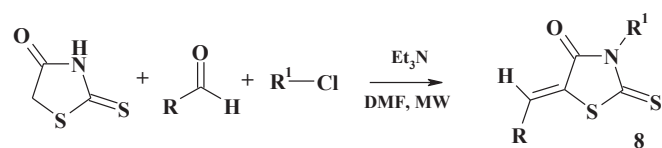
There has been developed a fast and efficient protocol for the generation of 3-substituted 5-arylidenerhodanines (**8**) (Scheme 5) in sequential one-pot, two-step process combining the Knoevenagel condensation and alkylation reaction under microwave assisted conditions [73].

*Other types of condensations.* The active methylene group can be condensed with dimethylformamide-dimethylacetal (DMF-DMA) in dioxane to yield the corresponding enamines (**9**).

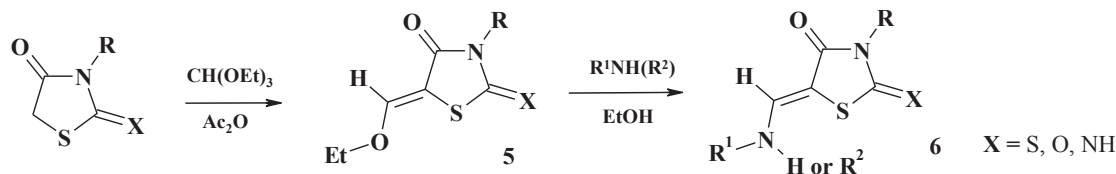
Moreover, the methylene group in 4-thiazolidinone can be

coupled with the aryl-diazonium salt in EtOH/NaOH to form the corresponding arylhydrazone (**10**) [3,74] (Scheme 6). Similar to 5-arylidene-4-thiazolidinones, in all cases only *Z*-isomers were formed (confirmed by X-ray data) [75]. The isosteric 2-*R*-substituted-4-thioxothiazolidines were also prepared in a single step on simultaneous treatment of thiazolidin-4-one with DMF-DMA and Lawesson's reagent in toluene medium [76]. Under the action of DMF/POCl<sub>3</sub> on 3-substituted 2-ylidene-thiazolidinones the related enamine derivatives of pyrrolo[2,1-*b*]thiazol-3-ones **11** were synthesized (Scheme 7) [77].

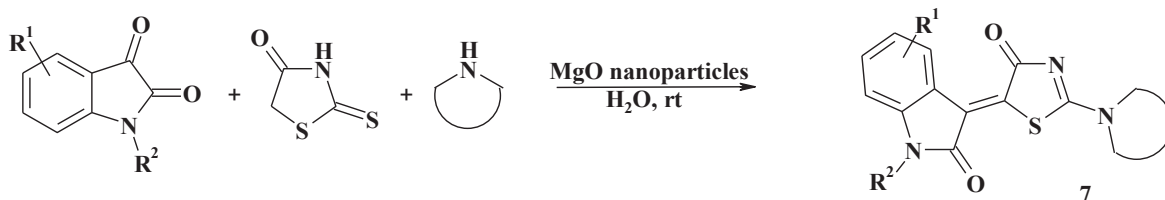
The active methylene group in the 4-thiazolidinones underwent nucleophilic addition reaction with the double bond of the various arylidene malononitriles via *Michael type addition reaction* (ethanol medium in the presence of piperidine) to give the same 5-ene-4-



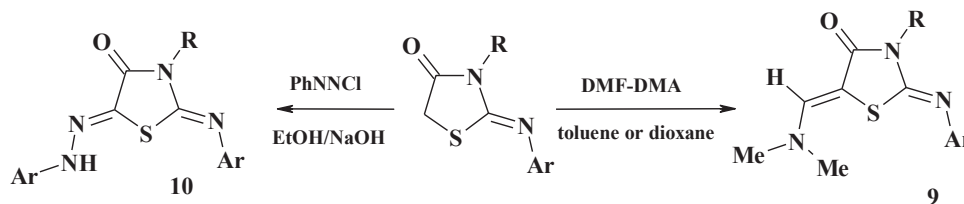
**Scheme 5.** One pot synthesis of 3,5-disubstituted thiazolidinones.



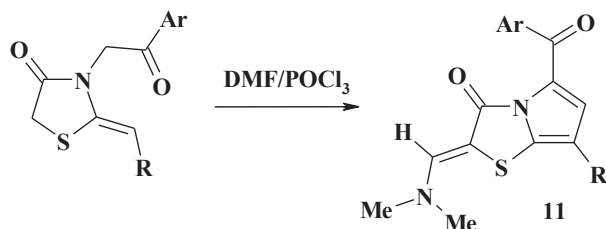
**Scheme 3.** 5-Enamine-4-thiazolidinones formation.



**Scheme 4.** One pot synthesis of 2,5-disubstituted thiazolidinones.



**Scheme 6.** Synthesis of 4-thiazolidinone based enamines and arylhydrazones.



**Scheme 7.** Synthesis of pyrrolo[2,1-*b*]thiazol-3-ones based on 4-thiazolidinones.

thiazolidinone derivatives (**12**) [75] (Scheme 8).

For instance, reaction of  $\alpha$ -cyano-3,4,5-trimethoxycinnamionitrile and/or ethyl- $\alpha$ -cyano-3,4,5-trimethoxycinnamate with 2-imino-4-oxo-thiazolidine provided appropriate 5-enes' formation (instead of the expected fused heterocycles) [78,79]. It was proposed that the reactions proceeded via nucleophilic addition of the thiazolidinyl-C-5 to the  $\beta$ -carbon of the activated double bond of nitriles forming the 1:1 adduct followed by the elimination of malononitrile or ethylcyanoacetate. The same step was proposed as a mechanism of dihydrothiophene derivatives formation via the four-component reaction of aldehyde, malonitrile, 2,4-thiazolidinedione and piperidine in the presence of  $\text{Bu}_4\text{NOH}$  as a basic ionic liquid in alcohol-aqueous medium [49] or via the triethylamine-catalyzed domino reaction [80,81].

**Isothiocyanate based synthesis.** The reaction of 2-arylimino-3-*R*-4-thiazolidinones with arylisothiocyanate in DMF in the presence of KOH provided the appropriate thioamides (**13**) [82,83], which may be treated as effective building blocks for the synthesis of polyfunctional compounds. The latter reacted with hydrazonol halides affording new 5-heterylidene derivatives **14** (Scheme 9).

One more efficient method for 5-ene-4-thiazolidinone synthesis

is the reaction of 4-thiazolidinones (e.g. rhodanine-3-acetic acid) with anilide-vinyl compounds [84] or with hemicyanines [85] with formation of dimethinemerocyanine and cyanine dyes (**15**, **16**) (Scheme 10).

Merocyanine dyes (**17–20**) are other examples of polycyclic heterocycles derived from 5-ene-4-thiazolidinones. Their synthesis involves C5 active methylene group of thiazolidinone core and methylated thioxo-group (C2 position of rhodanine-3-acetic acid [86] (Scheme 11)) or other heterocyclic S-Me salts [84,87,88] (Scheme 12).

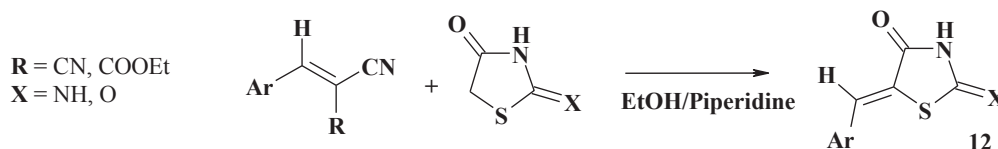
Rhodanine derivatives, such as rhodanine-3-carboxylic acids, via the action of thionyl chloride were exposed to dimerisation at the C5 position and yielded appropriate acyl chlorides (**21**), which can be used for further modification (**22**) [89] (Scheme 13).

Reaction of 3-alkyl(aryl)rhodanines with bis-(trimethylsilyl)formamide also led to dimerisation and formation of the bis-(3-*R*-rhodaninyl-5)methinoxynes (**23**) [90].

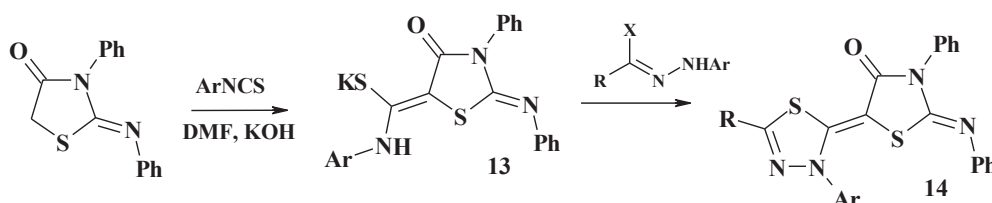
The reaction of 4-thiazolidinones with halogens led to simple 5-halogen-derivatives (**24**) (Scheme 14) which are the effective reagents for further synthetic transformation. Thus, based on ethyl ester of 5-bromo-2-thioxo-4-thiazolidone-3-acetic acid an original method for 5-ylidene derivative (**25**) synthesis was proposed [91].

Another efficient method for the 5-ene-4-thiazolidinones (**26**, **27**) synthesis (especially in the case of compounds containing carboxylic or carbonyl group in the C5 substituent) is a dehydrobromination reaction [92–94] (Scheme 15). 5-(2-Aryl-2-oxoethyl)-rhodanines reacted with bromine in acetic acid and formed a mixture of *E*- and *Z*-stereoisomers of 5-arylmethylenrhodanines.

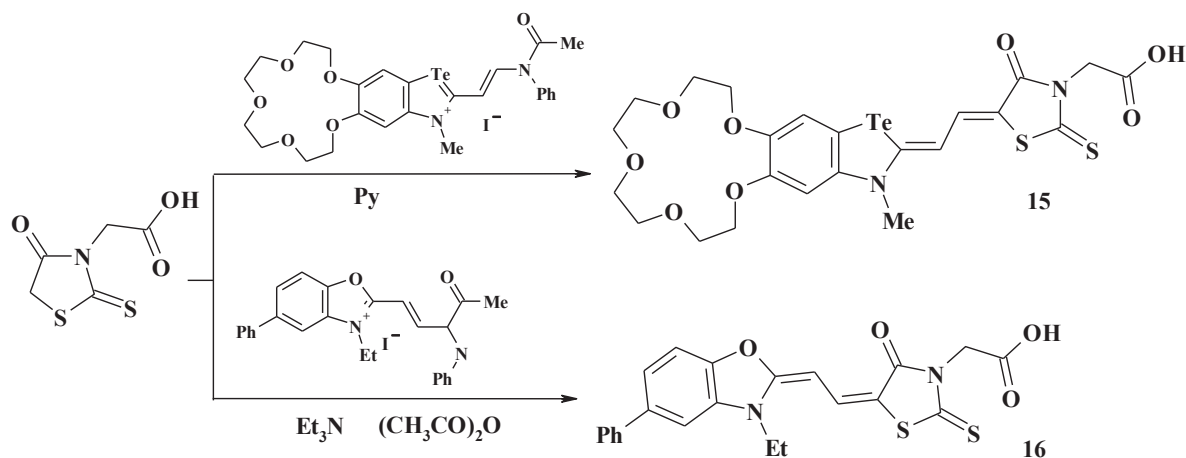
Described esters of 5-carboxymethylidene-4-thiazolidinone (2,4-dioxothiazolidin-5-ylidene-acetic acid) (**26**) are attractive building blocks for the various 4-thiazolidinone subtypes synthesis [94,95] including 5-ene derivatives. Addition of dithiocarbamates



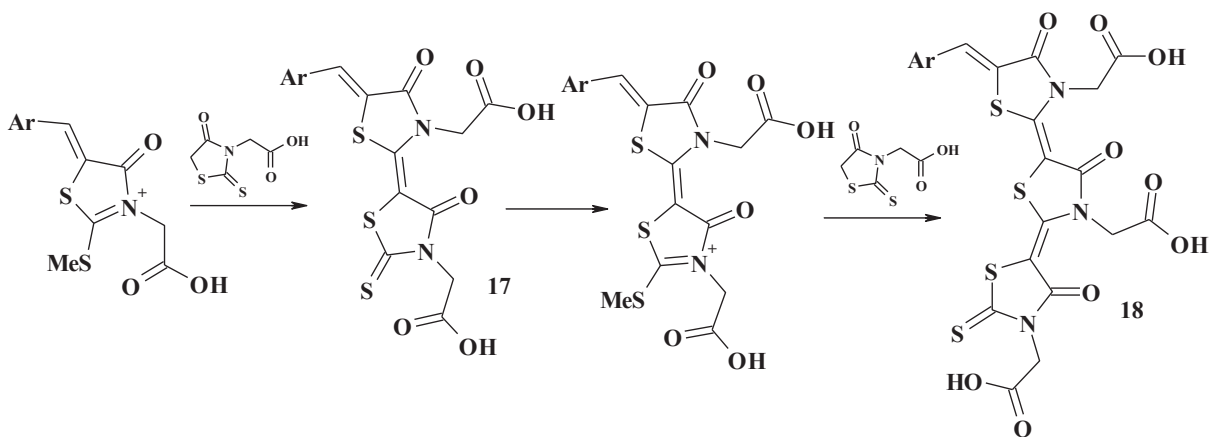
**Scheme 8.** Michael type addition reaction of 4-thiazolidinones.



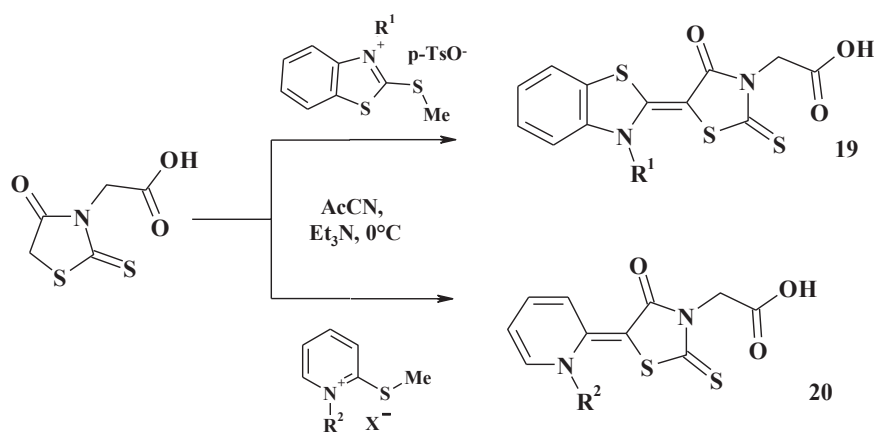
**Scheme 9.** Isothiocyanate based synthesis of 5-ene-4-thiazolidinones.



**Scheme 10.** 4-Thiazolidinone-based dimethinemerocyanine and cyanine dyes.



**Scheme 11.** Synthesis of 4-thiazolidinone based merocyanine dyes.

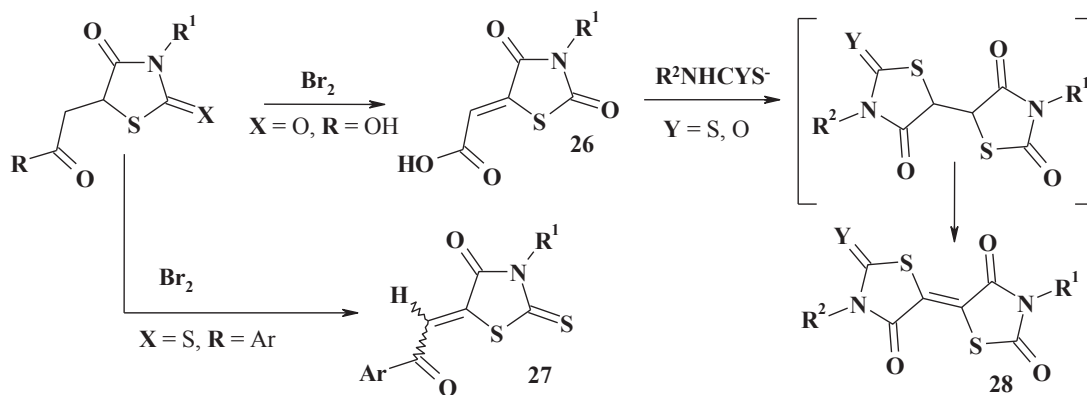
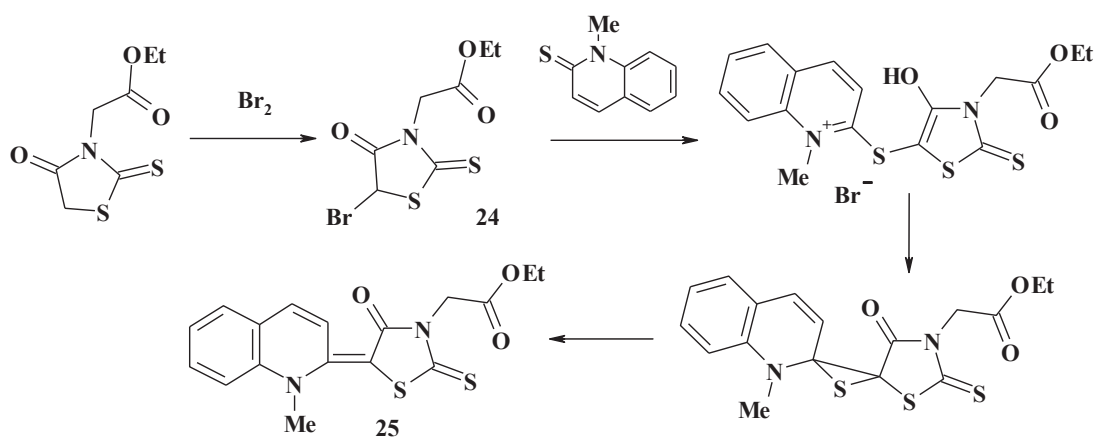
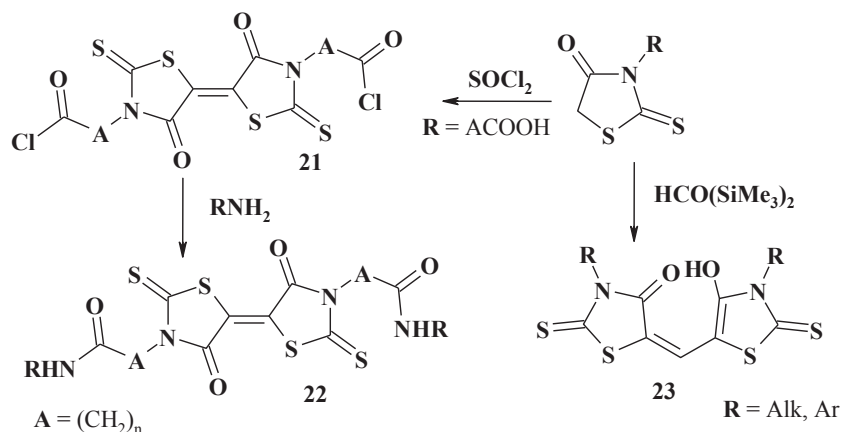


**Scheme 12.** Synthesis of 5-heterylidene 4-thiazolidinones.

and thiocarbamates to the double bond in 5-ene-4-thiazolidinones resulted in spontaneous heterocyclization to 5,5'-di-4-thiazolidinones intermediates, which were oxidized in the presence of triethylamine to **28** [96] (Scheme 15).

## 2.2. Simultaneous formation of heterocycle and C5 exocyclic double bond

Most of the protocols presented above are rather simple and most of them explore two- or three-step procedures. Considering



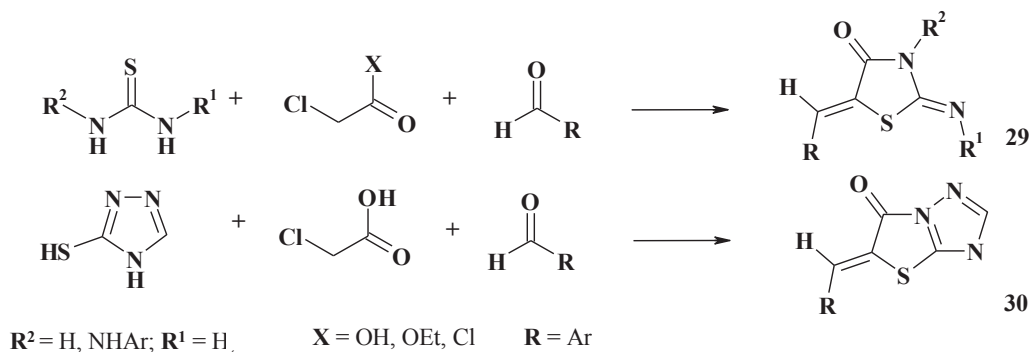
the current trends in organic/medicinal chemistry different one-pot multicomponent methods were proposed for 5-ene-4-thiazolidinones synthesis (**29**) (Scheme 16). The illustrative example is the one-pot method based on [2 + 3]-cyclocondensation of substituted thioureas/thiosemicarbazides with halogen-carboxylic acids followed by Knoevenagel condensation designed in our laboratory [59,97,98] and widely used [99] under wet chemistry conditions as well as under microwave irradiation or

in the green reaction media [55,100–102].

This approach can be successfully employed for the synthesis of fused heterocycles bearing 5-ene-4-thiazolidinones moieties e.g., 5-ylidene-[1,3]thiazolo[3,2-*b*]1,2,4]triazol-6-ones (**30**) [103] (Scheme 16).

The common approach to the synthesis of 5-ylidene-4-thiazolidinones with carboxylic group (**31**) based on [2 + 3]-cyclocondensation reaction is the utilization of unsaturated acids





**Scheme 16.** One-pot three component synthesis of 5-ene-4-thiazolidinones.

and their derivatives (Scheme 17). This approach is also efficient in the synthesis of various C2 substituted 4-thiazolidinones [104–106] (target compounds can be N-substituted or with unsubstituted N3 position). The condensation of thioamides with dimethylacetylenedicarboxylate in benzene (or acetonitrile or acetic acid for thioacetamide) led to appropriate thiazolidinone (**32**, **33**) [107,108] (Scheme 18). But there are reports about the formation of other products, such as 2-(1-iminoethylsulfanyl)-fumarate [28,109].

Similar ylidene derivatives (mixture of *E/Z* isomers) **34** were formed in the reaction of  $\alpha$ -carbamoyl(cyano)thioacetamides with dimethylacetylenedicarboxylate [28,110,111].

Thioamides of  $\alpha,\beta$ -unsaturated acids in the reaction with acetylenedicarboxylic acid, propionic acid and their esters in acetone medium also yield the thiazolidinones as well as thiazanones [28,112].

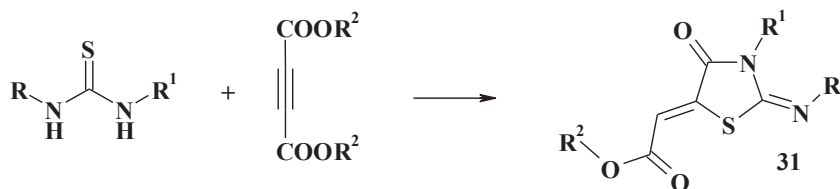
The three-component reactions of amine with dialkyl acetylenedicarboxylate and carbon disulfide yielded related rhodanine derivatives (**35**) [113,114] (Scheme 19). Isocyanate utilization instead of carbonyl sulfide under the same conditions led to malimide derivatives formation.

The exploration of  $\alpha$ -chloro- $\beta,\gamma$ -alkenoate esters in such type of multicomponent reactions led to the formation of 5-(*Z*)-alkylidene-2-thioxo-1,3-thiazolidin-4-ones (**36**) which are uncommon compounds [115].

Arylpropiolates are efficient building blocks for 5-ylidenethiazolidinone constructing (Scheme 20). Reaction of the latter with bifunctional sulfur pronucleophiles is the phosphine-catalyzed tandem process which includes umpolung addition and intramolecular cyclization (**37**). Similarly, rhodanine derivatives (**38**) [116] were synthesized from dithiocarbamates in the phosphine catalyzed reaction (Scheme 20).

Reaction of trisubstituted thioureas with dimethylacetylenedicarboxylate (DMDA) in methanol medium can also lead to 1:1 adducts (**39**) [108] (Scheme 21).

Similarly, pseudothiohydantoin (2-amino-1,3-thiazol-4(5*H*)-one) derivatives (**40**) can be easily obtained under the propenylthioureas oxidation (e.g., by bromine action) (Scheme 22) [117].



**Scheme 17.** General scheme of [2 + 3]-cyclocondensation of unsaturated acids.

Novel 2-hydrazolyl-4-thiazolidinone-5,6- $\alpha,\beta$ -unsaturated esters (**41**) were synthesized in the multicomponent reaction of aldehydes, thiosemicarbazides and dimethylacetylenedicarboxylate in the ethanol medium. Interestingly, the reaction doesn't depend on the presence of electron-withdrawing or electron donating groups. It involves thiosemicarbazone formation followed by Michael addition of the sulfur atom to the triple bond and sequential cyclization (Scheme 23) [118].

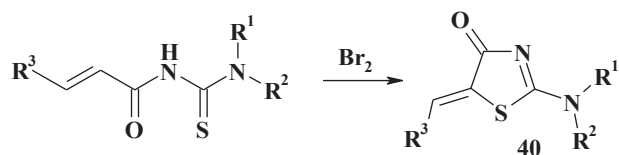
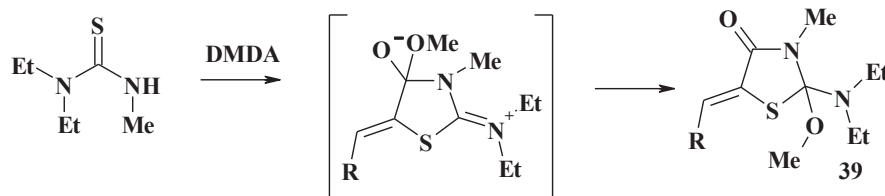
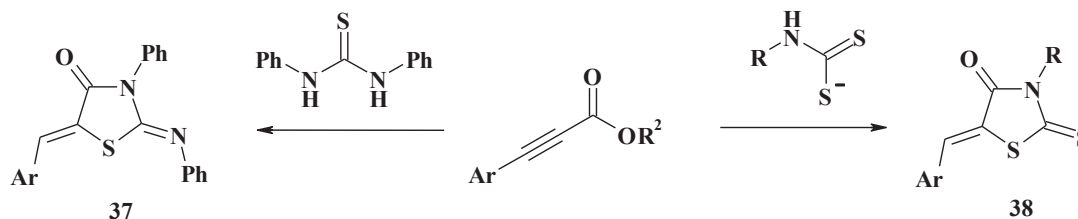
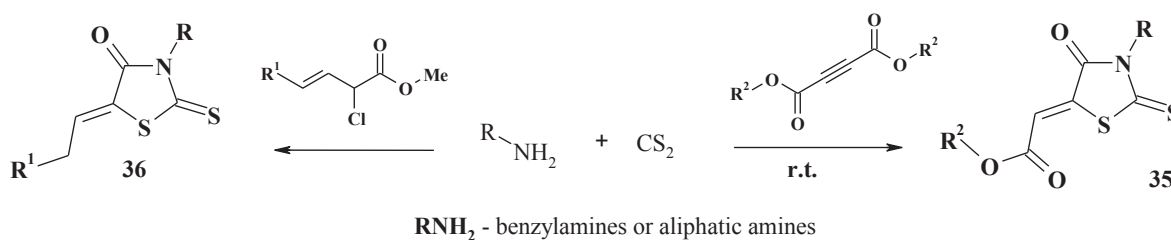
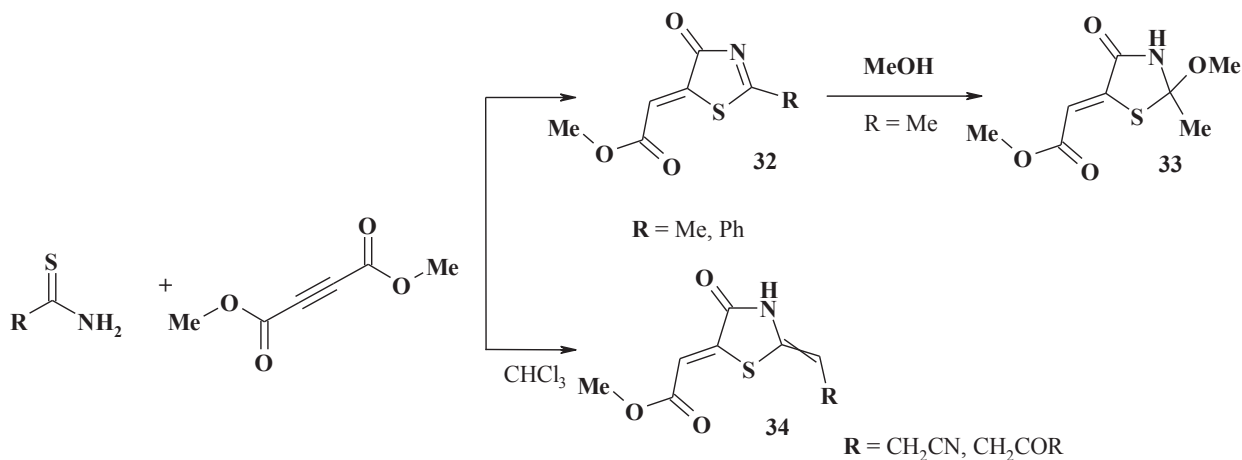
Some epoxy acids (*cis*- and *trans*-epoxysuccinic, 2,3-epoxybutyric and methyl-*cis*-epoxysuccinic acids) constitute another equivalent of the dielectrophilic synthon  $[C_2]^{2+}$  in [2 + 3]-cyclocondensation reactions with thiourea when obtaining 5-substituted pseudothiohydantoins (**42**) and 2,4-thiazolidinediones (**43**) [119] (Scheme 24).

A fast and high yielding protocol for the generation of substituted 5-arylidenerhodanines (**44**) in sequential one-pot two-step process combining the Holmberg method and the Knoevenagel condensation under microwave assisted conditions has been developed [73] (Scheme 25).

An important synthetic route to 3-substituted 4-thiazolidinones is the reaction of  $\alpha$ -mercaptocarboxylic acid derivatives with ethylcyanoacetate, cyanoacetamides, malonodinitrile etc. [2,3,6,120,121] as well as the cyclocondensation of oxonitriles or cyanoguanidines with 2-mercaptosuccinic acid derivatives [121] (Scheme 26). Obtained 2-methyl-4-thiazolidinones **45** were exposed to regioselective bromination and dehydrogenation to form 5-ene-4-thiazolidinone derivatives **46** [122,123].

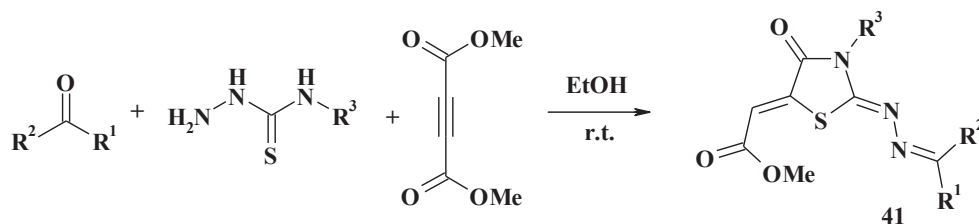
The most convenient method for 2-substituted-4-thiazolidinones synthesis is the one-pot three-component reaction of a primary amine, an oxo-compound, and a thiolic agent using various reaction conditions, such as extended heating with a dehydrating agent, using an acylation agent or microwave-assisted organic synthesis [124–129]. Based on the retrosynthetic approach the synthesis of 5-ene-2,3-disubstituted-4-thiazolidinones (**47**) was proposed [43] (Scheme 27). 3-Substituted-2-mercaptoacrylic acids obtained from 5-arylidenerhodanine were used as thiolic agents.

The 5-ene-4-thiazolidinones (**48**) were prepared in such one-

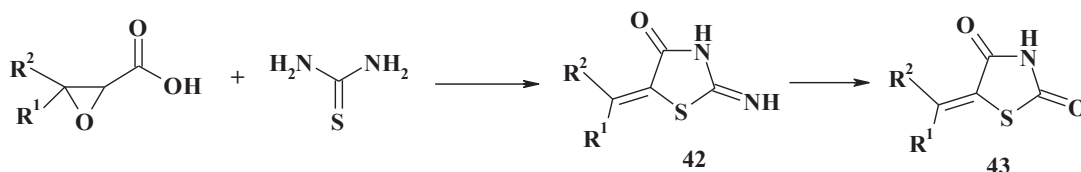


pot three-component reaction where nitriles were used instead of corresponding amines [130,131]. The similar three-component reaction was proposed for the fused heterocycles synthesis, namely thiazolo[3,2-*a*]pyridine derivatives (49) [132,133] (Scheme 28).

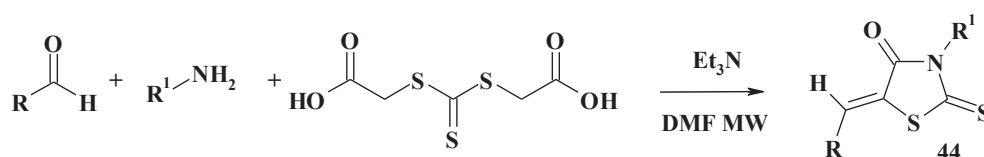
This type of three-component domino reaction of readily available thioglycolic acid/ethylthioglycolate, aromatic aldehydes and malononitrile/ethylcyanoacetate was described in the aqueous potassium carbonate at r.t [134].



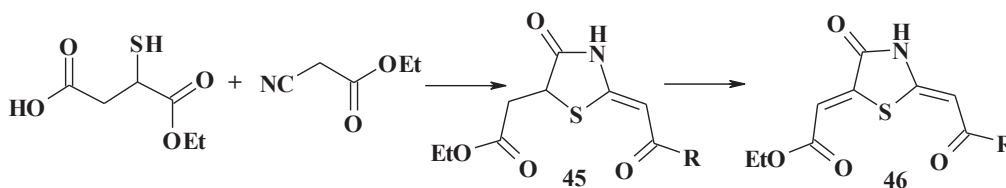
**Scheme 23.** Multicomponent reaction for 2-hydrazyl-4-thiazolidinones synthesis.



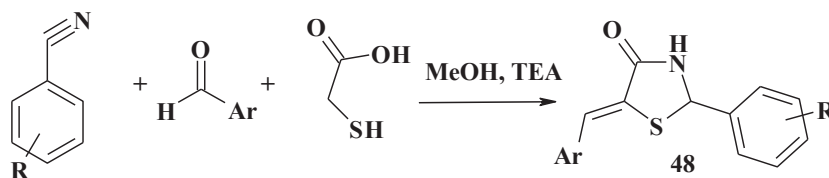
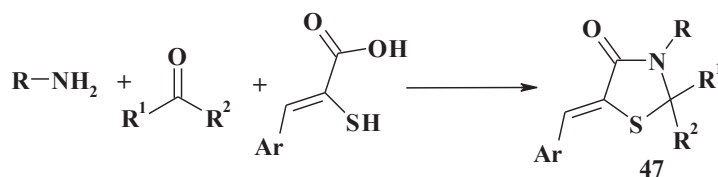
**Scheme 24.** Synthesis of pseudothiohydantoines and 2,4-thiazolidinediones from epoxy acids.



**Scheme 25.** Holmberg method and Knoevenagel condensation based one-pot method.



**Scheme 26.** Synthesis of 2,5-diene-4-thiazolidinone derivatives.



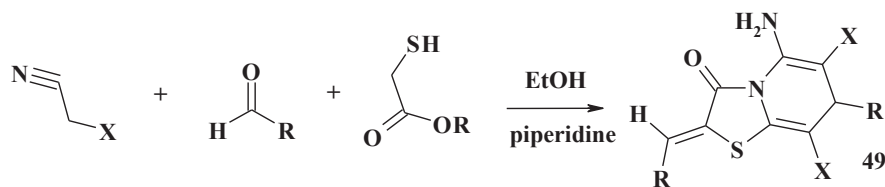
**Scheme 27.** Synthesis of 5-ene-2-R-4-thiazolidinones.

The one-pot reaction based on the condensation of ethylthiocyanacetate, arylidenehydrazine and hydrazine hydrate in glacial acetic acid also led to the formation of 5-arylidene-2-arylidenehydrazine-4-thiazolidinone (**50**) [135] (Scheme 29).

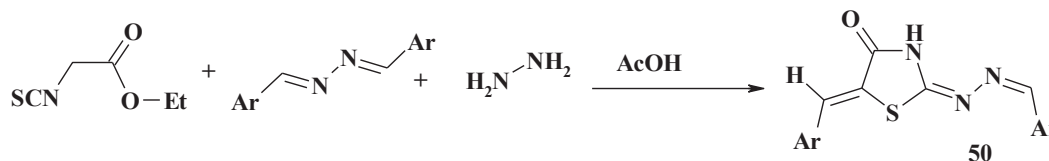
Similarly to the 5-unsubstituted 4-thiazolidinones synthesis,

the sequential three-component reaction involving primary amines, isothiocyanates, and 1,2-diaza-1,3-dienes was proposed as an efficient method for the 2-iminothiazolidin-4-ones-synthesis (**51**) [136] (Scheme 30).

Formation of the 2-iminothiazolidin-4-one was explained by



**Scheme 28.** Three-component reaction in the synthesis of fused heterocycles with 5-ene-4-thiazolidinone fragments.



**Scheme 29.** One-pot method of 5-ene-2-hydrazone-4-thiazolidinone synthesis.

the initial regioselective S-Michael addition of the thiourea intermediate, which resulted from the coupling of amine and isothiocyanate, to the electrophilic center of 1,2-diaza-1,3-diene. The next step was the intramolecular attack of the -NH of the obtained isothiourea derivative on the ester group in C4 of the hydrazone chain with a loss of an alcohol molecule [136]. The hydrolytic cleavage of the hydrazide moiety of **51** afforded new 5-hydroxyethylidene thiazolidinones **52** [136].

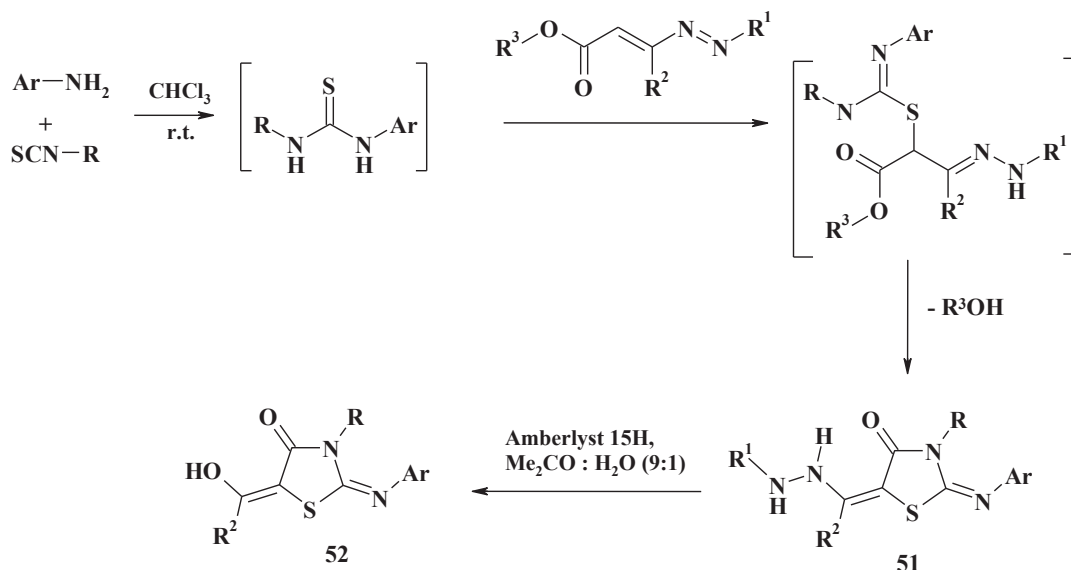
### 2.3. Transformation of related heterocycles

The transformation of related heterocycles aimed to form 5-ene-4-thiazolidinone is not very often explored in the 4-thiazolidinone synthesis due to the simplicity of the methods described above. However, in the reaction of monosubstituted ureas with 4-chloro-5-formylthiazolin-2-one (**53**) the rearrangement occurs yielding 2,4-dioxothiazolidin-5-ylidene-methyl-urea (**54**). The starting 4-chloro-5-formylthiazolin-2-one (**53**) was obtained in the reaction of 2,4-thiazolidinedione formylation [137] (Scheme 31).

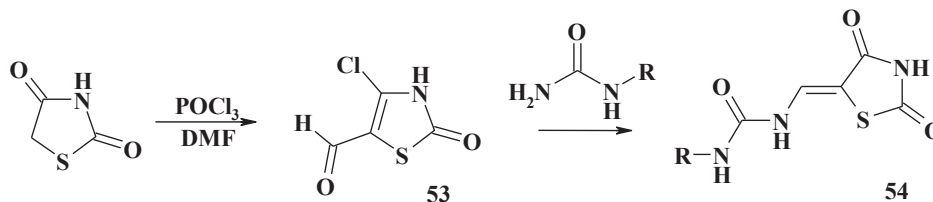
### 3. Pharmacological profiles of 5-ene-4-thiazolidinones

Most of the pharmacologically attractive agents among 4-thiazolidinone-based compounds are exactly 5-ene-4-thiazolidinones with the exocyclic double bond. This is reflected in crucial impact of the presence/nature (namely 5-ene) of C5 substituents in thiazolidinone ring on pharmacological effects [27,34,35,54,94,138–143]. At the same time, (ar)ylidene fragment conjugation with the carbonyl group at C4 of the thiazolidinone core makes such compounds electrophilic and potentially reactive due to possible Michael addition of the exocyclic double bond to the nucleophilic protein residues [144,145]. Moreover, 5-ene-thiazolidinones can react with glutathione and other free thiols within a cell [145–147] (Scheme 32).

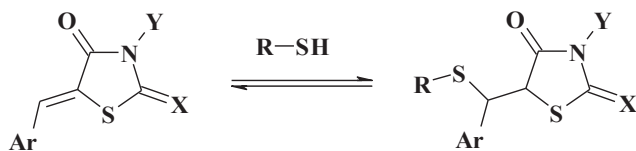
This property characterizes 5-arylidene-4-thiazolidinones (mainly rhodanine derivatives) as frequent hitters or pan assay interference compounds (PAINS) that are thought to be useless in the modern drug discovery process because of their possible/predicted insufficient selectivity [4,14,148–150]. This, along with other structural features, offers high probability of polar interactions and



**Scheme 30.** 1,2-Diaza-1,3-dienes in 5-ene-4-thiazolidinone synthesis.



**Scheme 31.** Recyclization in the synthesis of 2,4-dioxothiazolidin-5-ylidenemethyl-urea.



**Scheme 32.** General scheme of thia-Michael addition of 5-ene-4-thiazolidinones.

hydrogen bonds formation. Causing a promiscuous behavior at concentrations within the “screening range” this statement should not be regarded as a general knock out criterion that excludes such screening hits from further development. It is suggested that special criteria for target affinity and selectivity must be applied to these classes of compounds so that their exceptional and potentially valuable biomolecular binding properties are consequently exploited in a useful way [14].

Interpretation of 5-arylidene-4-thiazolidinones as frequent hitters is often not confirmed in experimental studies [24,151,152] and a large number of lead-compounds belong to 5-ene-4-thiazolidinones. The positive perspective may also be associated with the polypharmacological approach in drug discovery, where the affinity toward various targets is regarded as an advantage [14]. Moreover, mentioned compounds as the examples of privileged scaffolds can be treated as drug-like molecules that provide baseline affinity for a whole protein family [14,153]. Additionally, better results in drug design can be expected when responses are evoked by multipoint interventions in more than one mechanism and towards different targets [154] following the concept of multi-target drugs, also known as dual or symbiotic drugs [155]. The exploitation of 5-ene diversity allows achieving such desired combinations of molecular fragments. There have been many reports describing the presence of heterocyclic moieties, such as thiazole, pyrazole, flavones, chromone, furan etc. at C5 position of thiazolidinone core [8,27,34,35,65,66,138]. It is even considered that the more such fragments are in the molecule, the more effective it is when comparing with the molecules including simple aryl groups (see below). In this spirit, lack of strict specificity in ligand binding and possibility of the influence of both the compound and its metabolites on the other metabolic pathways are being actively discussed. This concept is one of the arguments in favour of the search for “nonspecific” biologically active compounds. Furthermore, many compounds possess different types of activity that are apparently due to their action towards different metabolic pathways (targets) or involving the same biological targets in metabolic pathways of various pathologies.

Thus, many authors consider that “thiazolidinones and related scaffolds should not be regarded as problematic or promiscuous binders *per se*” [14]. The intermolecular interaction profile of these scaffolds makes them prone to bind to a large number of targets with weak or moderate affinity. It may be that the observed moderate affinities, e.g. in screening campaigns, have been over-interpreted in the past and that these compounds have too easily

been put forward as lead compounds for further development.

In this context, it is worth mentioning that exactly the same Michael acceptors are among the most effective activators of Nrf2 through the Keap1 modification that opens new perspectives in the treatment of inflammation, cancer, etc. [144,156]. Moreover, Michael acceptors including 5-ene-thiazolidinones belong to a new class of highly specific and potent inhibitors of the mitochondrial pyruvate carrier [157].

In addition, it should be emphasized that the possibility of being Michael acceptors (calculated or predicted based on the molecular structure and used in the *in silico* studies) is often not confirmed experimentally under conditions close to physiological [156].

Besides, as was mentioned earlier, 5-ene-4-thiazolidinones are widely used in the design of complex heterocyclic systems within the hybrid pharmacophore approach [158,159]. The significant biological potency of compounds bearing 5-ene-4-thiazolidinone fragment in combination, for example, with heterocycles [27,34,65,138,160] or other scaffolds [161,162] was discovered. Satisfactory toxicological parameters of such compounds may be an additional argument in favour of their development and study [163].

The next chapter represents the most prominent pharmacological profiles of 5-ene from different 4-thiazolidinone subtypes which belong to hit-, lead-compounds, drug-candidates and drugs. Two main directions of the study of biological activity of 5-ene derivatives are presented: the identification of a number of compounds possessing some types of biological activity in screening procedure (without molecular targets identification); design of high-affinity ligands to established molecular targets (for instance, a lot of thiazolidinones are proved to be ligands to the biological targets presented in protein data bank ([www.rcsb.org](http://www.rcsb.org))). Moreover, several types of activity are often described for the same compounds that clearly follows from the above said.

A large number of publications are dedicated to the *in silico* study of 4-thiazolidinones and particularly 5-ene derivatives. In this paper we did not focus on such data as it is widely outlined in the review papers [164–170]. A wide range of established pharmacological activity of 5-ene-4-thiazolidinones does not allow to describe all its types in the given manuscript. Thereby, we focused on the most studied and described types of activity such as antimicrobial, antitumor etc. Besides, the compounds bearing fused 5-ene fragment (e.g. thiazolothioapyranes, thiazolopyridines etc.) are beyond the scope of this paper.

### 3.1. Antimicrobial agents

One of the earliest directions of the 5-ene-4-thiazolidinones biological assays lies in the field of antibacterial and antifungal activities search. Apparently, the structural similarity of 4-thiazolidinones with penicillin antibiotics was the stimulus to the study of such type of activity [1–3,6,167,168]. Though, recently it was discovered that manifestation of antibacterial effect is not always related to the penicillins' mode of action. Usually, there is a tendency to move from the detection of antimicrobial activity

[169–176] within screening programs to identification and design of high affinity ligands to the validated molecular targets. Regardless of the nature of the basic core (2,4-thiazolidinedione, rhodanine, etc.), modification and complication of C5 ylidene fragment are the benefits for realization of such type of activity (the role of the halogen-arylidene moieties should be stressed) [141,177].

The 3-substituted 5-ylidene-4-thiazolidinones, especially 3-carboxylic acids **55–59** [171,175–181] represent group of compounds with significant antimicrobial activity against gram-positive and gram-negative microorganisms. Their molecular mode of action is associated with the inhibition of: i) the last two stages of peptidoglycan cell wall biosynthesis (the most attractive targets for new antimicrobials design - mainly *penicillin-binding proteins family*, and *transferases – UDP-Mur-Nac-peptidases*); ii) the activity of *dehydrogenases* (compound **58** and related structures can cross the bacterial cell wall and lead to the identification of catechol-rhodanine core as privileged scaffold for design of the dehydrogenases inhibitors) [153]; iii) *peptide deformylase* [182] (for lead-compounds **60**, **61**  $IC_{50} = 0.89 \mu M$  and  $1.66 \mu M$  correspondly) etc (Scheme 33).

A series of 5-ene-rhodanine-3-acetic acid derivatives **62** (Scheme 34) were described as inhibitors of fungal *protein mannosyl transferase 1* (PMT1) at micromolar levels (design of compounds was also based on the complications of C5 moiety) [183]. High-throughput screening of 5-arylidene-4-thiazolidinone-3-alkanecarboxylic acids **63**, **64** proved them to be *anthrax lethal factor* (as one of the major virulence factors) inhibitors ( $IC_{50} \sim 10 \mu M$ ) [45,184].

Antimicrobial activity of such compounds are determined by inhibition of *penicillin-binding proteins family*, such as a group of *transferases* (including *UDP-Mur-Nac-peptidases*), most of their subtypes are characterized by distinct transglycosylase activity [185]. ATP-dependent amino acid ligases (MurC, MurD, MurE, and

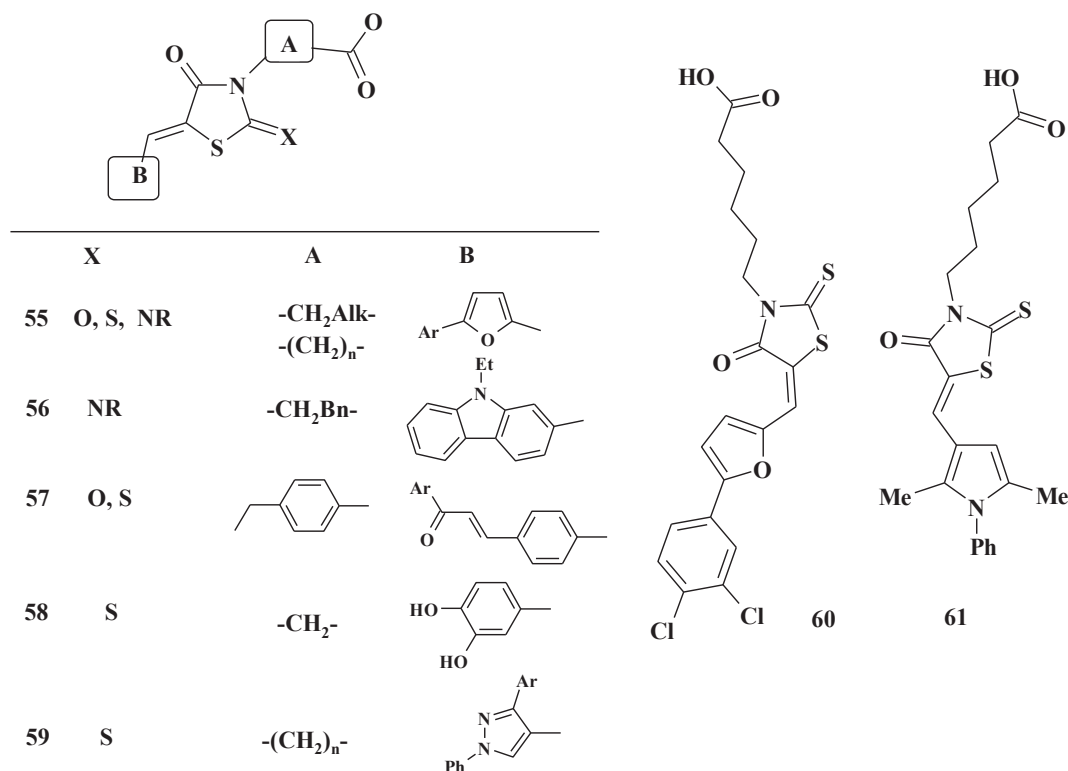
MurF, MurG) are an illustrative examples of the 5-ene-4-thiazolidinones antibacterial agents design [41,186–188]. For instance, **65** is an efficient inhibitor of MurC (*UDP-N-acetylmuramate/l-alanine ligase*) [139] and **66** – of MurG [189]. It should be emphasized that the 4-thiazolidinone and rhodanine cores are treated as novel phosphate mimics [190] (Scheme 34).

Structurally similar compounds are the inhibitors of *dTDP-rhamnose synthesis*. This is especially important for antimycobacterial agents search. The mycobacterial cell wall is unique because it contains an amycolyarabinogalactan layer bound to the peptidoglycan layer via a rhamnose–Glc–NAC sugar linker, where the dTDP-rhamnose can be treated as a precursor [191,192].

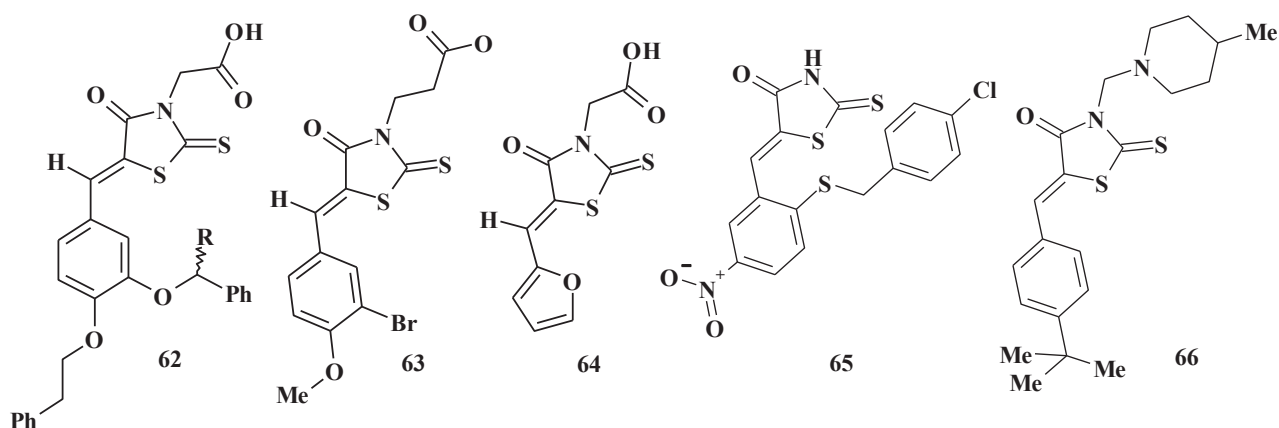
5-Heterylidene-2,4-thiazolidinedione derivatives **67** are competitive inhibitors of recombinant bacterial *arylamine-N-acetyltransferases* (NATs) [193], which were designed based on the structure modification of N-(2-naphthyl)-methyl substituted 1,1-dioxo-2,3-dihydrobenzo[1,2]-thiazine-4-ylidenethiazolidine-2,4-dione (weak inhibitor of NAT) [194] (Scheme 35).

One of the pathogenetic processes of pro- and eukaryotes is the mechanism associated with galactofuranose-based conjugation which involves *UDP-galactopyranose mutase* (UGM). The inhibition of such process leads to inhibition of microbial growth and reduction of virulence (especially for *Mycobacterium tuberculosis*) and improve the antimicrobial/antimycobacterial activity of UGM inhibitors. High inhibition activity of this enzyme was also discovered for 4-thiazolidinone-3-alkanecarboxylic acids **68**, **69** [180] and 2-imino derivatives **70** [145,195] (Scheme 35).

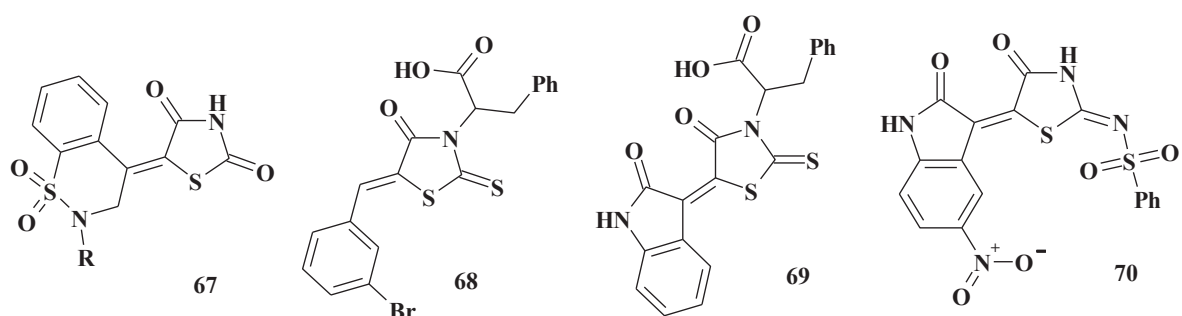
2-Amino(imino)-4-thiazolidinones have been widely investigated [141,177,196,197] as antimicrobial agents, e.g. compound **71** was identified as an inhibitor of the *type III secretion system* of *Gram-negative bacteria* [196,198]. *Pseudomonas aeruginosa* had shown reduction of *T2S-dependent elastase secretion* in the presence of **71** (Type II secretion (T2S) systems is well conserved among Gram-



Scheme 33. 5-Ene-4-thiazolidinone-3-carboxylic acids with antimicrobial activity.



Scheme 34. 5-Ene-rhodanines as antimicrobial agents.



Scheme 35. 5-Heterylidene-4-thiazolidinedione with antimicrobial activity.

negative bacteria and a key virulence factor of *P. aeruginosa*) [199]. The structure optimization aiming the increasing of solubility led to compound **74** which possessed superior activity (10  $\mu\text{M}$ ) in the *S. typhimurium* T3S secretion assay [196]. The N-3 position was established to be the most permissive optimization direction (Scheme 36).

The same findings are suitable for 2,4-thiazolidinedione derivatives – N3 modification provides to 5–40 folds increasing of the antimicrobial activity (**72**) [200,201].

Related 2-amino-4-thiazolidinone (**73**) was detected as high active *CysK1* inhibitor. *CysK1*-pyridoxal phosphate-dependent *O*-acetylsulfhydrylase which catalyzes the formation of L-cysteine from *O*-acetylserine and hydrogen sulfide. This cysteine biosynthetic pathway is one of the essential pathways in microbial pathogens, providing potential targets for the development of novel antibacterial compounds [202] (Scheme 36).

The row of 2-thiazolylimino-5-arylidene-4-thiazolidinone bearing the nitro group and small heterocyclic fragments (thiazole, benzthiazole, isatine, pyrazole, furane, thiophene) (**75–77**) (Scheme 37) in positions 2 and 5 showed sufficient antimicrobial activity levels too [203]; the nitro derivatives were characterized by high renal excretion that can be used in the design of potential diuretics [204]. The results of QSAR study revealed that the compounds with less number of atoms or less number of substituents are more likely to be active than their counterparts with higher molecular weight [205].

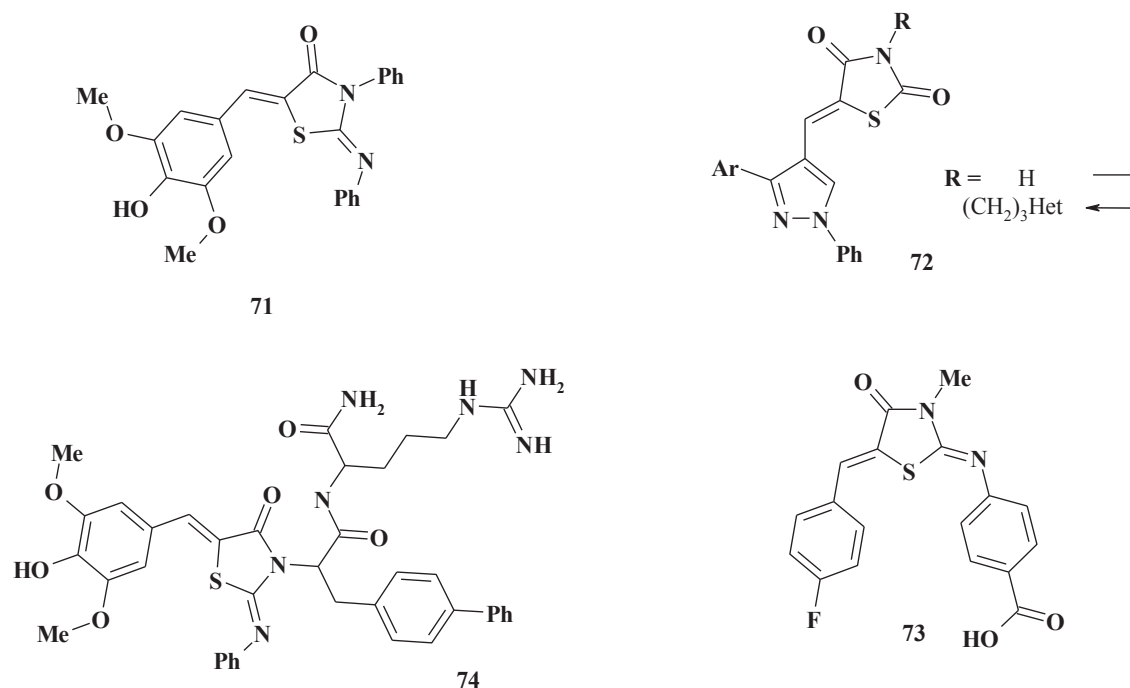
5-Heterylidenerhodanines and simple arylidene analogs are proposed as novel class of *b*-lactamase inhibitors that possessed selectivity for class C *b*-lactamases (**78** is a non-*b*-lactam with the  $\text{IC}_{50} \sim 2.6$  mM against the class C enzyme P99) [206].

Simple 5-alkylidene-2,4-thiazolidinediones **79** were discovered as effective inhibitors of *autoinducer-2* quorum sensing (mechanism through which bacteria regulate gene expression in response to population density including regulation of the production of virulence factors etc.) Virulence targeting is representing an emerging concept in antibacterial therapy for which there are examples of compounds that inhibit virulence functions [207]. N-3-Dipeptide-thiazolidinone hybrids **80** may provide a critical step toward the validation of this strategy and the development of novel therapeutics [196] (Scheme 38). Compounds having bulky aromatic substituents at position 5 and a tryptophan residue at position N-3 of the rhodanine ring were the most active against *InhA* (*trans*-2-enoyl-acyl carrier protein reductase) with micromolar  $\text{IC}_{50}$  [208].

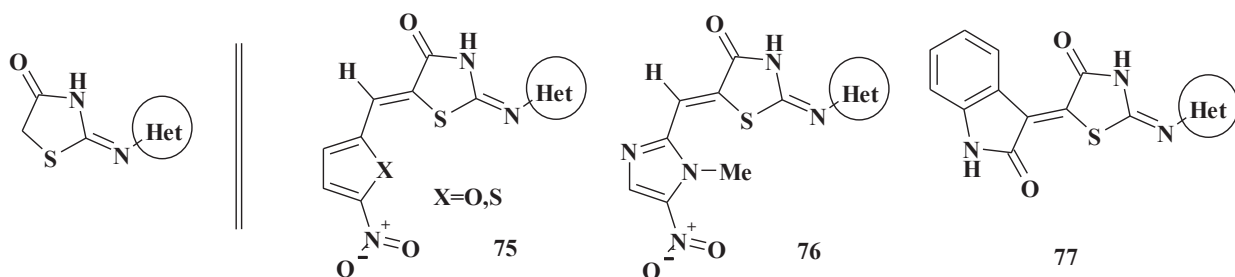
### 3.2. Antiparasitic agents

The *in vitro* antiamoebic activity of 3-substituted 2-amino-4-thiazolidinones **81** was evaluated against HM1:IMSS strain of *Entamoeba histolytica* and it exhibited promising activity ( $\text{IC}_{50}$  - 0.11–0.172 mM being lower than that of metronidazole  $\text{IC}_{50}$  - 1.64 mM) and low toxicity level [209] (Scheme 39).

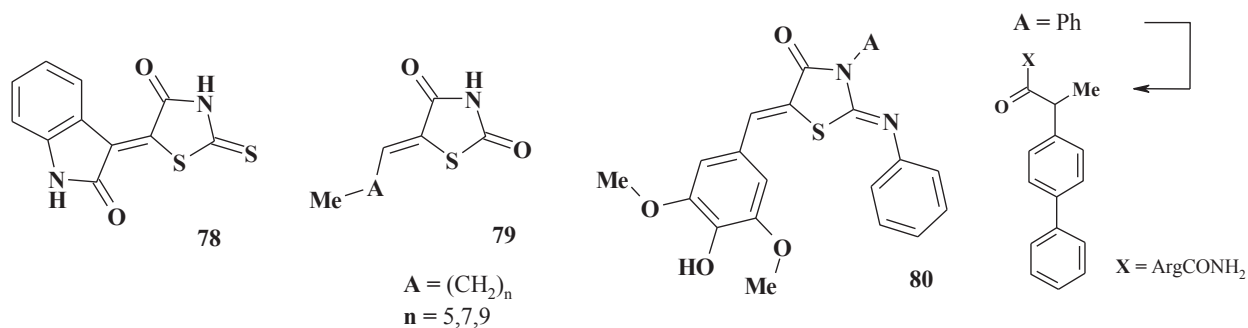
Several aza-fused rhodacyanines [210] were found as perspective agents when testing various heterocyclic rings on the anti-malarial activity. Among tested compounds **82** showed excellent inhibitory activity with an  $\text{IC}_{50}$  of 4.4 nM (K1 strain). Another compound **83** with quinoline ring and two rhodanine moieties showed 78% suppression of parasitemia (25 mg/kg/day) [211]. 4-Thiazolidinone-3-carboxylic acids belonging to rhodacyanine dyes **84** are characterized by distinct antimalarial activity [87,212]. Significant anticancer activity of the mentioned class of compounds



**Scheme 36.** 5-Ene-4-thiazolidinediones as inhibitors of the type II & III secretion systems.



**Scheme 37.** 2,5-Disubstituted-4-thiazolidinone hybrids with antimicrobial activity.



**Scheme 38.** Structure of antimicrobial 5-ene-4-thiazolidinones.

should be emphasized in this context (see below) (Scheme 40).

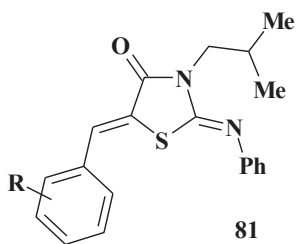
An *in vitro* structure–activity relationship investigation showed that the rhodacyanine **MKH-57** possesses high antimalarial activity (EC<sub>50</sub> = 12 nM) and significant selective toxicity [87] as well as a series of its analogs [212].

Screening of more than 13000 compounds for antimalarial activity using the agglomerative structural clustering technique

allowed identifying 47 starting points for lead optimization including 4-amino(imino)thiazolidinone derivatives **85** [213]. The positional isomer of mentioned 4-amino derivatives (**85**) – compound **86** was also described in the compound library of potential antimalarial leads [213] (Scheme 41).

In the area of antiprotozoal agents search the design of anti-trypansomal agents based on thiazolidinone scaffold is of special





**Scheme 39.** 3-Substituted 2-amino-4-thiazolidinones with antiamebic activity.

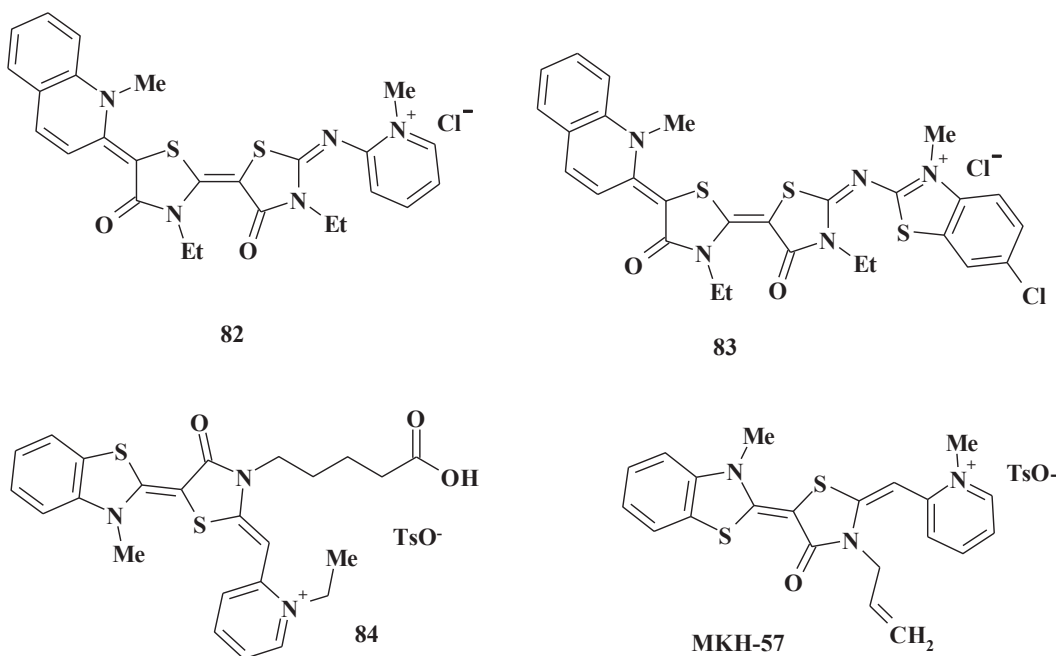
interest [214]. Compounds **87** showed the highest antiproliferative activity in comparison with 5-saturated analog **88** when screened on *Trypanosoma cruzi* epimastigotes but were inactive towards cruzipain [118] (Scheme 41). While **88**, obtained from a virtual screening of 500000 chemical structures (ZINC5 database) against cruzipain [215] inhibited this enzyme at micromolar concentration.

5-Benzylidenerhodanine-3-acetic acid derivatives **89** were

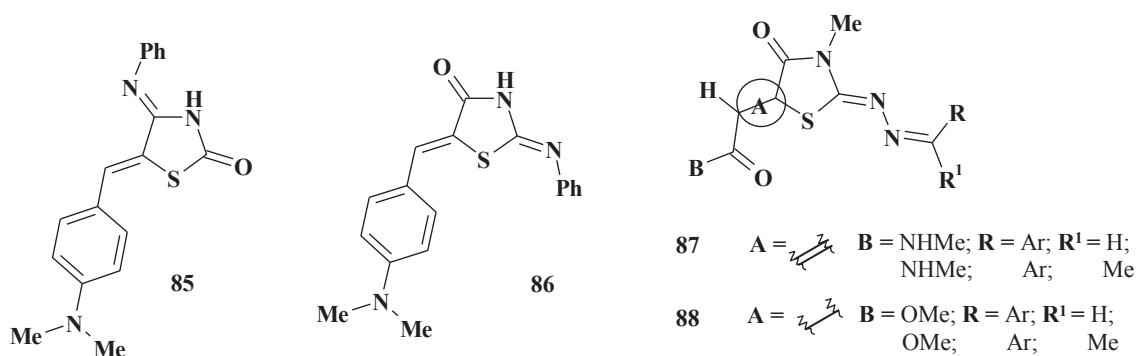
reported to possess inhibitory activity against *Trypanosoma brucei* dolicholphosphate mannose synthase and glycosylphosphatidylinositol anchor synthesis as well as *in vitro* trypanocidal activity against the blood stream form and were non-cytotoxic against HeLa cells. Dolicholphosphatemannose synthase is a mannosyl transferase critically involved in glycoconjugate biosynthesis in *T. brucei*. VSG dimmers covering the parasite cell-surface are linked to the trypanosomal plasma membrane via glycosyl phosphatidylinositol anchors, which biosynthesis is essential for viability of the blood stream form of *T. brucei*. The 3-benzyloxy-substituted analog and the 2-hydroxyderivative **89** showed the best trypanocidal activity ( $ED_{50} \sim 100 \mu\text{M}$ ) [215] (Scheme 42).

Simple 5-(hydroxyphenylmethylidene)thiazolidine-2,4-diones were described as novel inhibitors of *Leishmania pteridine reductase 1* where the thiazolidinone ring was treated as a bioisosteric replacement for pteridine/purine ring [216].

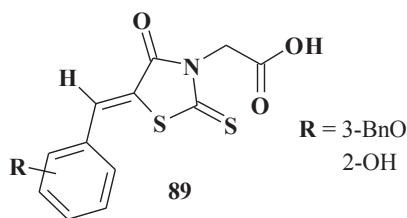
One of the discussed modes of action of thiazolidinone based compound is the DNA-binding process. In this study 2-imino derivatives **90** were designed and the most potent molecule bound at the DNA minor groove involving Van der Waals, H-bonding and



**Scheme 40.** Rhodanine-based dyes with antimalarial activity.



**Scheme 41.** 5-Ene-4(2)-thiazolidinones as antiparasitic agents.



**Scheme 42.** 5-Benzylidenerhodanine-3-acetic acid derivatives as antitrypanosomal agents.

hydrophobic interactions [217] (Scheme 43).

### 3.3. Antidiabetic agents

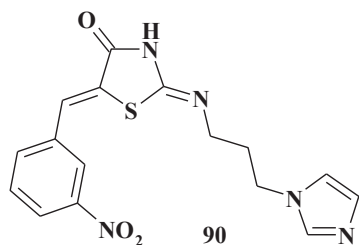
Search for new antidiabetic agents among 4-thiazolidinones is one of the most studied fields and had resulted in the introduction of new class of the antidiabetic drugs – glitazones. Their mechanism of action is associated with activation of PPAR $\gamma$  (peroxisome proliferation activated receptors) [19,218–220] (Scheme 44).

However, 5-ene derivatives including C5-unsaturated analogs of glitazones are to lesser extent activators of PPARs [221,222]. The introduction of carboxylic acid residue in the N3 position leads to decrease of hepatotoxicity of glitazones as well as unsaturated structural analogs (5-arylidene-thiazolidine-2,4-dione-3-acetic acids **91**). Compound **91** and related derivatives are reported to have low or no activity on PPAR, but have high antidiabetic activity *in vivo* (confirmed in sucrose-loaded model) [223].

This indicates other mode of antihyperglycemic action of 5-ylidene-4-thiazolidinones which can be treated as glitazone bioisosters. 5-Arylidene-3-benzyl-2,4-thiazolidinedione derivatives (**92, 93**) possess antihyperglycemic activity opposed to troglitazone under the experimental conditions (evaluation of *in vitro* insulin releasing activity, INS-1 cells); the latter has not decreased the level of hyperglycemia [224] (Scheme 45). Structurally related 5-ene-2,4-thiazolidinediones **94** with bulky C5 fragments are treated as potent euglycemic and hypolipidemic agents too [225] as well as their simple analog **95** (the alloxan-induced hyperglycemia, *in vivo* mice model) [226] (Scheme 46).

However, studies of PPAR-related actions of 5-ylidene-4-thiazolidinones are continuing. Virtual screening tools including SQUIRREL (Sophisticated QUantification of InteRaction RELationships) procedure allowed detecting a set of potential PPARs ligands [227]. 14 Compounds including 4-thiazolidinones **96–99** showed PPAR $\alpha$  and PPAR $\gamma$  agonistic activity (lead-compound **99** possessed the nano-level of activity ( $EC_{50}$  PPAR $\alpha$  = 0.044  $\mu$ M)) (Scheme 47).

A new series of PPAR $\gamma$  agonists known as ( $\beta$ -carboxyethyl)-rhodanine derivatives were identified based on ligand-centric and receptor-centric approaches. An *in vitro* assay had confirmed the nanomolar binding affinity of **100**. In a cell-based transactivation



**Scheme 43.** 2-(3-Imidazol-1-yl-propylimino)-5-(3-nitro-benzylidene)-thiazolidin-4-one as potential DNA-binding compound.

assay similar PPAR $\gamma$  agonistic activity to that of the known PPAR $\gamma$  drug, pioglitazone, was shown. Based on CoMFA model and docking data it was discovered that the electrostatic interaction of the carboxyethyl group with the rhodanine core is important for its binding in the pocket of PPAR $\gamma$  and the rhodanine heterocycle played a different role than the thiazolidine group of rosiglitazone [228].

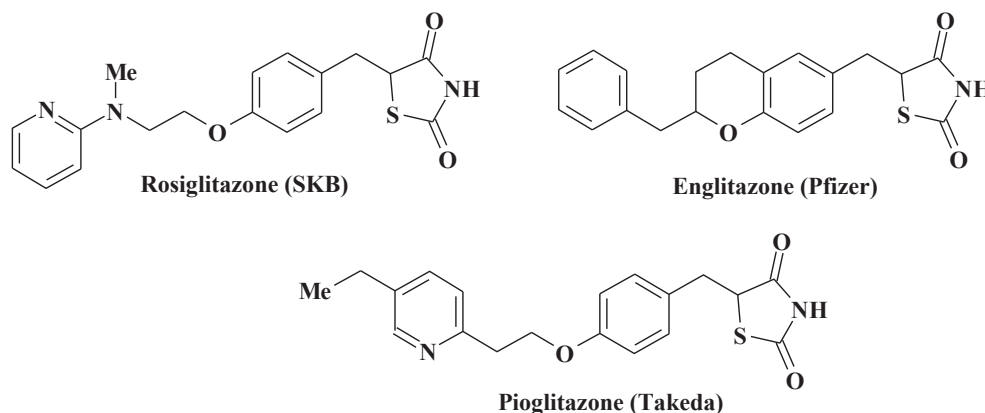
Currently the investigation of PPAR $\gamma$  antagonists is also of the great interest in the treatment of diabetes and obesity [229,230] including study of the 5-ene-4-thiazolidinones.

The most investigated mechanism of antidiabetic mode of action of 5-ene-4-thiazolidinones is the inhibition of *aldose reductase* (AR). *Aldose reductase* is the limiting enzyme of polyol/sorbitol pathway of glucose oxidation, excessive activation of which leads to the accumulation of glucitol and the development of diabetic complications [231]. 5-Ene-rhodanine-3-alkanecarboxylic acids are high affinity inhibitors of *aldose reductase* [232]. The illustrative example of the mentioned compounds' row is epalrestat – (*Z,E*)-5-(2-methyl-3-phenyl-2-propenyldiene)-2-thioxo-4-thiazolidinone-3-acetic acid. Optimization of these compounds structures is mainly associated with C5 fragment modification [53,233–235]. Study of epalrestat analogs revealed that *Z*-isomers possessed higher activity level. There is a great interest in 2,4-thiazolidinedione derivatives as AR inhibitors since they can be viewed as hydantoin and rhodanine bioisosters potentially free of the hypersensitive reactions which are linked to the presence of the hydantoin system [55,236,237]. In fact, to date, several thiazolidine-2,4-diones have been patented with dual activity as anti-hyperglycaemic and AR2 inhibitory agents [238,239]. The findings suggest that the activity of these compounds might correlate with their AR2 inhibitory ability by preventing the stimulation of PKC or MAPK and the subsequent activation of NF- $\kappa$ B [240]. AR2 plays a pivotal role in mediating oxidative stress-induced inflammation and is implicated in the development of various inflammatory pathologies [232] (see below). This enzyme catalyzes the reduction of lipid peroxidation-derived aldehydes, thus producing metabolites which transduce inflammatory signaling by means of the activation of protein kinases such as PKC and MAPK. This in turn activates NF- $\kappa$ B that is responsible for the transcription of many proinflammatory genes [241,242].

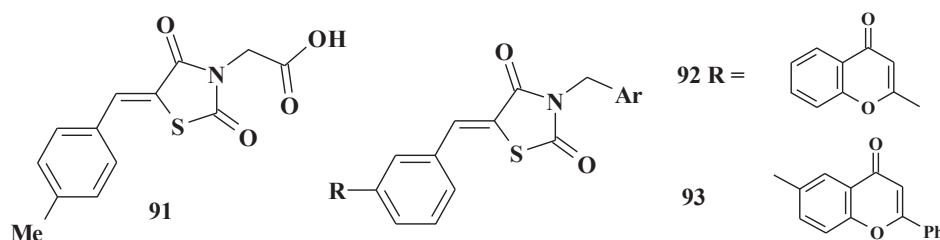
Antidiabetic activity of target compounds is often related to the inhibition of *PTP 1B* (protein tyrosine phosphatase 1B), which is an intracellular *PTP* and a key negative regulator of the insulin signaling pathway as well as to *LMW-PTP* (low molecular weight protein tyrosine phosphatase). This possible mode of action may be regarded as an attractive approach to the design of new therapeutic agents for the treatment of type 2 diabetes mellitus, obesity and, therefore, of the states associated with complex metabolic disorders known as metabolic syndrome. 4-(5-Arylidene-2,4-dioxothiazolidin-3-yl)methylbenzoic acids **101** were indicated as inhibitors of both *PTP 1B* and *LMW-PTP* (Scheme 48). One of the directions in this study is the example of utilization of phosphotyrosine-mimetics to identify effective low molecular weight nonphosphorus inhibitors of *PTPs* (*p*-methylbenzoic acid residue at N-3 position of the 5-arylidene-2,4-thiazolidinedione scaffold can act as a monoanionic *pTyr*-mimetic group replicating the interactions of *pTyr* with the catalytic site of the enzyme) [243]. In this study the authors also noted the importance of the 5-arylidene fragment. Alkylated/acylated phenolic groups and methoxy groups are desirable for the inhibitory effect.

5-Substituted 2-cyanimino-4-thiazolidinone (**FPFS-410**) – a compound related to pioglitazone (PPAR-agonist) also possesses antidiabetic activity. *In vivo* data revealed the ability to reduce blood glucose and triglycerides levels and reduce the obesity [244].

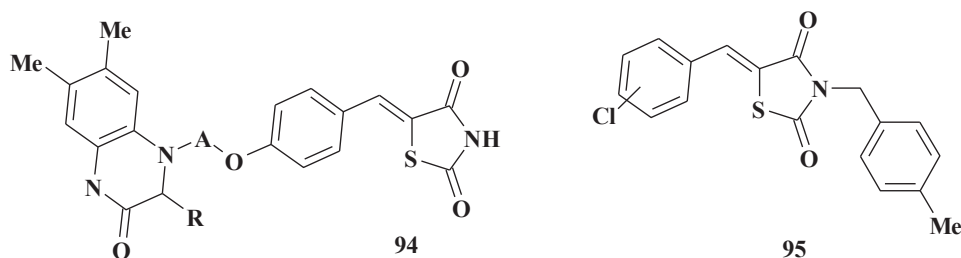
Screening study allowed identifying and confirming the activity



Scheme 44. Structures of known glitazones.



Scheme 45. 5-Ene-2,4-thiazolidinediones with antihyperglycemic activity.



Scheme 46. 5-Ene-2,4-thiazolidinones based hypolipidemic agents.

of 5-arylidene derivatives as inhibitors of *glycogen synthase kinase-3* (GSK-3) which, in turn, has been emerging as a key therapeutic target not only for type 2 diabetes, but also for Alzheimer's disease, cancer and chronic inflammation [245].

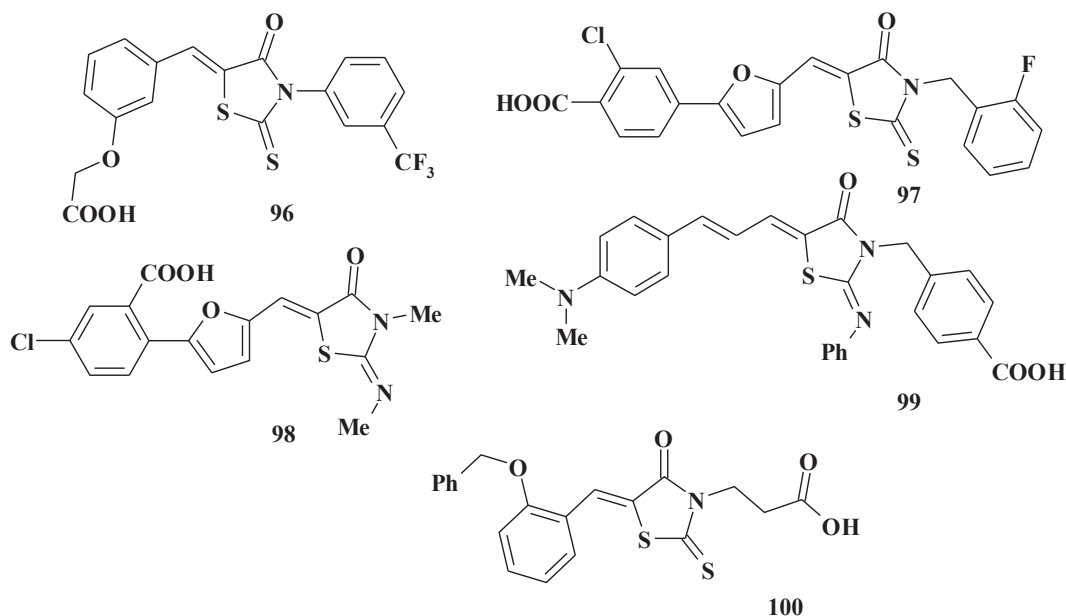
Simple 5-benzylidene-1,3-thiazolidine-2,4-dione derivatives **102** were presented as a new class of  $\alpha$ -glucosidase inhibitors [246] (Scheme 49).  $\alpha$ -Glucosidases ( $\alpha$ -D-glucosideglucohydrolases) are membrane bound exo-acting enzymes responsible for catalyzing the final step in the digestive process of carbohydrate metabolism.  $\alpha$ -Glucosidases are the enzymes that hydrolyze O- and S-glycosyl residues and are involved in the biosynthesis and processing of oligosaccharide chains of N-linked glycoproteins in the endoplasmic reticulum [247].

5-Benzylidenethiazolidine-2,4-diones carrying 2,3-dihydrobenzo[1,4]dioxine fragment **103** were proved to be *glycogen phosphorylase* inhibitors (Scheme 49) (*glycogen phosphorylase* is a key enzyme in the regulation of blood sugar level and it catalyzes the formation of glucose-1-phosphate from glycogen) [248] that may be relevant to the control of blood glucose concentrations in type 2 diabetes [249].

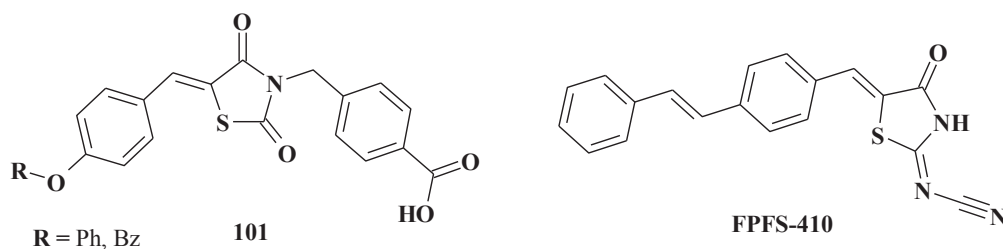
### 3.4. Anticancer agents

Search for new anticancer agents is the most dynamically developing area of medicinal chemistry. A lot of papers and patents are devoted to the search for efficient anticancer agents among 4-thiazolidinones, including 5-ene derivatives (selected row of patents see) [5(ESI),250]. Research in this area could be divided into the next groups:

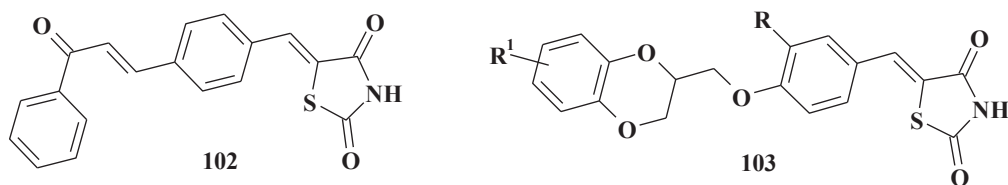
- i) *in vitro* screening of highly active/selective hit-compounds for further optimization, mainly with unknown mode of action (including the international programs, mainly Developmental Therapeutics Program, NCI, NIH - <https://dtp.cancer.gov>);
- ii) design of the high-affinity ligands to the "validated" anticancer biotargets;
- iii) creation of the hybrid molecules that combine several pharmacologically attractive scaffolds [158,159,251,252];
- iv) search for antitumor agents among the compounds with known biological activity (anti-inflammatory, antidiabetic, anti- or prooxidant etc.).



Scheme 47. 5-Ene-4-thiazolidinones with PPAR $\alpha/\gamma$  agonistic activity.



Scheme 48. 5-Ene-4-thiazolidinones with antidiabetic activity.



Scheme 49. Structures of  $\alpha$ -glucosidase and glycogen phosphorylase inhibitors.

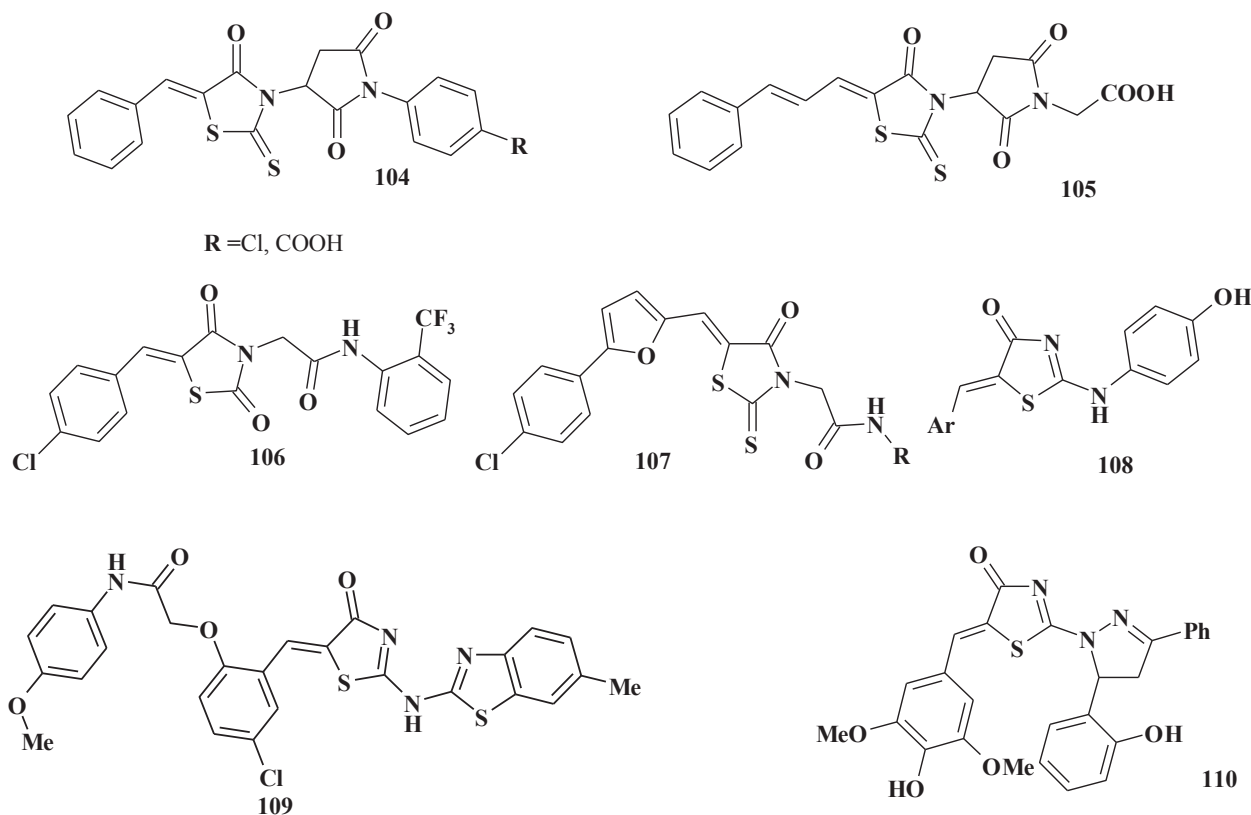
4-Thiazolidinones are known to possess good activity against different types of cancer including relatively simple 5-ene derivatives as well as complex or hybrids/conjugates bearing non-fused 5-ene-4-thiazolidinone fragment. Mentioned compounds don't belong to any "classic" anticancer agent types [8,26,27,94,253–256].

Despite the diversity of 5-ene-4-thiazolidinones, the search for antileukemic agents is one of the most promising directions. It was found the tendency of the maximum sensitivity of leukemia cell lines to various subtypes of thiazolidinones [8,25–27,34,35,66,94,100,138,142,143,162,257–260]. The crucial role of the C5-(ylid)ene fragment is also confirmed and complication of ene-fragment is considered as a benefit. But anti-leukemic effects of such compounds have been less documented in comparison with all other cancer types [261].

Among 4-thiazolidinone-3-carboxylic acids derivatives, amides

**104–107** (Scheme 50) with anticancer activity were identified including samples possessing strong antileukemic activity (**107**). The SAR study revealed that anticancer activity has significantly decreased or disappeared after transformation into related isosteric compounds (replacement of C5 arylidene moiety by the C5-carboxymethylidene or 5-carboxymethyl fragments) or in case of compounds based on the related heterocyclic cores (e.g. 2,4-imidazolidinedione) [26,94,253]. Moreover, novel 4-thiazolidinone-3-carboxylic acid amides **107** bearing furan moiety exhibited significant cytotoxicity and induction of apoptosis in human leukemia cells [259].

Among 5-arylidene-2-arylamino(imino)-4-thiazolidinones **108** a set of active compounds with micromolar IC<sub>50</sub> levels has been detected (log GI<sub>50</sub> ~ -5.77) [143]. Based on the obtained results the compounds with bulky C5-ene fragment and benzothiazole core were designed: compound **109** (pGI<sub>50</sub> = 4.97) selectively inhibited



**Scheme 50.** Structures of 5-ene-4-thiazolidinones with anticancer activity.

growth of the HOP-92 cell lines (CNS cancer,  $pGI_{50} = 6.34$ ) [138]. Study of the anticancer activity of 4-thiazolidinones with pyrazoline moiety in the C2 position of the main core has revealed high anticancer potential of the mentioned compounds **110** (Scheme 50). SAR study confirmed the dependence of anticancer activity from the structure of C5 fragment [142]. The isomeric 4-amino thiazolidinones possessed much less activity levels [25].

Thiazolidinone-isatin conjugates are good examples of polycyclic compounds with high anticancer potential and their design illustrates the molecular hybridization approach when two “pharmacophores” are combined into a single molecule [262]. For instance, **111** possessed micromolar activity level and also selectively inhibited the leukemia cell lines [27]. Further structure optimization led to increasing of the anticancer activity which was reflected in the design of thiazolidinone-isatin-pyrazole hybrids **112**, **113** [34,35] (Scheme 51). Similar isatin-pyrazoline conjugates (without thiazolidinone core) didn't show the anticancer activity.

Another example of anticancer isatin-thiazolidinone hybrids are compounds **114** [263] and **115** [264] (Schemes 51 and 52). The latter are the result of the structure optimization of sunitinib (SU11248, Sutent TM; Pfizer Inc) which is currently used in the clinics as a multi-targeting *tyrosine kinase* inhibitor with anti-angiogenic activity [265,266]. The same approach of molecular hybridization was used in the design of thiazolidinone-2,4-diones **116** bearing  $\alpha$ -bromoacryloylamido moiety [267,268].

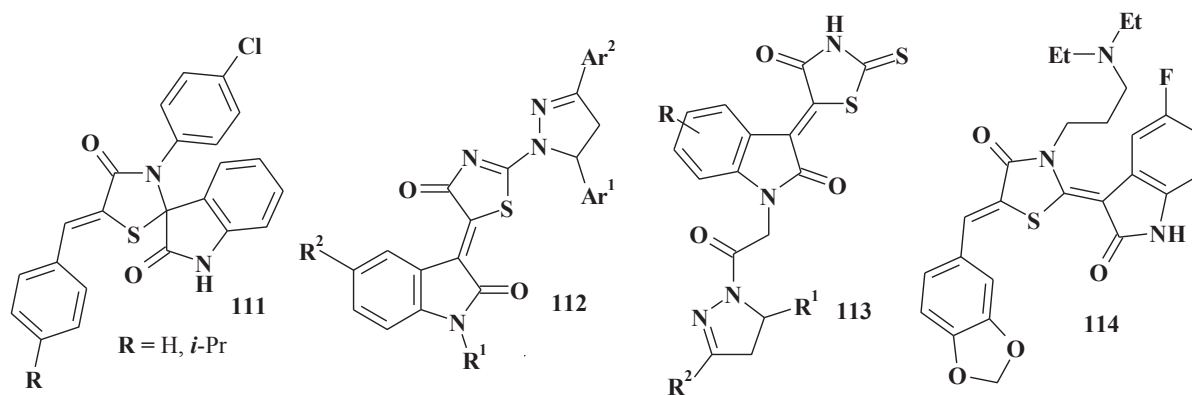
Compound **MKT077** is known anticancer agent [269] (Scheme 53) with apoptosis related mechanism of action and is an illustrative example of above mentioned compounds, though, its study has been proceeding till now. Thus, it is shown that it acts through differential interaction with the *Hsp70* (*Heat shock protein 70 kDa*) allosteric states and reactivation of *p53* function. **MKT-077** therefore can be treated as an “allosteric drug” [270–273].

One more example of the hybrid approach in anticancer agents design is the combination of the natural compound, e.g. oleanane scaffold, with thiazolidinone core (Scheme 54). Among oleanane-thiazolidinone hybrids 3-(2,4-thiazolidinedione-5-ylidene)-carboxyimino]olean-12-en-28-oic acid methyl ester (**117**) was identified as the most active substance ( $pGI_{50} = 5.57$ ,  $pTGI = 5.13$  and  $pLC_{50} = 4.64$  NCI NIH protocol) with low toxicity and moderate activity level in *in vivo* Hollow Fiber Assay [162]. Another example of this approach is 5-arylidene-2,4-thiazolidinedione bearing cholesterol fragment **118**. Moreover, the level of activity and selectivity of antimetabolic effects depends on the substituents in the C5 position of thiazolidinone core [161]. The maximum effect such compounds exhibited towards HeLa cancer cells line.

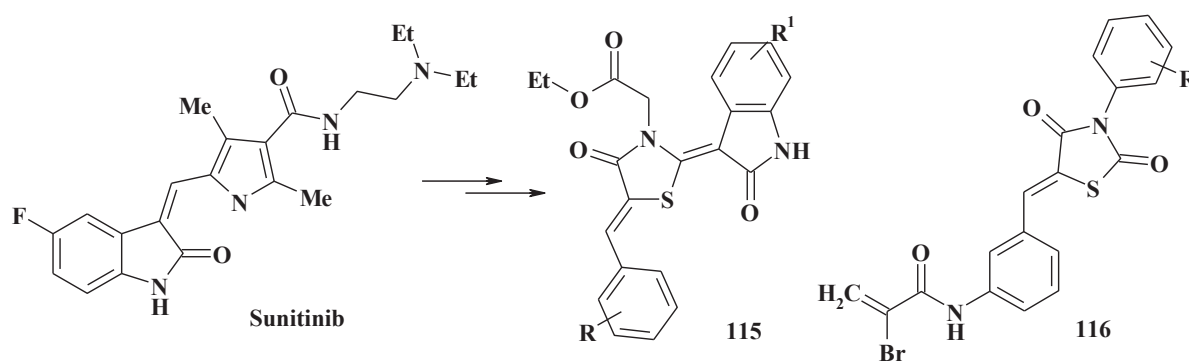
Promising active molecules based on the combination of thiazolidinone and chromene cores **119** were also found [160] (Scheme 55).

Once again it should be emphasized that for majority of mentioned compounds the tendency towards maximum sensitivity of leukemia and lung cancer cell lines is shown. This, most probably, may be a platform for the effective anti-leukemic agents design. For example, 5-isopropylidene-3-ethylrhodanine and 5-benzylidene-3-ethylrhodanine demonstrated cytotoxicity towards leukemic cell line CEM by inducing apoptosis [38,274]. Besides this, the modification of known drugs, for example sorafenib, with 5-ene-4-thiazolidinone fragments **120** is reported [275,276] (Scheme 56).

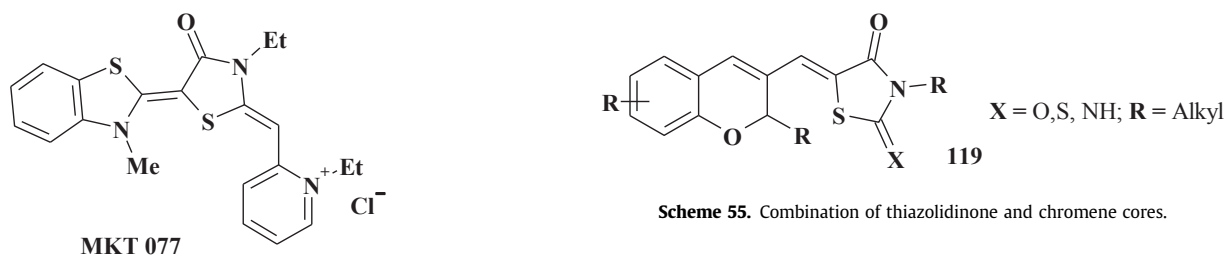
Whereas, a lot of potential biotargets for new anticancer agents design are known at present, there have been almost no attempts to systematize the 4-thiazolidinones as anticancer agents in the review papers. For example, three aspects of the PPARs-independent antitumor activities of thiazolidinones had been outlined [10]: i) inhibition of *Bcl-2/Bcl-x* function, ii) proteasomal degradation of



**Scheme 51.** Thiazolidinone-isatin conjugates with anticancer activity.



**Scheme 52.** 4-Thiazolidinones hybrids as anticancer agents.



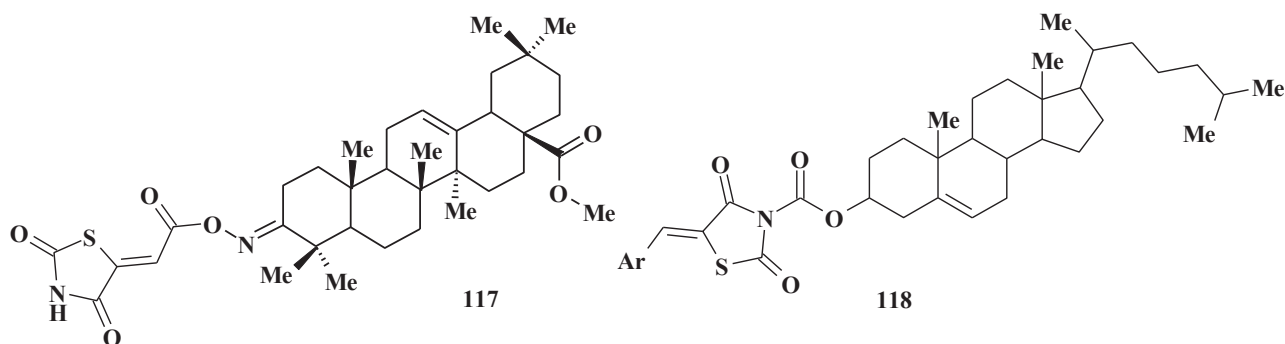
**Scheme 53.** Structure of MKT 077.

**Scheme 55.** Combination of thiazolidinone and chromene cores.

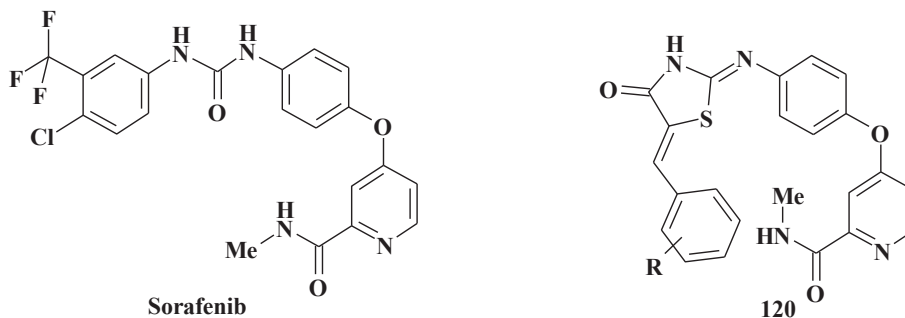
target proteins, iii) transcriptional repression of *AR* through Sp1 degradation [277]. Though, the latter definitely does not represent

the whole spectrum of experimental data and is not enough for the design of novel hit- and lead-compounds.

Taking into account the great number of papers, we tried to outline the most referred biotargets and their ligands among 5-ene-4-thiazolidinones. It should be noted that the majority of



**Scheme 54.** Combination of natural compounds and 5-ene-4-thiazolidinones fragments.



**Scheme 56.** Modification of known drug with 5-ene-4-thiazolidinone fragment.

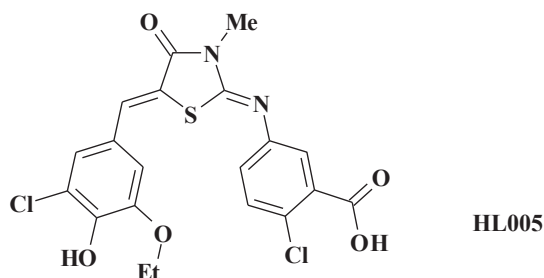
high-affinity ligands belong to 4-thiazolidinone-3-carboxylic acids, 5-benzylidenerhodanines, 2-amino(imino)derivatives and 2,3-disubstituted-4-thiazolidinones.

Based on the established role of PPARs in the cancer and inflammation progress [219,278–280] considerable part of investigations is dedicated to the study of glitazones and related derivatives as possible anticancer agents. However, 5-ene analogs as synthetic precursors of glitazones that do not contain exocyclic double bond in the C5 position possess less expressed affinity to PPARs as their agonists.

PPAR $\gamma$  antagonists in turn represent a new drug class that holds promise as a broadly applicable therapeutic approach for cancer treatment [229,281]. Among them 5-ene derivatives occupy their deserved place. For instance, the novel 3-thiazolidine-modified benzoic acid derivative **HL005** (Scheme 57) being a potent PPAR $\gamma$ -specific antagonist inhibits the proliferation of the MCF-7 cell line at the concentration-dependent manner, induces cell cycle arrest at the G2/M phase and interferes with cell adhesion [282].

PPARs independent anticancer effects of troglitazone are mediated mainly via the repression of *cyclin D1* (MCF-7 breast cancer cells) by facilitating proteasome-facilitated proteolysis [283] and partial depletion of intracellular Ca<sup>2+</sup> stores that leads to inhibition of translation initiation [284]. The troglitazone structure modification led to the **STG28** identification – the first small-molecule agent mediating the proteasomal degradation of *cyclin D1* with high specificity (exposure to STG28 did not cause any appreciable change in the expression levels of a series of other cyclins and CDK-dependent kinases) [283] (Scheme 58).

Following the structure optimization and screening data it was shown that the 5-arylidenerhodanines **121** are equipotent to troglitazone in Ca<sup>2+</sup>-releasing activity, induction of eIF2 $\alpha$  phosphorylation and more potent in inhibiting cancer cells proliferation [285]. Further modification allowed to state that a series of 5-benzylidene-2,4-thiazolidinediones and -thiones inhibited cell growth at low micromolar concentrations via the inhibition of translation initiation which involves partial depletion of



**Scheme 57.** Structure of HL005 – PPAR $\gamma$ -specific antagonist.

intracellular Ca<sup>2+</sup> stores and strong phosphorylation of eIF2 $\alpha$ .

Structurally similar benzylidenerhodanines **122** showed high inhibition of protein tyrosine phosphatase PRL-3 (IC<sub>50</sub> = 0.9  $\mu$ M), which is one of the probable prognostic markers of metastatic cells [286].

Among 5-ene-rhodanines **123** was identified as a promising and selective inhibitor of enzymes of dual-specificity phosphatases group – phosphatases JSP-1 (JNK-stimulating phosphatase-1). Mentioned compounds are as well perspective agents that can be explored in the treatment of the inflammatory disorders [140] (Scheme 59).

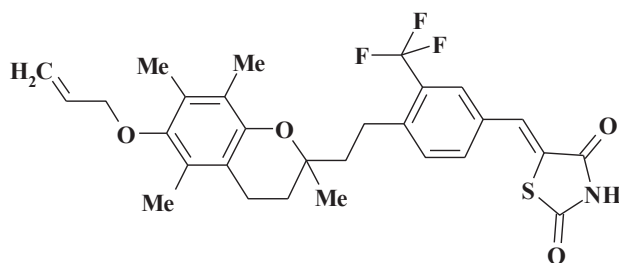
Necrostatin-7 (**Nec-7**) (Scheme 60) and related heterocycles belong to new class of “small molecules” – inhibitors of necroptosis that is regulated caspase-independent pathway of the cell death, morphological features of which are close to necrosis. This may be used in FADD-changed variant of the treatment of JurkatT cancer cells under the use of TNF $\alpha$  [287,288].

On the other hand, derivatives of hydantoin-5-acetic acid are non-hydroxamate inhibitors of TNF $\alpha$  converting enzyme [289] that allows to treat them as promising anti-inflammatory agents and gives the prospects to establish anticancer potential of the given class of compounds. Moreover, the ability of hydantoincarboxylic acids, especially with the thiazole fragments, to inhibit activity of *Ras farnesyl transferase* (Ftase) was proved [290]. *Ras* proteins play an essential role in the processes of cell growth and differentiation and need post translational modification including farnesylation catalyzed by *Ras farnesyl transferase*. That is the reason why *Ras-Ftase* inhibitors are considered as potential anticancer agents [291–293]. Structural analogs of the given substances are the ligands for neuro-immunophilin FK506-binding protein (FKBP) [294].

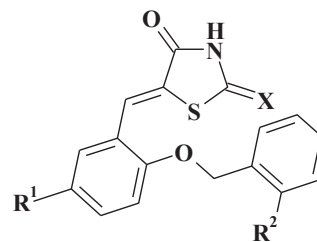
5-Substituted rhodanine-3-carboxylic acids **124** (Scheme 61) are the inhibitors of protein-protein interaction of antiapoptotic proteins of the *Bcl-2* and *Bax* family and their binding to the appropriate receptor domains [257,295–299].

Apart from the directions shown above, 5-aryl(hetaryl)idene-thiazolidine-2,4-diones **125**, **126** (Scheme 62) were identified as potent and selective insulin-like growth factor-1 receptor (IGF-1R) inhibitors [230].

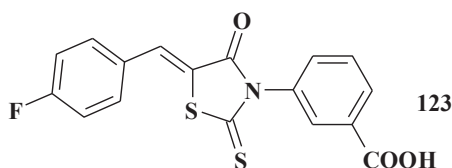
IGF-1R is a growth factor receptor of tyrosine kinase family, acting as a critical mediator of cell proliferation and survival. Although, being highly related to insulin receptor, it plays a different role in organism development, being responsible for normal growth and development as opposed to glucose homeostasis. Epidemiological studies indicate that the IGF-1R is overexpressed in human cancer and is primarily responsible for tumor genesis. Signaling through IGF-1R includes the activation of PI3K and Raf pathways [300]. Inhibition of both these pathways makes IGF-1R kinase a promising target for cancer therapy. Moreover, series of 3,5-disubstituted thiazolidine-2,4-dione analogs [301] and



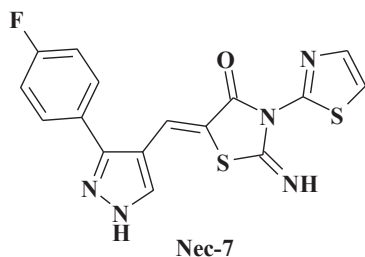
STG28



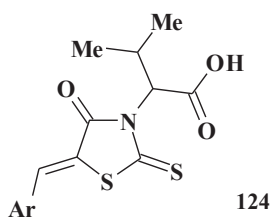
121 Inhibitors of translation initiation

(R<sup>1</sup> = Hal, *t*-Bu, Me, NO<sub>2</sub>; X = S, O; R<sup>2</sup> = H)122 PRL-3 inhibitors (R<sup>1</sup> = R<sup>2</sup> = Br, X = S)**Scheme 58.** Structure of 5-ene-thiazolidinones with anticancer activity derived from troglitazone structure modification.

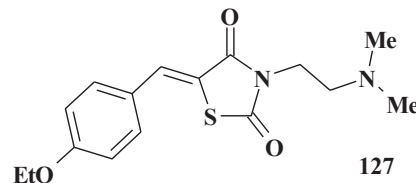
123

**Scheme 59.** 3-[5-(4-Fluorobenzylidene)-rhodanin-3-yl]-benzoic acid - *JSP-1* inhibitor.

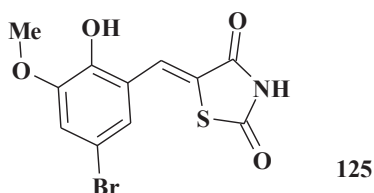
Nec-7

**Scheme 60.** 5-[3-(4-Fluorophenyl)-1*H*-pyrazol-4-ylmethylene]-2-imino-3-(thiazolyl-2)-4-thiazolidinone – necroptosis inhibitor.

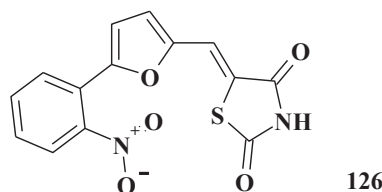
124

**Scheme 61.** 5-Arylidenerhodanine-3-carboxylic acids - *Bcl-2* inhibitor.

127

**Scheme 63.** Structure of signal-regulated kinases inhibitor.

125



126

**Scheme 62.** Structure of insulin-like growth factor-1 receptor inhibitors.

3-(2-aminoethyl)-5-(3-phenylpropylidene)-thiazolidine-2,4-dione [302] were shown to be potential anticancer agents via the inhibition of the *Raf/MEK/ERK* and *PI3K/Akt* signaling cascades.

The inhibitors of extracellular *signal-regulated kinases-1 and 2* (*ERK1/2*) – (e.g. (*Z*)-3-(2-aminoethyl)-5-(4-ethoxybenzylidene)thiazolidine-2,4-dione **127**) are the examples of compounds with greater selectivity for inhibiting the proliferation of melanoma cells [303] (Scheme 63).

*Polo-like kinase 1* (*Plk1*) is a key regulator of mitotic progression and cell division. In eukaryotes it acts in concert with *cyclin-dependent kinase 1 – cyclin B1* and *Aurora kinases* to conduct a wide range of critical cell cycle events. Because *Plk1* has been preclinically validated as a cancer target, small-molecule inhibitors of *Plk1* have become attractive candidates for anticancer drugs development [304]. Thiazolidinone **128** (Scheme 64) selectively inhibits human *Plk1* (IC<sub>50</sub> 19 nM) and various human and mouse tumor cell lines (IC<sub>50</sub> 0.2–1.3 μM) and cause a prometaphase-like mitotic arrest [305].

Simple 5-ene-rhodanines (**129**, **130**) (Scheme 65) may also be considered as “*Myc*-*Max* compounds” that inhibit or reverse the association between *c-Myc* and its obligated *HLH-LZ* heterodimerization partner *Max* [306–308].

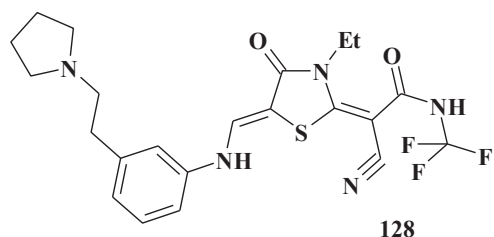


Among 5-ene derivatives of 2-iminothiazolidine, 2,4-thiazolidinedione and rhodanine the *estrogen-related receptor- $\alpha$*  (*ERR- $\alpha$* ) modulators were identified. They can be useful for the prophylaxis or treatment of *ERR- $\alpha$*  associated diseases such as breast cancer [309,310].

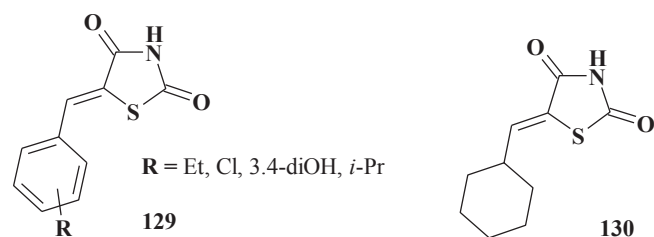
Following the modification of 5-(3-trifluoromethylbenzylidene)thiazolidine-2,4-dione (high selectivity *Pim-1* inhibitor) a series of substituted thiazolidine-2,4-dione derivatives were identified as highly active and selective *Pim-1* and *Pim-2* inhibitors (nanomolar values of  $IC_{50}$  for *Pim-1* and  $\sim 2.0 \mu M$  for *Pim-2*) [54]. *Pim-1* and *Pim-2* are serine/threonine protein kinases frequently overexpressed in prostate cancer and certain forms of leukemia and lymphoma [311]; *Pim* can phosphorylate the proapoptotic protein BAD (the Bcl-2-associated death promoter) leading to sequestration of 14-3-3 proteins and inhibits the apoptosis [312,313].

As it was already mentioned, 5-ylidene-2-amino(imino)-4-thiazolidinones **131** (Scheme 66) comprise one of the most investigated thiazolidinone subtype as compounds with anticancer activity [138,142,143,314,315]. Among them the derivative **MMPT** was identified as a hit-compound being able to effectively inhibit the growth of some lung cancer cell lines (H460 and H460/TaxR) and at the same time do not influence normal fibroblasts in a dose response manner [151,316,317]. Study of the structure-activity relationship in a group of 372 compounds revealed some structural peculiarities: i) the nitrogen atom of thiazolidine core has to be unsubstituted; ii) dimethylaminobenzylidene fragment is the best in the C5 position; iii) 2-phenylamino moiety may contain substituents in different positions of aromatic ring [151].

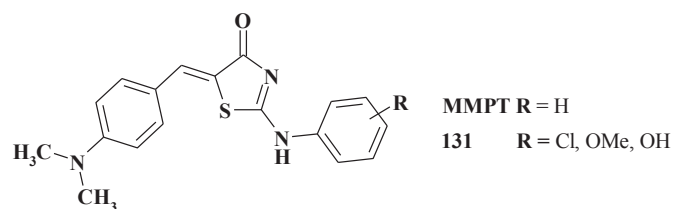
5-[(4-Methylphenyl)methylene]-2-(phenylamino)-4(5*H*)-thiazolone (**MMPT**) and 5-(2,4-dihydroxybenzylidene)-2-(phenylimino)-1,3-thiazolidine (**DBPT**) are effective in the treatment of multidrug-resistant (MDR) cancer. Multidrug-resistance is a phenotype of cross-resistance to multiple drugs with diverse chemical structures. One of the well-documented MDR mechanisms is the overexpression of the MDR-1 gene that encodes the transmembrane, ATP-dependent drug efflux transporter *P-glycoprotein* (*P-gp*) in response to chemotherapy [318–320]. *P-gp* prevents the intracellular accumulation of many cancer drugs by increasing their refflux out of cancer cells as well as through hepatic, renal, or intestinal clearance pathways [319]. Attempts to coadminister *P-gp* modulators or inhibitors to increase cellular availability by blocking the actions of *P-gp* have met with limited success [321–323]. Therefore, a more promising approach lies in the design and discovery of novel compounds that are not substrates of *P-gp* and are effective against drug-resistant cancer while at the same time exhibit minimal toxicity to normal cellular functions. **MMPT** inhibited the growth of human non-small-cell lung cancer and colon cancer cells (drug-sensitive (H460) and drug-resistant (H460/TaxR cell lines) independently of *P-glycoprotein* and p53 status [151,316]. Besides this, it selectively killed drug resistant cancer cells and induced apoptosis [317]. Among 5-ylidene-2-arylamino-4-thiazolidinone derivatives effective



Scheme 64. Structure of Polo-like kinase 1 inhibitor.



Scheme 65. Simple 5-ene-rhodanines as "Myc-Max compounds".



Scheme 66. Structure of simple 5-ylidene-2-amino(imino)-4-thiazolidinones with significant anticancer activity.

growth inhibitors of HT29 cell line (with a high COX-2 expression) were identified [324].

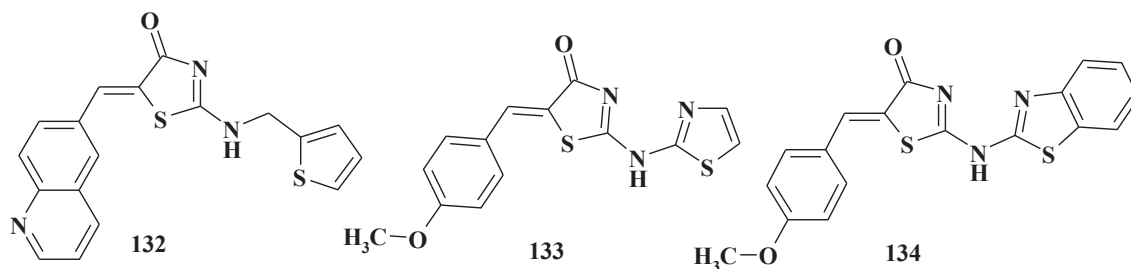
Among mentioned 4-thiazolidinone derivatives efficient *CDK1* **132** [325], *CDK1/cyclinB* inhibitors [326–328] and *SHP-2* inhibitors **133** and **134** (Scheme 67) (*SHP-2* is a non receptor protein tyrosine phosphatase that mediates cell signaling by growth factors and cytokines acting via the *RAS/MAP kinase* pathway) [329,330] were discovered. Benzo[d]thiazole derivatives turned out to be more potent than their thiazole analogs.

2-Substituted thiazolidinone and oxazolidinone derivatives were established as the inhibitors of *phosphatases* and anticancer agents [331]. Modifying the imidazolidine derivatives the new cell division cycle 7 kinase inhibitors were designed **135** and (*Z*)-2-(benzylamino)-5-(1*H*-pyrolo[2,3-*b*]pyridin-3-ylmethylene)-1,3-thiazol-4(5*H*)-one] was selected as a lead compound [332] (Scheme 68).

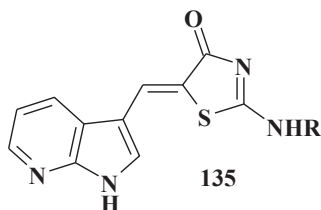
2-*N,N'*-Disubstituted diamines bearing 5-arylidene-4-thiazolidinone moiety **136** (Scheme 69) had shown nanomolar inhibition potency ( $IC_{50}$  40 nM) towards *tyrosine phosphorylation-regulated kinases 1A* [333]. This result prompted to explore the symmetric 1,2-diamino-linker grafted on N-3 position of two different 5-arylidenerhodanine platforms in order to modulate potential biological activity and led to the synthesis of unsymmetrical linked bis-5-arylidenerhodanine derivatives with anticancer effects [334].

One of the established modes of action of 4-thiazolidinones anticancer activity is their antagonistic activity towards  $\alpha_v\beta_3$  receptors. The value of inhibition of the  $\alpha_v\beta_3$  activity is proved by the establishing of the correlation between progression of factor's expression and cancer growth. Search for effective inhibitors was held based on the pharmacophore model and virtual screening of 600000 compounds following by further confirming of the activity *in vitro*. This allowed to select promising compounds including 4-azolidinones. 2-Substituted 4-thiazolidinone derivatives among selected ones appeared to be efficient *integrin*  $\alpha_v\beta_3$  antagonists **137** [335] (Scheme 70).

One of the aspects of anticancer effects realization of 4-azolidinone-3-alkanecarboxylic acids is the ability to influence the oxidative homeostasis of the cancer cells and the impact on the reactive oxygen species production. The modulating effect of the 5-



Scheme 67. Structures of CDK1 and SHP-2 inhibitors.



Scheme 68. Structure of cycle 7 kinase inhibitors.

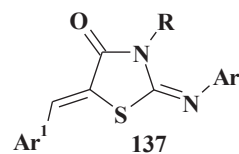
ene-rhodanines on the proliferation and apoptosis of the cancer cells was identified as well as the influence on metabolism of NO alone with antioxidant and immunomodulating actions [336]. In this context interesting is the combining anticancer activity with anti-inflammatory effects; with antioxidant and/or other types of activity in some of the compounds [337] that is important in the development of “classic triad”: “oxidative stress – inflammation – cancer”. Additionally, the pharmacological profile of 5-arylidene-4-thiazolidinones derivatives is related to free radicals scavenging activity [106,338,339].

Besides this, notes about prooxidant effect of thiazolidinones with anticancer activity are frequently found in the papers. It has been shown that the derivatives of 5-ylidene-2-imino-4-thiazolidinone increased levels of reactive oxygen species (ROS) (HT29 cells), moreover, the ROS increasing was blocked by the ascorbic acid addition [340]. 5-Benzilidene-3-ethylrhodanine treatment led to increased level of ROS production and DNA strand breaks suggesting activation of apoptosis for induction of the cell death (leukemic cell line, CEM) plus by inducing a block at S phase [274]. Cell exposure to the selected compound was associated with the production of ROS, and the induction of autophagy which could lead to cell death [341].

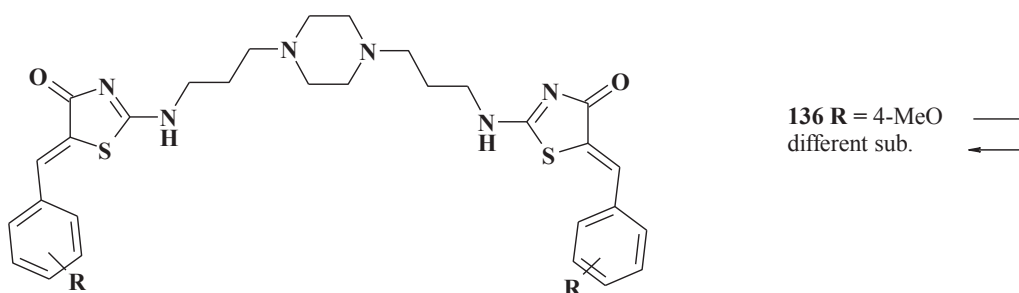
Recent observation has been made in favour of the alternative chemotherapeutic strategy against cancer that consists in increasing the production of reactive oxygen species [340,342].

Moreover, generation of ROS could activate the *NF-2E related factor 2/Kelch like ECH-associated protein 1 (Nrf2/Keap1)* pathway involved in protection of the cells against oxidative stress [343]. Activation of the *Nrf2/Keap1* pathway leads to the stabilization of *Nrf2* which translocates in nucleic db in ds to Maf protein. The complex, after binding to specific DNA sequence, defined as antioxidant response element localized in the promoter of *Nfr2/Maf* target genes, increases the transcription of genes involved in reactive species-mediated response such as *HemeOxygen-1 (HO-1)*, *NADH quinoneoxidase-1 (NQO1)* or glutamylcysteyl ligase. It could also indicate the indirect impact of the given class of compounds on the pro/antioxidant balance [156]. ROS play a key role in mitochondria mediated apoptosis. Mitochondria are the prime source of ROS which are byproducts of aerobic respiration [344–346]. High levels of ROS in mitochondria can result in free radical attack of membrane phospholipids and cause mitochondrial membrane depolarization. This is an irreversible step associated with the release of mitochondrial factors triggering caspase cascades [347,348].

On the other hand, immunoblotting analysis showed that 5-(4-hydroxy-3-dimethoxybenzylidene)-2-thioxo-4-thiazolidinone (RD-1) significantly elevated the Parkin and Miro 2 expression levels in acute MPTP treated mice and improved mitochondrial membrane potential and ATP synthesis in MPP + -treated Neuro-2a cells. Moreover, RD-1 attenuated impaired mitochondrial transport and vesicle release dysfunction has been evoked by MPP + cytotoxicity in cultured primary mesencephalic neurons. Taken together, the results indicate that improving the mitochondrial dysfunction may be a good choice to delay the



Scheme 70. General structure of integrin  $\alpha_v\beta_3$  antagonists.



Scheme 69. Structure of tyrosine phosphorylation-regulated kinases 1A inhibitors.

neurodegenerative progression commonly associated with parkinson diseases as well as cancer [349].

Among the proposed mechanisms for the antitumor effect of target compounds apoptosis induction, cell cycle arrest and differentiation have been extensively reported [38,66,252,274,277]. Anticancer effect of such compounds can be also achieved by blocking the cell cycle progression at the G2/M phases border (not affect the G1 to S phase transition) in reversible manner and by the induction of apoptosis [252,325]. FACS (fluorescence-activated cell sorting) analysis of 5-ylidene-rhodanine-3-carboxylic acids, which possessed strong antiproliferative activity against human leukemia cells, showed a remarkable accumulation of subploid cells, the sub G1 phase (G0/G1) followed by the decline of both G1 and G2/M phases. Moreover, the presented findings suggest that the observed growth inhibition could be due to apoptosis [259]. The related 5-ylidene thiazolidinones with heterocyclic fragments induced cell cycle arrest of leukemic cells at G2/M phase and induced cell death that resulted in increased level of SubG1 phase population, thereby affecting its proliferation and causing depolarization of mitochondrial membrane potential [260]. The similar results were found for 2-hetarylamino 4-thiazolidinones that induced cell accumulation at G2/M and in sub G0/G1 phases of the cell cycle. Furthermore, dissipation of mitochondria membrane potential was observed as well as red/ox changes in the treated cells (HT29 cell lines) [340]. Treatment of cancer cells with mentioned **MMPT** and **DBPT** led to a time-dependent accumulation of cells arrested in G2/M phase [316]. 5-Ene-4-thiazolidinones caused a prometaphase-like mitotic (G<sub>2</sub>–M) arrest (as the ATP-competitive inhibitors of Plk1) [305,350].

Despite the diversity of presented biotargets, the notes about thiazolidine derivatives being inducers of apoptosis in various cancer cells have become more frequent [351–357]. Above all, apoptosis-related mechanism is associated with the inhibition of Bcl-2/Bcl-x function. However, there has been described another feasibility of target compounds to affect diverse apoptotic signaling pathways, namely, induction of peroxisome proliferator-activated receptor-associated caspase-dependent [250,317,358] mitochondria-mediated apoptosis. 4-Thiazolidinones can decrease mitochondrial membrane potential which is one of the important mechanisms for the mitochondrial mediated apoptotic cell death [359] (an example of such compound is **MKT 077**) [269,271].

### 3.5. Anti-inflammatory agents

Progress in the anti-inflammatory agents search is reached via both high affinity ligand design and pharmacological screening of the compounds with unknown molecular mode of action. Anti-inflammatory activity of 4-thiazolidinones is associated, primarily, with their ability to inhibit isoforms of *cyclooxygenase* (COX) and *lipoygenase* (LOX). The most successful representative of anti-inflammatory agents on the base of 5-ene-4-thiazolidinones is darbufelone – (5-(3,5-ditertbutyl-4-hydroxybenzylidene)-thiazol-4-one [33,360,361]) (Scheme 71) that has attracted broad attention as dual inhibitor of cellular prostaglandin and leukotriene production via cyclooxygenase activity inhibition including inhibition of *prostaglandin endoperoxide synthase-1* (PGHS-1) and PGHS-2 [362].

Chemical structure of darbufelone has been considered as lead-compound for novel anti-inflammatory agents design till now. Optimization of the latter and application of the bioisostere concept allowed the elaboration of new bioactive compounds **138** (GS26) and **139** (GS28) (Scheme 71) with significant anti-inflammatory activity as well as anti-edematogenic and ulcerogenic activity *in vivo* [363]. Further studies of related compounds allowed identifying selective inhibitors of COX-2 as promising anti-

inflammatory agents with fewer side effects. Obtained data and SAR analysis resulted in identifying the most active compound **140** (Scheme 71) from the group of thiazolones and oxazolones with di-*tert*-butylphenol fragment. Compound **140** inhibited human recombinant COX-2 (IC<sub>50</sub> 1.7 μM) and inhibited the COX-2 activity in cell line J774A.1 (IC<sub>50</sub> 0.17 μM). This compound turned out to be inactive towards COX-1 at the concentration of 100 μM and did not inhibit the COX-1 in thrombocytes at 20 μM [360].

Among 5-ene-4-thiazolidinones **CT-8** (Scheme 72) was found to be potent inhibitor of *15-hydroxyprostaglandin dehydrogenase* (15-PGDH) [364]. 15-PGDH type I is NAD<sup>+</sup>-dependent (while Type II is NADP<sup>+</sup> preferred) cytosolic enzyme which catalyzes oxidation of prostaglandins to 15-ketoprostaglandins. Inhibition of this enzyme is related to prostaglandin E2 action and can lead not only to anti-inflammatory effects but, for instance, to reduce hair loss [365]. Structure-activity analysis indicated that the N-methylation of **CT-8** abolished the inhibitory activity. It was also established that the nature of the moiety linked to benzylidenethiazolidine-2,4-dione through another linkage plays an important role in its inhibitory activity [364]. Further modification led to the new related compound **141** identification (IC<sub>50</sub> = 0.031 μM) [366] (Scheme 72).

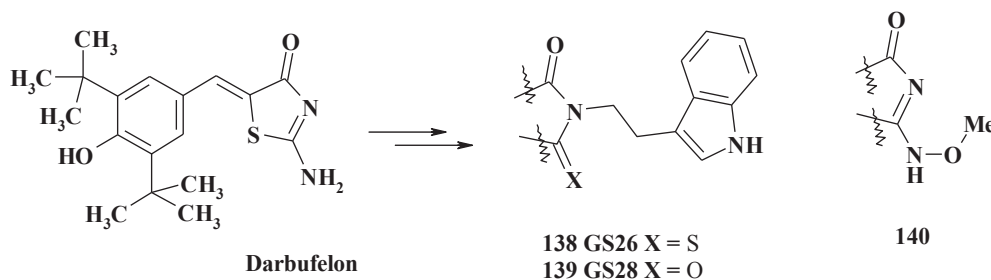
Another mechanism of anti-inflammatory activity has been the inhibition of *phosphodiesterase* (PDE4 and PDE2). *Phosphodiesterase* is responsible for the hydrolysis of secondary messenger cAMP, the level of which increases under inflammation processes. Besides this, *phosphodiesterase* inhibitors may be effective agents in asthma and obstructive lung diseases treatment. It has been established the ability of 5-arylidenerhodanines, including 3-substituted carboxylic acids [367] to inhibit above mentioned enzyme. Moreover, unlike other rhodanine derivatives, carboxylic derivatives selectively inhibit only *phosphodiesterase-4* that may be an argument for their study as probable agents for Parkinson's and Alzheimer's diseases.

The antineoplastic effect of 5-benzylidene-4-thiazolidinones with benzothiazole **142** and isothiazole **143** moieties (Scheme 73) on human chondrocytes culture was estimated when studying potent inhibitors of *metalloproteinase* (MMP). Given experimental model reproduces the mechanisms involved in osteoarthritis [240,368]. The compound **143** (Ar = 4-MeO-C<sub>6</sub>H<sub>4</sub>) showed MMP-13 inhibition activity at nanomolar concentration (IC<sub>50</sub> 0,036 μM).

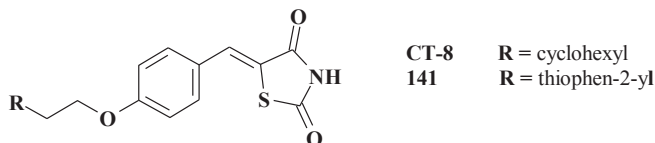
Moreover, among anti-inflammatory 5-ene-4-thiazolidinones a series of furan-2-ylmethylene-2,4-thiazolidinediones have been investigated as the *ATP-competitive PI3Ks inhibitors* **144** (Scheme 74) (IC<sub>50</sub> 0.2–0.9 μM). Class I *phosphoinositide 3-kinases* (PI3Ks), in particular PI3Kγ, have become attractive drug targets in inflammatory and autoimmune diseases treatment [369]. An acidic NH group in the thiazolidinedione core and a hydroxyl group in the furan-2-yl-phenyl part of the molecule play crucial roles in binding to PI3K and contribute to class IBPI3K selectivity. Besides the compound **145** inhibited PI3Kγ (IC<sub>50</sub> 33 nM) (but not PI3Kα, PI3Kβ) dependent pathways inside cells and in a murine peritonitis model, it produced a similar decrease in leukocyte infiltration.

The anti-inflammatory properties of 5-arylidene-2-phenylimino-4-thiazolidinones **146** (Scheme 75) are related to their ability to block the production or action of the degenerative factors induced by IL-1b [370] and possessing antidegenerative activity on human chondrocyte cultures.

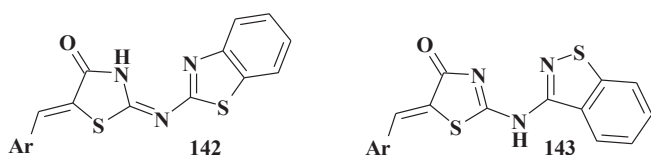
5-Arylidene-2,4-thiazolidinedione derivatives without substituent in the N3 position [371] as well as N3-substituted analogs **147** [372] (Scheme 76) possessed anti-inflammatory activity and related type of activities, such as analgesic activity and *in vitro* antioxidant activity or even antimicrobial [167]. The structural affinity to PPARγ agonists (*in silico* correlation studies and PPAR-competition binding assay) indicates the possibility of PPAR mediated mode of anti-inflammatory action [372].



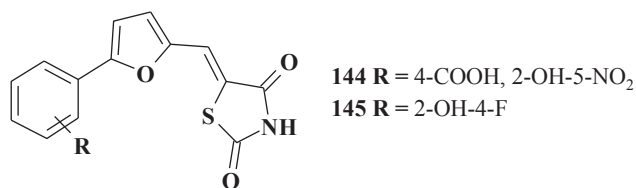
**Scheme 71.** Darbufelone structure and directions of the structure modification.



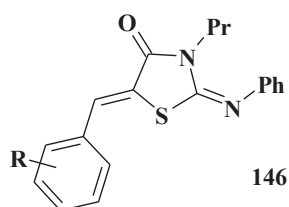
**Scheme 72.** Structures of 15-hydroxyprostaglandin dehydrogenase inhibitors.



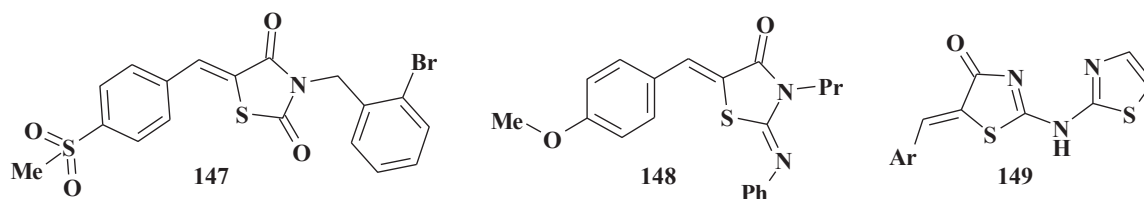
**Scheme 73.** Structures of 15-hydroxyprostaglandin dehydrogenase inhibitors.



**Scheme 74.** Structure of ATP-competitive PI3Ks inhibitors.



**Scheme 75.** 5-Arylidene-2-amino-4-thiazolidinones with anti-inflammatory activity.



**Scheme 76.** 5-Ene-4-thiazolidinones as active anti-inflammatory agents.

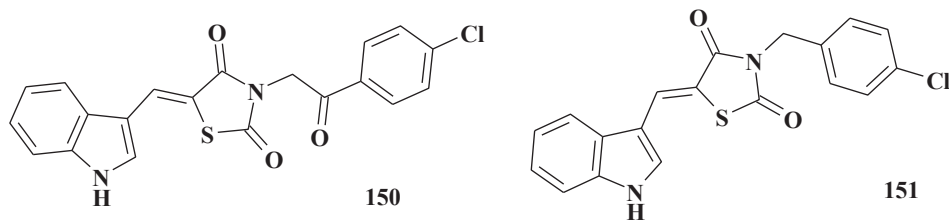
Similarly, 5-arylidene-2-imino-4-thiazolidinones **148** (Scheme 76) exhibited anti-inflammatory effect (carrageenan-induced paw edema model) causing the reduction of *PGE2* level together with insignificant *COX-2* inhibition when compared with celecoxib. It should be noted that 5-unsaturated thiazolidinones possess much less expressed effect or are inactive [373]. Applying procedures of virtual and highthroughput screening for 2-(thiazole-2-ylamino)-thiazol-4-ones study led to identification of compounds **149** (Scheme 76) with anti-inflammatory activity. In the *in vivo* cyclooxygenase and lipoxygenase inhibition assays as well as anti-inflammatory assay the compounds turned out to be promising agents for further studies in this field [374].

The row of hybrids **138** [363] (Scheme 71), **150** [375], **151** [376] (Scheme 77) based on indometacine, roziglitazone and darbufelone molecules was designed. The molecules possessed *in vivo* anti-inflammatory activity in air pouch and peritonitis models or carrageenan induced paw edema model and inhibited the *cyclooxygenase-1* and *2*.

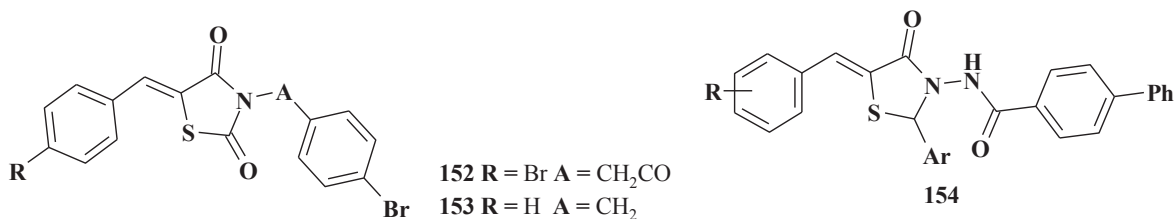
A number of related 3-substituted-5-arylidene-thiazolidine-2,4-diones (**152**, **153**) (Scheme 78) was screened for anti-inflammatory effects. Compounds exhibited significant levels of anti-inflammatory activity in the assay of induced edema in mouse paws [377].

Biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides **154** (Scheme 78) had also shown significant activity in carrageenan test [378].

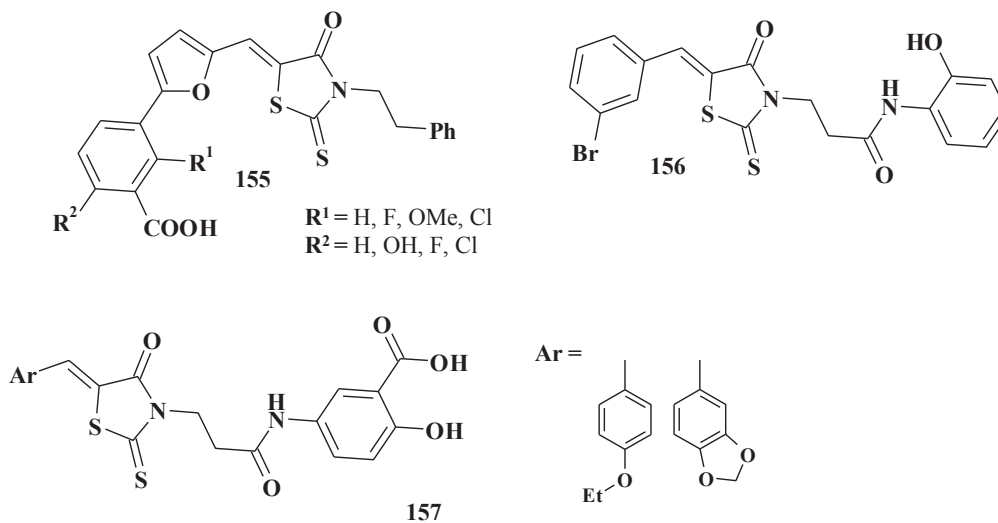
Application of polypharmacological approach and the advances in the pathophysiological role of various biotargets had resulted in the great interest in search for new anti-inflammatory agents. For example, it was established that *aldose reductase* (*AR*) is critically involved in inflammatory processes under both normoglycemic and diabetic conditions. This enzyme, which is overexpressed under various oxidative conditions, intervenes in multiple signaling pathways leading to inflammation and tissue degeneration. Accordingly, it was ascertained that *AR* inhibition prevents multiple inflammatory pathways [379–381] and, therefore, new more effective and safer *AR* inhibitors were designed not only as anti-diabetic (see above) but also anti-inflammatory agents [232]. 2-(Benzylamino)-5-((thiophen-2-yl)methylene)-thiazol-4-(5*H*)-one showed the highest anti-inflammatory response on PBMCs



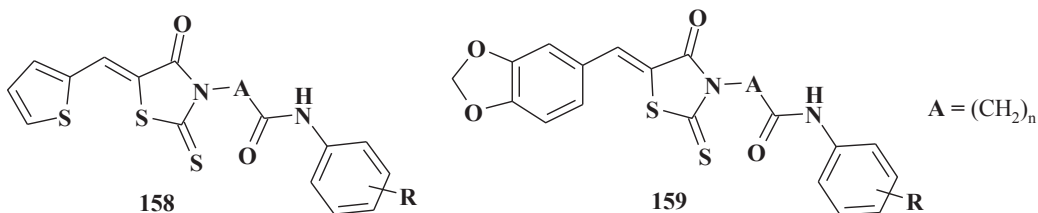
**Scheme 77.** 5-Ene-4-thiazolidinones designed based on indometacine modification.



**Scheme 78.** 5-Ene-4-thiazolidinones being active in induced edema paws model.



**Scheme 79.** 5-Ene-4-thiazolidinone derivatives with antiviral activity.



**Scheme 80.** Structures of inhibitors of HIV-1 integrase.

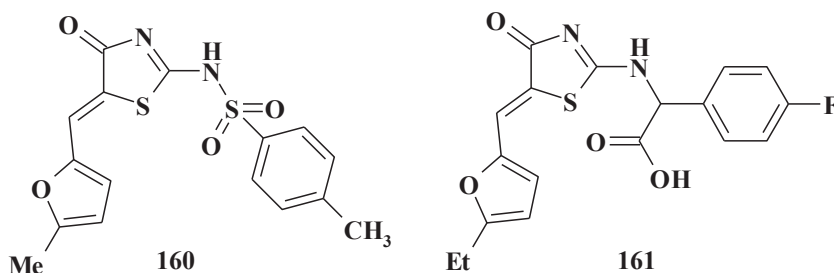
(peripheral blood mononuclear cells) exerted through the *NF-κB* inhibition. This and related compounds also had antioxidant activity and xanthine oxidase inhibitory potency [152].

### 3.6. Antiviral agents

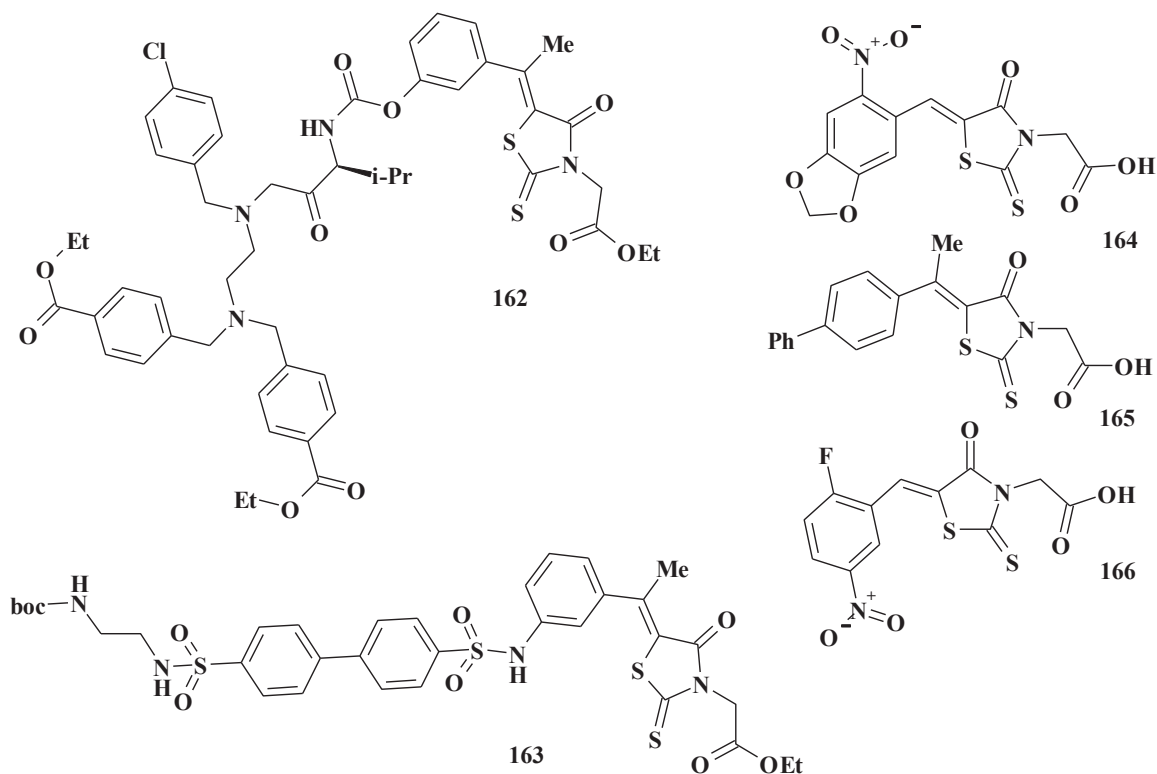
Investigation of antiviral activity of 4-thiazolidinone derivatives

has been carried out mainly in two directions: search for anti HIV agents and search for agents used in hepatitis C treatment. Tested compounds are small molecule inhibitors of validated targets such as HCV NS3 and 5' proteases [39,382], HIV RT [383] etc.

Recently, rhodanine derivatives, namely 2-aryl-5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidene)methyl)-furans **155** (Scheme 79) were reported to exhibit anti-HIV-1 activity [384].



Scheme 81. Structures of HCV NS5B polymerase inhibitors.



Scheme 82. Structures of HCV NS3 protease inhibitors.

Among 5-arylidenerhodanine derivatives the first small molecule able to inhibit HIV replication by targeting a cellular enzyme – the RNA helicases *DDX3* had been identified [385]. The precise combination of functional groups on the rhodanine scaffold was shown to be responsible for the *DDX3* inhibitory activity and selectivity of the hit compound **156** (FE15) (Scheme 79).

The 2-thioxo-4-thiazolidinones and salicylic acid containing compounds were the most potent *HIV-1* integrase inhibitors (*HIV-1* integrase catalyzes the integration of proviral DNA in to the host genome, an essential step for viral replication) among several compounds retrieved from a database of small-molecules. Compounds **157** (Scheme 79) inhibited strand transfer activities of *HIV-1* integrase with similar  $IC_{50}$  values (10–20  $\mu$ M). The replacement of either the rhodanine or salicylic acid fragments is found to reduce *HIV-1* integrase inhibitory potency [386].

Rhodanine-3-alkanecarboxylic acids, their amides and bicyclic analogs **158**, **159** (Scheme 80) represent a new class of inhibitors of *HIV-1* integrase as antiviral agents [387]. They were identified in

*silico* studies when modeling *HIV-1* integrase inhibitors as well as in *in vitro* investigations.

Employing HCV proteins as targets, directly acting antiviral agents were identified and collectively described as specifically targeted antiviral therapy for HCV (STAT-C) [388–390].

Most approaches to small molecule inhibitors search for Hepatitis C virus treatment have mainly focused upon inhibition of essential viral targets, such as the *NS3-4A* protease (analogous to *HIV* protease), *NS5B* polymerase, *NS3* helicase and *NS5A* [391,392]. A literature survey on *HCV NS5B* polymerase inhibitors clearly indicates that 4-thiazolidinones could inhibit this enzyme and might be promising candidates for the development of novel antiviral agents against HCV. Screening of in-house library allowed identifying derivative **160** (Scheme 81) as hit-compound ( $IC_{50}$  2.0  $\mu$ M) acting towards *NS5B*-polymerase of HCV. Based on the results of rational design and virtual screening (GOLD docking) novel 2-imino-4-thiazolidinone derivatives were synthesized and compound **161** (Scheme 81) with the  $IC_{50}$  (3.0  $\mu$ M) level close to that of

**160** was identified [393–395].

Further investigation led to N-substituted (aryl)alkylidene-rhodanines synthesis which inhibit *HCV NS3 protease* and also are good inhibitors of other serine proteases (*chymotrypsin* and *plasmin*). But, the selectivity of some compounds (**162**, **163**) (Scheme 82) with bulkier C5 fragments bearing hydrophobic functional groups as well as simple analogs (**164–166**) (Scheme 82) was increased by ten fold towards *HCV NS3 protease* respectively [39].

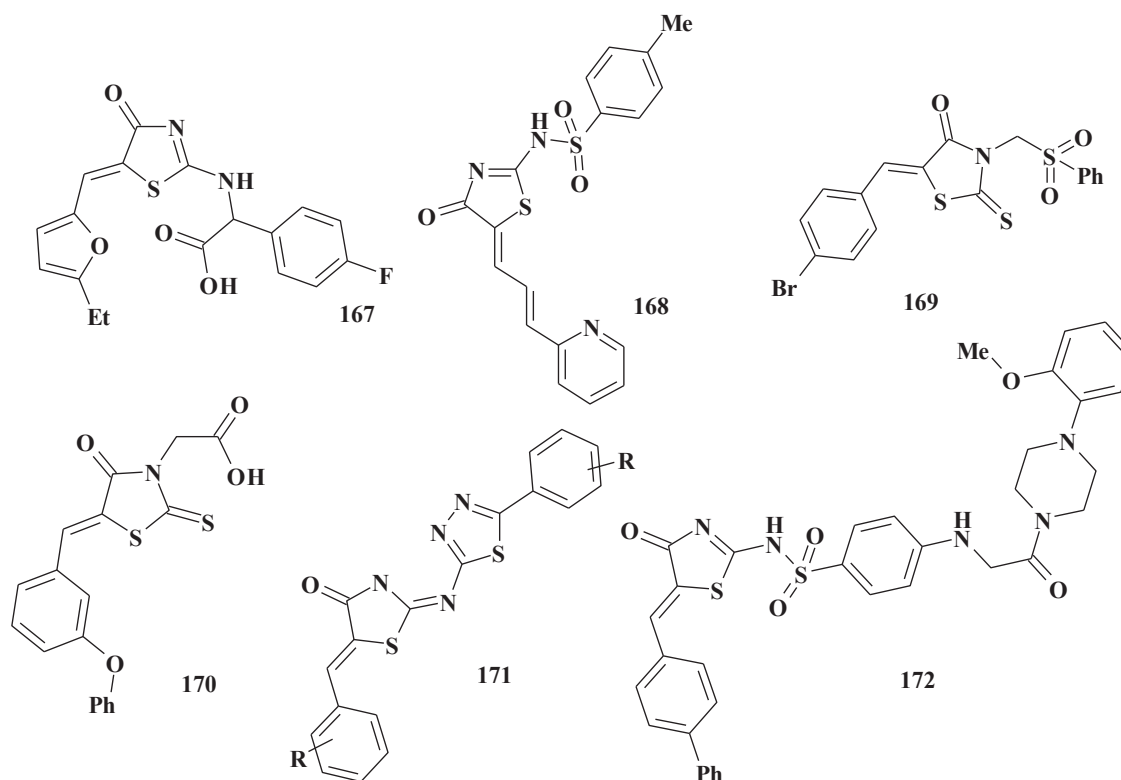
The 4-thiazolidinones from the groups of 2,3-diaryl-4-thiazolidinones [382,396]; 2-amino-5-arylidene-4-thiazolinones [397,398]; and 5-arylidene-3-substituted rhodanines [399,400] (**167–171**) (Scheme 83) were the initial structures for new inhibitors of *HCV NS5B polymerase* design, mainly 2-heteroaryl-imino-5-arylidene-4-thiazolidinones. In all cases the 5-ylidenethiazolidinones inhibited *NS5B* at lower  $IC_{50}$  values ranging between 19.8 and 64.9 mM. Moreover, the authors argued about the contribution of these (ar)ylidene groups in stabilizing the binding mode to *NS5B* active site.

Further investigation led to new lead-compound identification

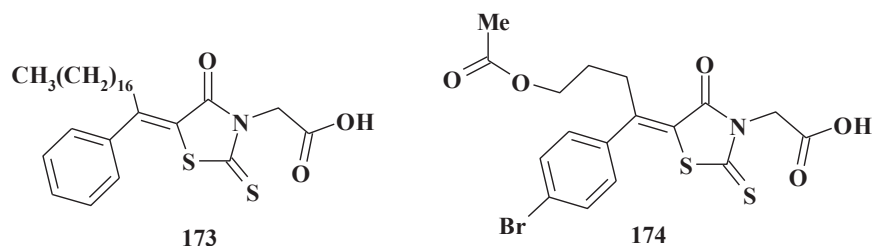
**172** [401]. Thus the derivatives of 5-ene-rhodanine-3-acetic acids **173**, **174** were active towards *HCV* inhibiting virus protease [402]. Additionally, it was established the ability of the derivatives of this compounds' class to inhibit human *serine proteases*. SAR analysis showed that substitution of arylidene moiety by the carboxy methylidene fragment led to insignificant loss of the activity (Scheme 84).

Based on the previous data [403] a series of 2(4)-pyrazolyl-4(2)-thiazolidinones **175**, **176** (Scheme 85) were synthesized and their antiviral activity against *Influenza viruses* (Type A and B), *Corona virus SARS*, *Tacaribe virus*, *Dengue virus*, *Rift Valley Fever virus*, *Respiratory Syncytial virus*, *Vaccinia virus* and *Venezuelan Equine Encephalitis virus* was tested *in vitro*.

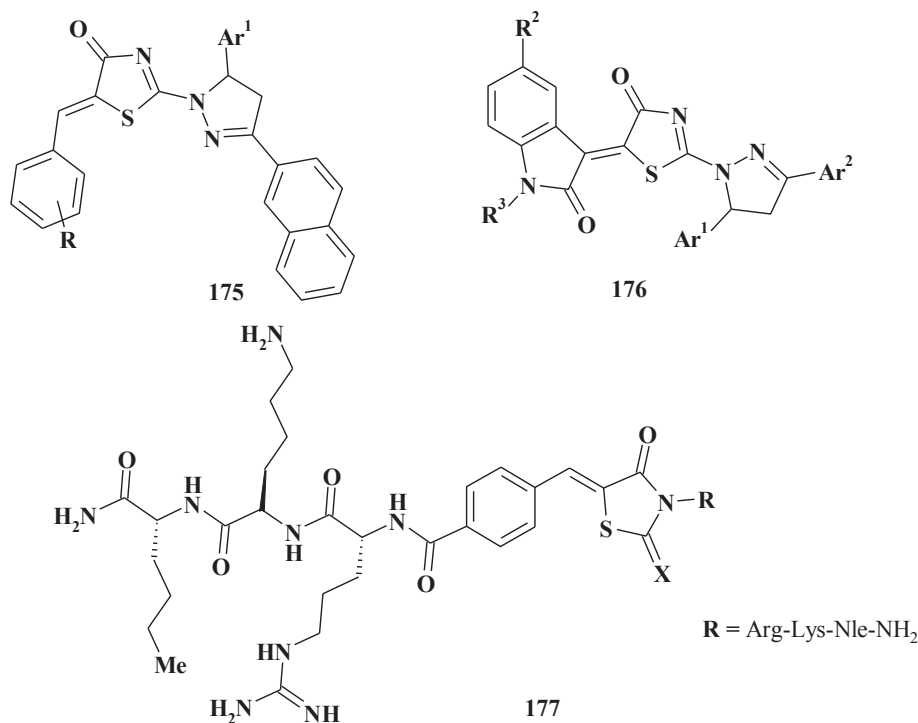
Molecular hybridization method allowed obtaining thiazolidinone-peptide hybrids **177** (Scheme 85) that inhibited *Dengue virus protease*. Moreover, it was determined that thiazolidinone core (2,4-thiazolidinedione and rhodanine) and the peptides should be accomplished by relatively rigid arylidene moieties using para-substitution [404].



Scheme 83. 5-Ene-4-thiazolidinones as inhibitors of *HCV NS5B*.



Scheme 84. Structures of *HCV protease* inhibitors.



**Scheme 85.** Structures of hit-compounds with antiviral activity.

### 3.7. Anti- and prooxidant agents

Violation of the antioxidant defence system and the balance of the pro/antioxidants are described under majority of pathologies including above mentioned. Therefore, a lot of papers are dedicated to the study of the 4-thiazolidinones antioxidant activity [339]. Most of the articles describe investigation of the antiradical properties of 5-ylidenethiazolidinones in the model systems and evaluation of their efficiency as free radical scavengers (e.g. scavenging activity to DPPH (1,1-diphenyl-2-picrylhydrazide) [106]) combined with the study of other types of activity, in particular, antitumor and anti-inflammatory (see above) [405]. Such data concern all the classes of 4-thiazolidinones bearing different types of ylidene fragment. 4-Thiazolidinone derivative **178** (Scheme 86) possesses anti-radical activity including the ability to inhibit superoxide anion formation [406] and it is known that antioxidant activity increases when additional carboxylic group is introduced in the substituent at the position C5 of the heterocyclic core in both N3 substituted and N3 unsubstituted derivatives [407].

For the simple 5-benzylidene rhodanines antioxidant activity in various LDL oxidation models, such as TBARS assay, conjugated diene formation, REM of ox-LDL, fragmentation of apo  $\beta$ -100 by SDS-PAGE, radical DPPH scavenging activity, and macrophage-mediated LDL oxidation was showed [405]. It should be noted that the branched aliphatic fragments prevalence (spatially-screened phenols) largely contributes to the imitation of the known agents, e.g. BHT or probucol [336].

Antioxidant properties of a series of 2,4-dichlorothiazolylthiazolidine-2,4-dione and 4-chloro-2-benzylsulfanylthiazolylthiazolidine-2,4-dione derivatives **179** (Scheme 86) were reported in two different *in vitro* assays: superoxide anion radical formation and DPPH radical scavenging activity [408].

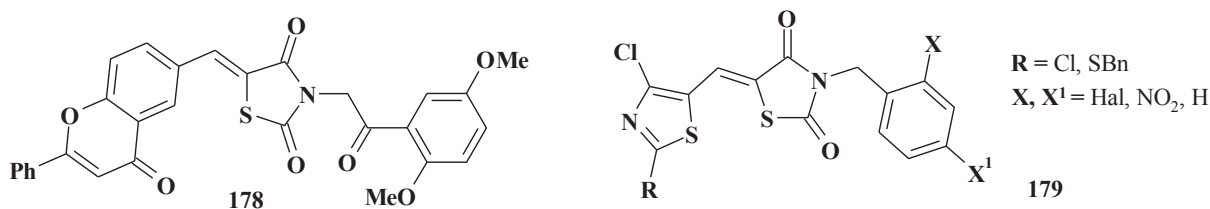
The presence of the benzylsulfanyl group at the second position

of the thiazole ring plays a significant role in increasing the superoxide anion scavenging activity. No correlation was observed in results on superoxide radical and DPPH radical scavenger capacity.

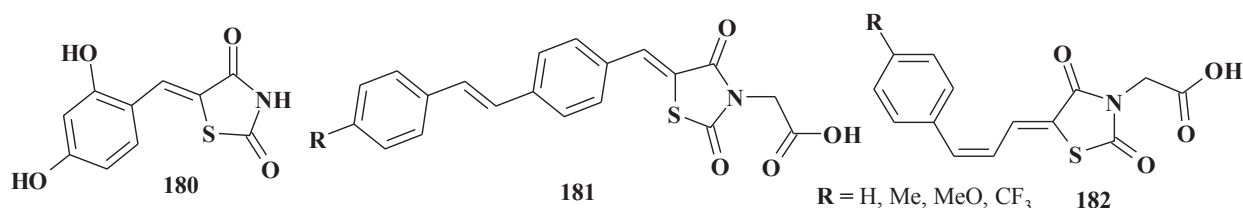
Simple thiazolidinedione derivative (*Z*)-5-(2,4-dihydroxybenzylidene)-thiazolidine-2,4-dione **180** (Scheme 87) plays a crucial role in UV-induced melanogenesis, which is known to be related to the induction of *tyrosinase enzyme*. Compound inhibited nitroprusside-induced NO generation dose-dependently and suppressed tyrosinase activity and melanin synthesis (B16F10 melanoma cells) [409].

Series of 5-arylidene-2,4-thiazolidinediones **181**, **182** (Scheme 86) and their 2-phenylimino analogs inhibiting AR [236,410–412] possess dual activity as antidiabetic and antioxidant agents for the treatment of diabetic complications [413]. The results indicate that latter possess excellent antioxidant properties inhibiting the production of TBARS in the test of compounds effect on hydroxyl radical-dependent lipoperoxidation induced in rat brain homogenate by the oxidant system  $\text{Fe}^{3+}$ /ascorbic acid. It was observed that the presence of electron releasing substituents on the distal phenyl ring differentiates the antioxidant activity of the compounds. Detailed mechanisms of antioxidant effects of compounds of this class is still unclear and can be explained not only by the ability to inhibit superoxide anion (or other ROS) production, but also by influencing other parts of the pro/antioxidants system. Because of the changes in the classic approaches to the evaluation of pro/antioxidants [414], emerging of new approaches to the interpretation of antioxidant effects [415] and study of other (not related to free radical scavenging) mechanisms of the antioxidants [156], more attention is paid to the study of the molecular mechanisms of stimulation of antioxidant defence system [416,417] including the possibility of these substances pro-oxidant impact with subsequent stimulation of antioxidant defence system (see above – anticancer agents).





Scheme 86. Structures of 4-thiazolidinones with anti-radical activity.



Scheme 87. Structures of 4-thiazolidinones with dual activity.

### 3.8. Other types of activity

A large number of bio-targets of 5-ene-4-thiazolidinones are involved in different pathologies and there are a lot of data on the efficacy of 5-ene-thiazolidinones in different experimental models [5–7,100,418].

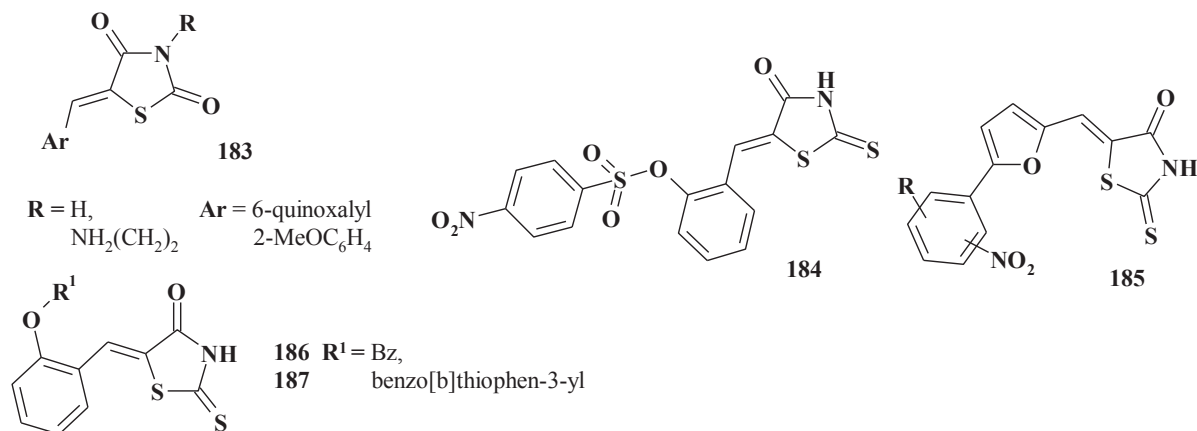
For instance, molecular docking studies indicated that the 5-ene-thiazolidinone moiety was a likely candidate for its selectivity to *monoamine oxidase-B*. This hypothesis was confirmed by the identification of two lead-compounds **183** (Scheme 88) with  $IC_{50}$  13–20  $\mu$ M [419].

Some 5-ene-rhodanine-3-carboxylic acid derivatives, namely 4-(5*Z*)-5-[5-(4-bromophenyl)-2-furyl]methylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl-butanoic acid and 6-((5*Z*)-5-[5-(4-bromophenyl)-2-furyl]methylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)hexanoic acid are efficient inhibitors of *apoptosis signal-regulating kinase 1* [420] which is involved in the variety of cellular processes [421] and can be considered as a promising target for the treatment of the various cardiovascular diseases, neurodegenerative diseases, several liver and kidney diseases etc.

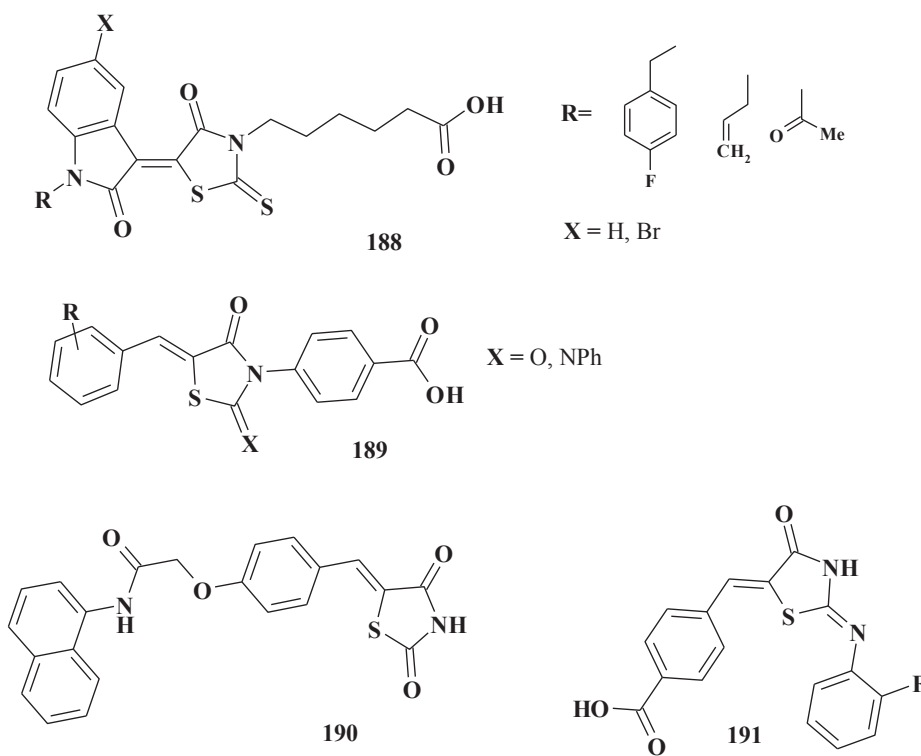
At the same time several other kinases, for example a *cyclin-dependent kinase* family are attractive targets for the design of high affinity inhibitors based on 5-alkylidenrhodanines [52]. 5-

ylidenes **184**, **185** (Scheme 88) were identified in the virtual screening as representatives of novel *glycogen synthase kinase-3* (*GSK-3b*) inhibitors and their activity was confirmed experimentally [245] ( $IC_{50}$  1.56–5.56  $\mu$ M). *GSK-3b* has been emerging as a key therapeutic target for type-2 diabetes melitus, Alzheimer's disease, cancer and chronic inflammation. There is experimental evidence that *GSK-3b* inhibitors activate negative regulation of *NF-kB* activity, p53-dependent apoptosis, and enhance the TRAIL-induced cell death [422,423].

3-(3-Trifluoromethyl)phenyl]-5-arylidene-2-thioxo-4-thiazolidinone was identified as a potent and selective blocker of the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) *Cl*-channel. Moreover, it acted differently from other known blockers of the *CFTR* channel. Rather than blocking the channel pore, it affects the mechanism of channel gating, possibly by binding to nucleotide binding domain (NBD-1) [424–426]. *CFTR*, a member of the ATP-binding cassette transporter superfamily, is an epithelial chloride channel that plays a critical role in fluid absorption and secretion. Defective *CFTR* function causes cystic fibrosis, the most common lethal genetic disease in caucasians that produces severe lung disease, pancreatic insufficiency, neonatal intestinal obstruction and infertility where the hyperfunction of *CFTR* chloride channels, usually resulted from bacterial enterotoxins, constitutes



Scheme 88. Examples of 5-ene-4-thiazolidinones with different types of activity.



**Scheme 89.** Structures of 5-ene-4-thiazolidinones with action on different targets.

the basic cause for secretory diarrhea. Thiazolidinone *CFTR* inhibitors may be useful in developing large-animal models of cystic fibrosis and in reducing intestinal fluid loss in cholera and other secretory diarrheas.

Benzylidenerhodanine derivatives showed good inhibitory activity against recombinant human *PRL-3* (phosphatase of regenerating liver, the representant of *protein tyrosine phosphatases*). Compounds **186** and **187** (Scheme 88) were the most active *in vitro* in this series and showed the ability to reduce the invasiveness of tumor (**186**) [286].

Following virtual screening of potent *serotonin N-acetyltransferase* (member of the *GCN5N-acetyltransferase* superfamily catalyzing the penultimate step in the biosynthesis of melatonin) inhibitors the class of 5-ene-rhodanine-3-carboxylic acids **188** (Scheme 89) was identified that exhibited low micromolar competitive inhibition against acetyl-CoA and proved to be effective in blocking melatonin production in pineal cell [427].

5-Arylidene-4-thiazolidinone derivatives **189** (Scheme 89) exhibited antidegenerative activity and could block multiple cartilage destruction during the osteoarthritic process by reducing NO release and restoring normal levels of glycosaminoglycans in chondrocytes treated with beta L-1, and possessed *MMP-13* inhibition activity (*MMPs* are a large family of calcium dependent, zinc containing endopeptidases responsible for the tissue remodeling and an extracellular matrix degradation) [240]. These compounds were found to be endowed with interesting activity levels in models of acute inflammation, such as carrageenan-induced paw and pleurisy edema in rats and to be inhibitors of COX isoforms [373].

5-Benzylidene 2,4-thiazolidinedione derivatives are proposed for the treatment of Non-Alcoholic Fatty Liver Disease [428]. Compound **190** (Scheme 89) was found to upregulate the adiponectin protein expression and down regulate the secretion of leptin protein in 3T3-L1 adipocytes at a respective concentration of

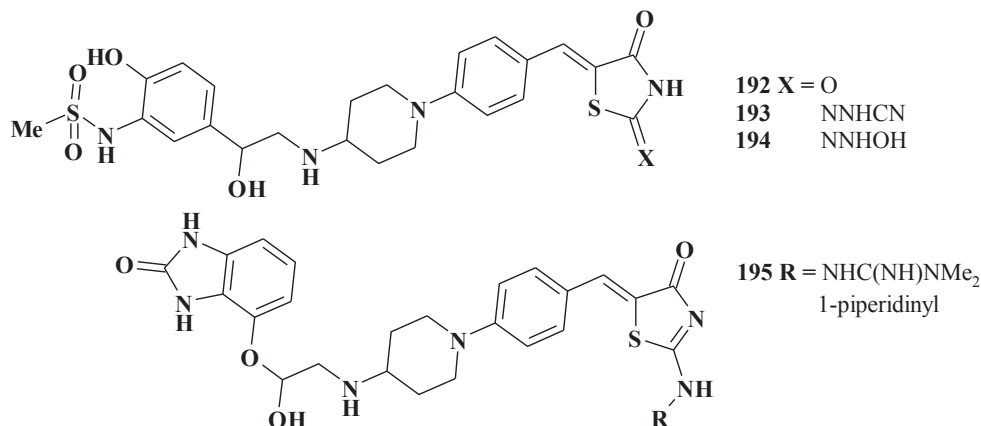
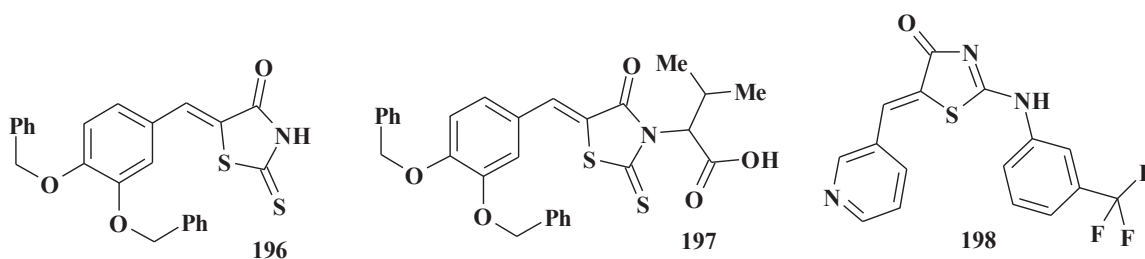
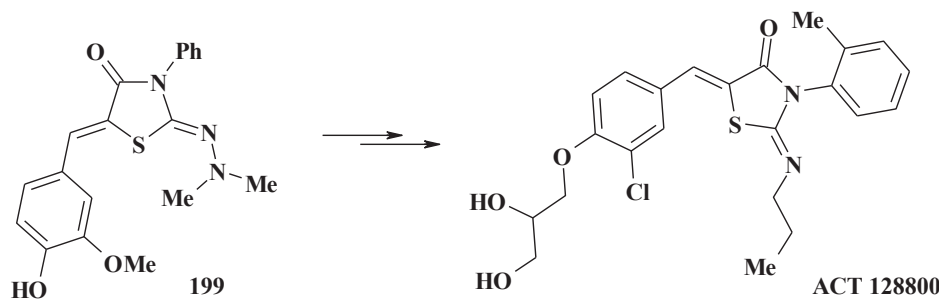
10 mM.

4-((Z)-(2Z)-2-(2-Fluorobenzylidene)-4-oxo-1,3-thiazolidin-5-ylidene)methyl}benzoic acid **191** (Scheme 89) was described as the most potent full agonist to human *GPR35* [429]. A class of orphan receptors *GPR35* has been described as a potentially novel drug target [430] for the design of compounds with therapeutic application in a number of diseases including inflammation, metabolic disorders, nociception and cardiovascular diseases. The olefinic thiazolidinedione **192** (Scheme 90) was found to be potent and selective *b3-adrenergic receptor* (*b3-AR*) (*b3-AR* EC<sub>50</sub> 0.006 mM, IA = 1.03) agonists (96-fold vs *b2* and 492-fold vs *b1*) being more active than primary hits (5-saturated analogs) [431]. *b3-AR* Agonists are potential drugs for the treatment of obesity, type II diabetes, frequent urination and related diseases [432]. Related thiazolidinones with a cyanamide (**193**), hydroxylamine (**194**) (Scheme 90) or 4-amino-1-benzylpiperidine substituents were generally very potent towards the *b3* receptor, however, they were not very selective against both the *b2* and *b1* receptors. Related benzimidazolones (**195**) (Scheme 90) displayed a good *b3* agonist selectivity profile.

5-Benzylidene-2-thioxo-4-thiazolidinones **196**, **197** were described as inhibitors of *Aggrecanase-2* that are members of the *ADAMTS* (*adisinte grin and metalloprotease with thrombospondin motifs*) family of zinc metalloproteases. The inhibition of *Aggrecanase-2*, therefore, protect cartilage from damage and provide the first potential therapy to halt and/or reverse the progression of osteoarthritis and the compounds were at least 3-fold more active than 2,4-thiazolidinedione analogs [433].

In the result of virtual screening **198** (Scheme 91) was found as potent *canabinoid receptor type 1* antagonist with promising binding affinity (IC<sub>50</sub> 125 nM) and also displayed good pharmacokinetic profile in rats as well as in human plasma [434,435].

Novel class of *sphingosine-1-phosphate* (*S1P1*) receptor agonists based on the 2-iminothiazolidin-4-one scaffold **199** and **ACT-**

Scheme 90. Structures of 5-ene-4-thiazolidinone *b*<sub>3</sub>-adrenergic receptor agonists.Scheme 91. Structures of 5-ene-4-thiazolidinone *b*<sub>3</sub>-adrenergic receptor agonists and cannabinoid receptor type 1 antagonist.

Scheme 92. Novel class of sphingosine-1-phosphate receptor agonists.

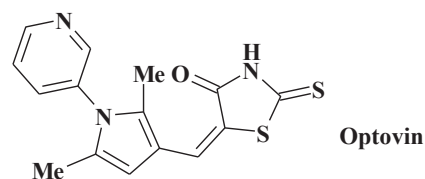
**128800** (Scheme 92) was found as the most active compound in *in vitro* and *in vivo* assays. Selective agonists of *S1P1* receptor are of therapeutic interest for their ability to halt the exit of lymphocytes from lymph nodes. This interruption of lymphocyte migration promises a new immunomodulatory therapeutic principle for a variety of autoimmune diseases [436].

New class of benzisothiazolylimino-5-benzylidene-4-thiazolidinones was identified as new metalloproteinase-3 inhibitors and chondroprotective agents. The mode of action is also related to the decreasing of *NF-κB* level [437].

**Optovin** ((*E*)-5-[(2,5-Dimethyl-1-pyridin-3-yl)pyrrol-3-yl]methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one) (Scheme 93) was detected as a small molecule that enables repeatable photo activation of motor behaviors in wild type animals. Optovin acts as a light-sensitive ligand for anion channel involved in the detection of painful sensory stimuli. It activates human *TRPA1* via structure-dependent photochemical reactions with redox-sensitive cysteine residues. Optovin treatment enables control of motor activity in the

paralyzed extremities by localized illumination. These studies identify a light-based strategy for controlling endogenous *TRPA1* [146,147]. It should be mentioned that optovin is a rare example of the *E*-isomers of 5-heterylidenerhodanines.

Among rhodanine-3-carboxylic (sulfonic) acids the new inhibitors of histone acetyltransferases (**200–202**) (Scheme 94) were identified. Histone acetyltransferases (*HATs*) are promising epigenetic drug targets involved in the pathogenesis of a wide range of



Scheme 93. Structure of optovin.

diseases [427,438].

Summarizing all the above, 5-ene-4-thiazolidinones deservedly can be considered as privileged heterocycles with the wide spectrum of biological activity. Assigning 5-ene-thiazolidinones as PAINS due to possible Michael acceptor functionality is not so unambiguous and requires further study; therefore, most compounds can not be rejected *per se*. There are two main directions of the presented literature data: i) screening of the compounds activity without confirmed mode of action and ii) search for highly active and selective ligands to so-called “validated” bio-targets, which definitely don't negate each other. Search for antitumor, hypoglycemic, antimicrobial, antiviral and anti-inflammatory agents are the main fields of the 5-ene-4-thiazolidinones study. Moreover, most of the works are dedicated to the investigation of the antitumor potential of these compounds. Despite a series of established bio-targets, a detailed mode of anti-cancer effect undoubtedly depends on the structure of a particular derivative and needs further study. However, for the majority of 5-ene-thiazolidinones apoptosis-dependent as well as the ROS mediated modes of action are established.

The main directions of the active 5-ene-thiazolidinones optimization can be divided as follows: i) complications of the C5 fragment (bulky-substituents), while N3 unsubstituted position is preferred; ii) introduction of substituents in N3 position (especially fragments bearing carboxylic group or its derivatives); iii) annulation of 5-ene-thiazolidinones in complex fused heterocyclic systems; iv) combination with other pharmacologically attractive fragments within hybrid pharmacophore approach.

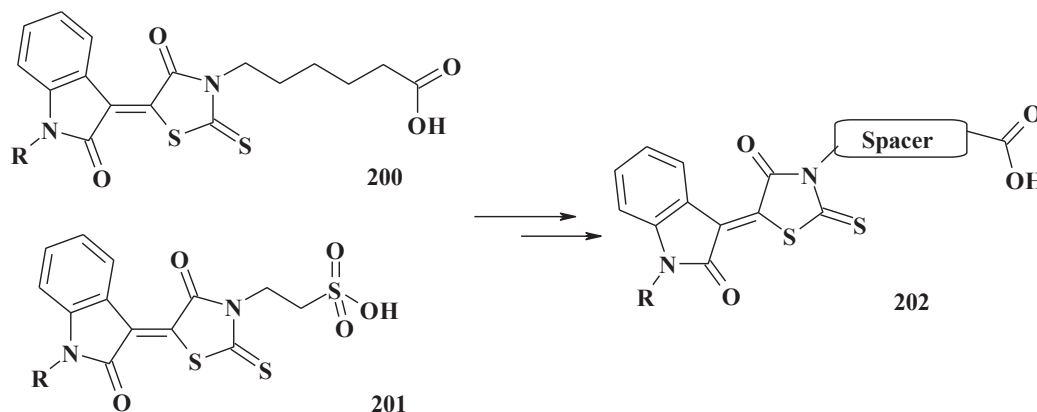
#### 4. 5-Ene-4-thiazolidinones based synthesis

Following the diversity of the chemical and pharmacological properties of 5-ene-4-thiazolidinones they can be treated as the building blocks for the synthesis of various derivatives and as a step of so-called privileged substructure-based diversity oriented synthesis strategy [15–17,439], which is proved to be a fruitful tool to rapidly discover biologically active lead-compounds. Moreover, recently the following thesis was put forward: the compounds based on 5-ene-4-thiazolidinones, mainly annelated systems (e.g. thiopyrano[2,3-*d*]thiazoles) possess the similar to 5-ene-4-thiazolidinones pharmacological profiles and can be considered as cyclic bio-mimetics of their synthetic precursors [440–444]. Regardless of the type of thiazolidinone core, we tried to outline the reactions common for all 5-ene-4-thiazolidinones and in particular for those involving the C5 exocyclic double bond [445].

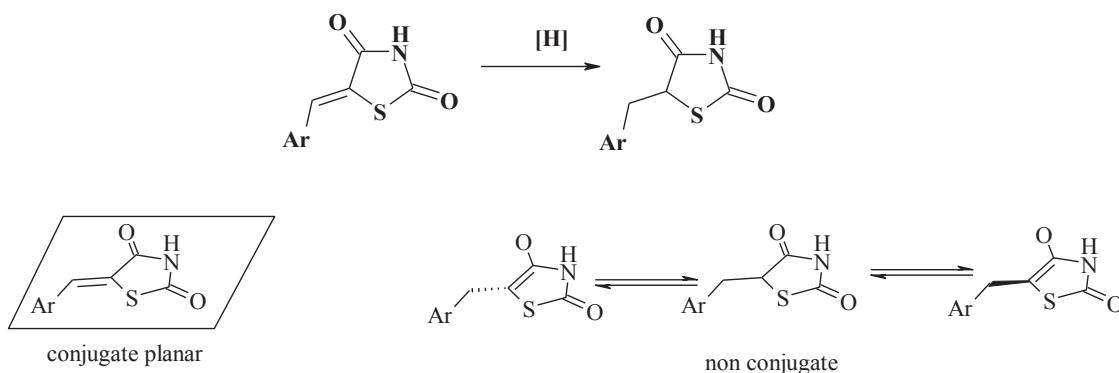
##### 4.1. Addition reactions

**Reduction.** The C5 exocyclic double bond of 5-ene-4-thiazolidinones which formed the planar conjugated systems could be relatively easy reduced leading to the formation of corresponding unconjugated structures (Scheme 95). Challenging problem of such type of non-conjugated systems (that are basically most studied on the example of glitazones (see above)) is the relative simplicity of enolization at the 5-position under physiological conditions, which makes the stereochemistry difficult to maintain at this position [446].

Lithium and sodium borohydride and sodium hydrides



Scheme 94. Structures of inhibitors of histone acetyltransferases.

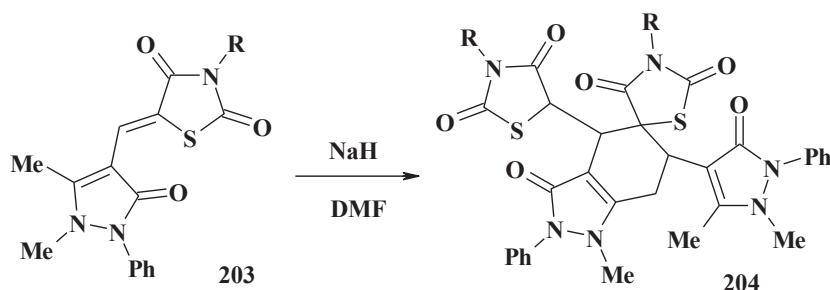


Scheme 95. General scheme of reduction and enolization.

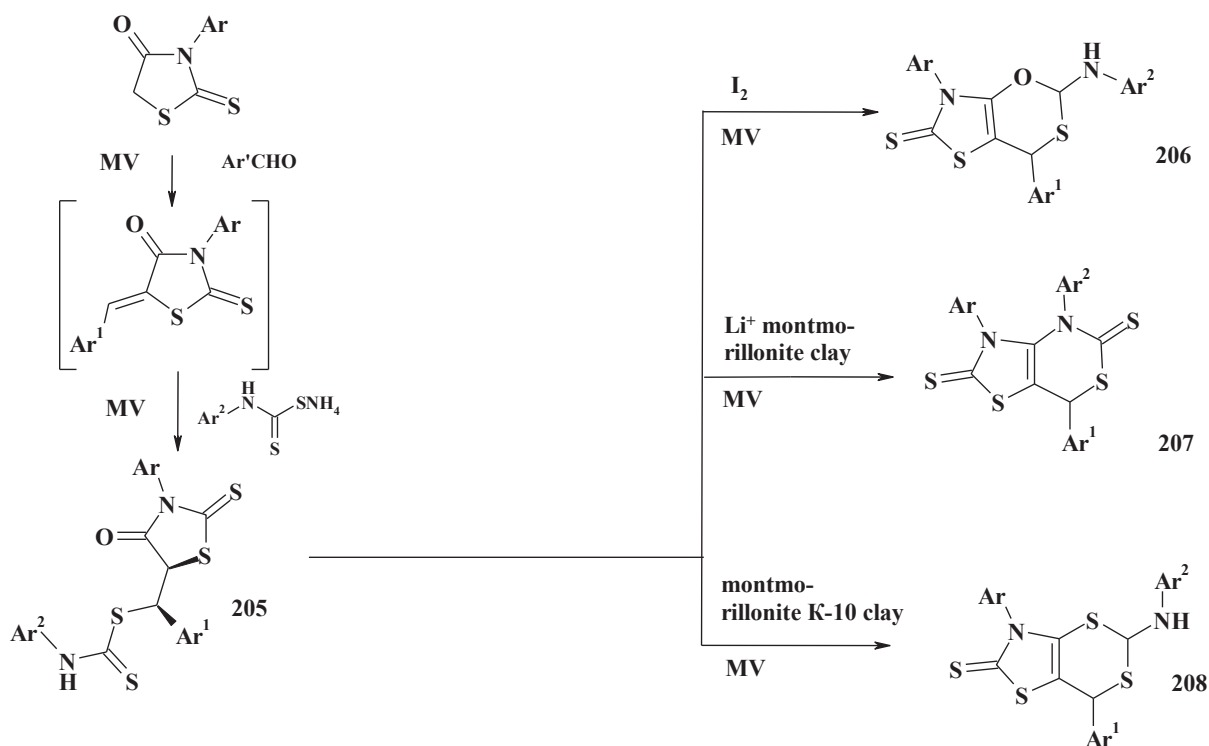
[234,303,447],  $H_2$ -Pd/C in dioxane [223], Na/Hg, THF/H<sub>2</sub>O [431], Mg in methanol or zinc in acetic acid [448] etc. have been used as reducing agents. This reaction is mainly studied as a phase of glytazone synthesis [449]. An appropriate reaction conditions allow selective reducing of the double bond leaving intact other molecular fragments, e.g. in the case of the rhodanine-3-carboxylic acids. Under reduction of the complex 5-heterylidene-4-thiazolidinones **203** (Scheme 96) the formation of fused heterocyclic systems **204**

was described. The treatment of pyrazole–thiazolidinone derivatives with sodium hydride in N,N-dimethylformamide caused dimerisation reaction to give the corresponding spiro compounds **204** [450].

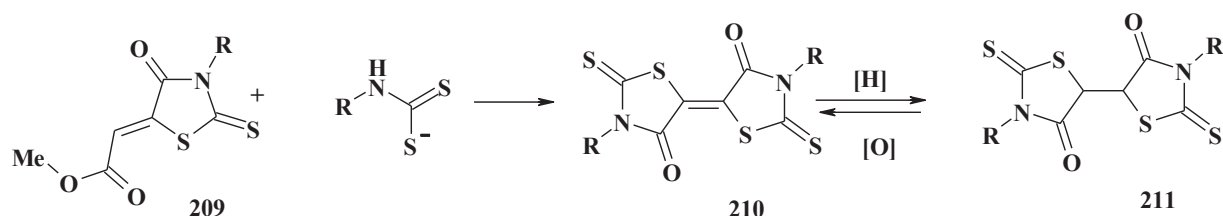
The exocyclic double bond of 5-arylidene-3-methyl-2-thioxo-4-thiazolidinones is a good olefin for variety addition reactions, e.g. *Michael addition* [451]. The reaction conditions (e.g. microwave irradiation) confirm the doubts about the realization of such



**Scheme 96.** Synthesis of spiro compounds under complex 5-heterylidene-4-thiazolidinones reduction.



**Scheme 97.** Michael addition as a phase of multicomponent reaction in the synthesis of fused heterocycles.



**Scheme 98.** Synthesis of bis-thiazolidinones.

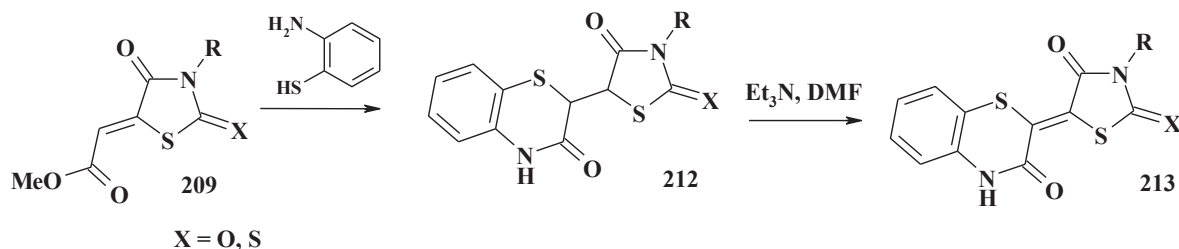
reaction under physiological conditions (see above) considering 5-ene-thiazolidinones as Michael acceptors. While the Michael addition (followed the Knoevenagel condensation) [452] is a phase of domino or tandem multicomponent reactions. Reaction of 3-arylrhodanines, aromatic aldehydes and *N*-dithiocarbaminates involves the consecutive Knoevenagel condensation and Michael addition (Scheme 97). The reaction is stereoselective and is carried out in dry conditions under microwave irradiation. Dithioester **205** under intermolecular cyclization and iodine (**207**), montmorillonite Li<sup>+</sup> clay (**206**) or montmorillonite K-10 clay (**208**) action gave the appropriate heterocycles [453].

Utilization of the 5-carboxymethylidene-rhodanines **209** (as [C<sub>2</sub>]<sup>2+</sup> synthones) in the known [2 + 3]-cyclocondensation reaction led to bis-thiazolidinones **210** formation. The latter can be easily

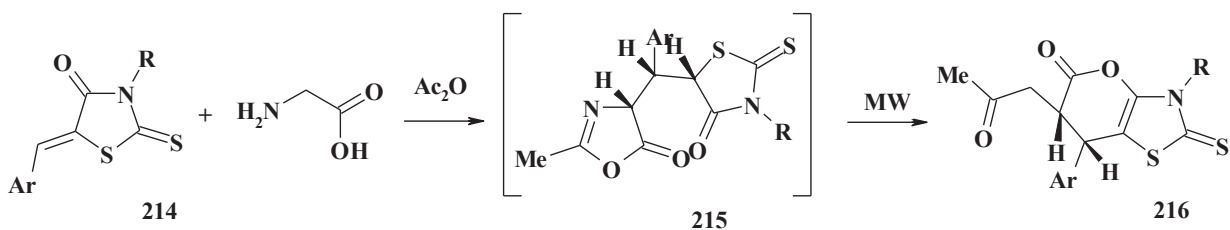
reduced (adding zinc in acetic acid) to bis-thiazolidinones **211** which can readily be oxidized to starting **209** (in the presence of catalytic amounts of triethylamine) [454,455] (Scheme 98).

Similarly, 5-heterylidene-4-thiazolidinones **213** (Scheme 99) have been synthesized based on 5-methoxycarbonylmethylidene-4-thiazolidinones **209** in the reaction with *o*-aminothiophenol and following dehydrogenation of appropriate 5-alkyl-4-thiazolidinones (**212**) in the presence of triethylamine in DMF [456].

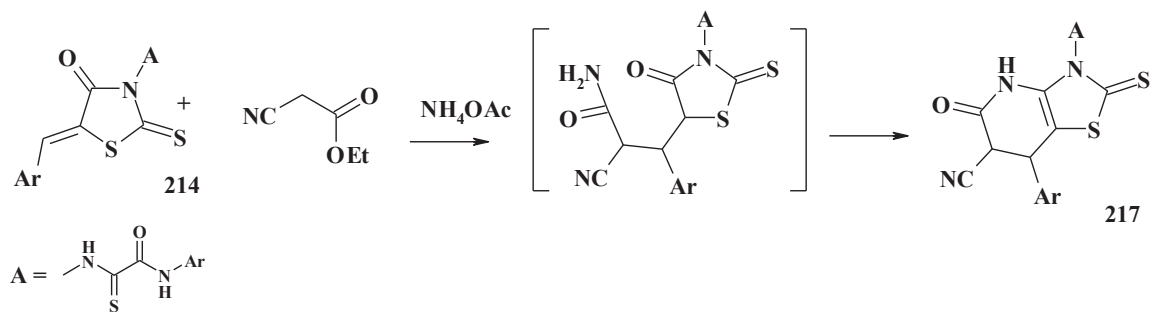
Three-component, one-pot procedure for the synthesis of pyran-annulated thiazoles **216** involving the *in situ* generation of azlactone (**215**) and formation of pyranthiazoles is best explained by Michael addition of azlactone to 5-ene-rhodanine (**214**) affording the corresponding Michael adducts which underwent ring



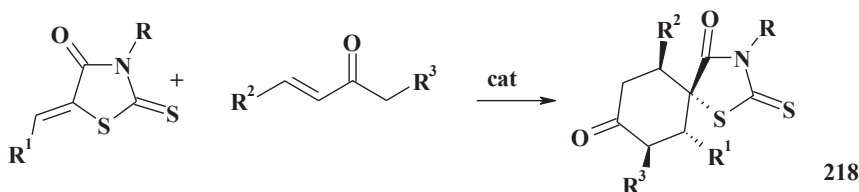
Scheme 99. Synthetic approach to C5 fragment complication.



Scheme 100. Synthesis of 5-oxo-2-thioxo-2,3,6,7-tetrahydropyrano[2,3-*d*]thiazol-5-ones.

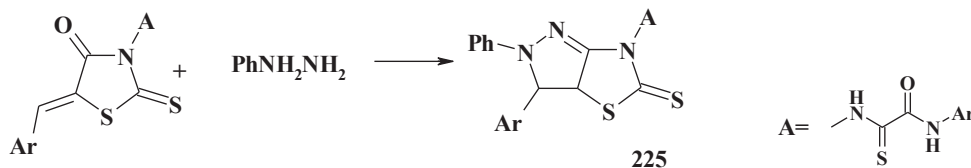


Scheme 101. Synthesis of 5-oxo-2-thioxo-2,3,4,5,6,7-hexahydro[1,3]thiazolo[4,5-*b*]pyridines.



Scheme 102. Synthesis of spiro rhodanines.



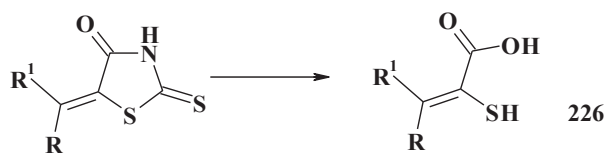


**Scheme 107.** Synthesis of pyrazolothiazole starting from 5-benzylidene thiazolidinone.

#### 4.2. Hydrolytic cleavage

4-Thiazolidinone core is not stable in the alkali medium and this feature has been often explored in their cyclization reactions. 5-Ylidene-rhodanines are attractive starting reagents for the synthesis of 3-substituted-2-mercaptoacrylic acids **226** [43,470]. Alkaline hydrolysis of 5-ylidenerhodanines leads to the mentioned acids formation [471] (Scheme 108).

The possibility of 3-substituted-2-mercaptoacrylic acids utilization as thiolic agents in the one-pot, three-component reaction for the synthesis of 5-ene-2,3-disubstituted-4-thiazolidinones was proposed based on the retro-synthetic approach [43]. The 5-arylidene-4-thiazolidinones containing substituents in the *ortho* position of arylidene fragment are of special interest. The efficient approach to the synthesis of isothiocoumarin derivatives **227** and related compounds **228–231** (structures of which depends on the nature of substituent in the *ortho*-position of aryl(heter)ylidene fragment) is based on the above mentioned 5-ene-4-



**Scheme 108.** Synthesis of 3-substituted-2-mercaptoacrylic acids under the alkaline hydrolysis of 5-ene-rhodanines.

thiazolidinones [472–477] (Scheme 109).

In the base hydrolysis of rhodanines two-step reaction occurs in which intermediates of the hydrolysis undergo heterocyclization with the formation of the 1-oxo-1*H*-2-benzothiopyran-3-carboxylic acids, 3-mercaptocoumarins [478,479], ketocinchoninic acids, 2-indole-carboxylic acids etc.

5-Arylidene-4-thiazolidinones under the action of hydrazine/thiosemicarbazone yield pyrazoline **232** and 1,2,4-triazine **233** derivatives [480] (Scheme 110).

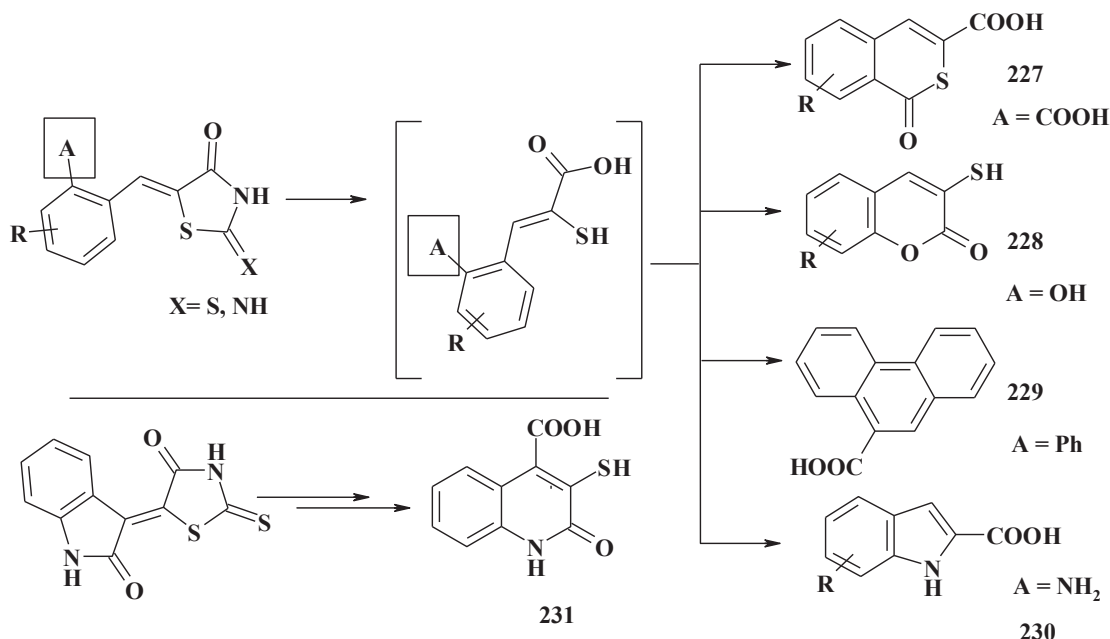
The synthesis of similar pyrazole derivatives **234** is also described starting from 2-ylidene-substituted 4-thiazolidinones [481] (Scheme 111).

Simple synthesis of 2-thioxo-6-azauracils was developed based on the reaction of 5-substituted 2,4-thiazolidinediones with thiosemicarbazide in alkaline medium [482]. Based on the above mentioned approach to C5-moiety optimization, the introduction of bulky heterocyclic fragments into 4-thiazolidinone molecule via the recyclization of C5 ylidene fragment containing highly reactive groups (mainly in *ortho* position) was proposed (Scheme 112).

Though, presented protocols for **235–237** [75,483] are not persuasive, taking into consideration the transformation (instability) of 4-thiazolidinone core in the basic medium (see below) [1,2,6].

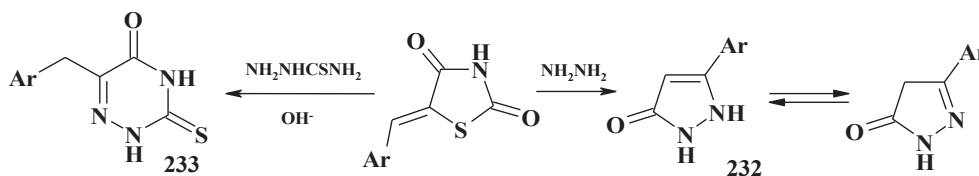
#### 4.3. Hetero-Diels-Alder reaction and related processes

The thionation is one of the effective approaches to the modification of 4-thiazolidinones (mainly in the position 4) and one of

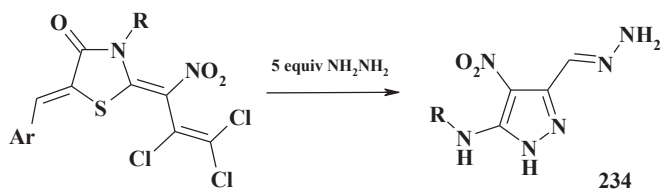


**Scheme 109.** Synthesis of different polycyclic compounds based on 5-arylidene-4-thiazolidinones (adapted from [477]).





**Scheme 110.** Transformation of 5-arylidene-thiazolidinones under the action of hydrazine/thiosemicarbazone.



**Scheme 111.** Synthesis of pyrazoles from 2-ylidene-substituted 4-thiazolidinones.

the steps of the multicomponent reactions in the synthesis of fused heterocycles. For example, thiation of 5-arylmethylidene- or 5-arylmethylrhodanines led to 2,3-dihydro-2-thioxothieno[2,3-*d*]thiazoles **238** [93] (Scheme 113).

In order to synthesize the pyrazolo[3,4-*d*]thiazole system the condensation of 5-ene-4-thioxothiazolidine with hydrazines were studied [484]. Thiazolidine-thione condensation with hydrazine derivatives in DMF yielded a single product in regioselective synthesis of 1,3,5-trisubstituted-5,6-dihydro-2*H*-pyrazolo[3,4-*d*]thiazoles **239** [76] (Scheme 114).

4-Thioxothiazolidines are efficient heterodienes in *hetero*-Diels–Alder cycloaddition being one of the most powerful methods in the construction of fused heterocycles **240** bearing thiazolidinone fragment (Scheme 115).

Thiopyrano[2,3-*d*][1,3]thiazoles are usually synthesized via [4 + 2]-cycloaddition in *hetero*-Diels–Alder reaction of 5-arylidene-2,4-dithioxothiazolidines (5-arylidene-thiorhodanines) or 5-arylidene-4-thioxo-2-thiazolidinones (5-arylideneisorhodanines) which contain C = C<sub>5</sub>–C<sub>4</sub> = S group in their structure and are active heterodienes [21,440–444,482]. Thiopyrano[2,3-*d*][1,3]thiazoles are of a special interest as cyclic isosteric mimics of their synthetic precursors 5-arylidene-4-thiazolidinones without Michael

accepting functionalities (see above) [440–444]. Maleic acid and its derivatives, acrylic acid and its derivatives, acrylonitrile,  $\beta$ -nitrostyrene, norbornene, 5-norbornene-2,3-dicarboxylic acid derivatives, cinnamic acids, propionic acid, aroylpyruvic acid etc. have been studied in such heterodiene condensation as dienophiles [21,440–444,485–488]. The cycloadditions are highly regio- and stereoselective and form products according to Frontier Orbital Theory [67,69,489,490].

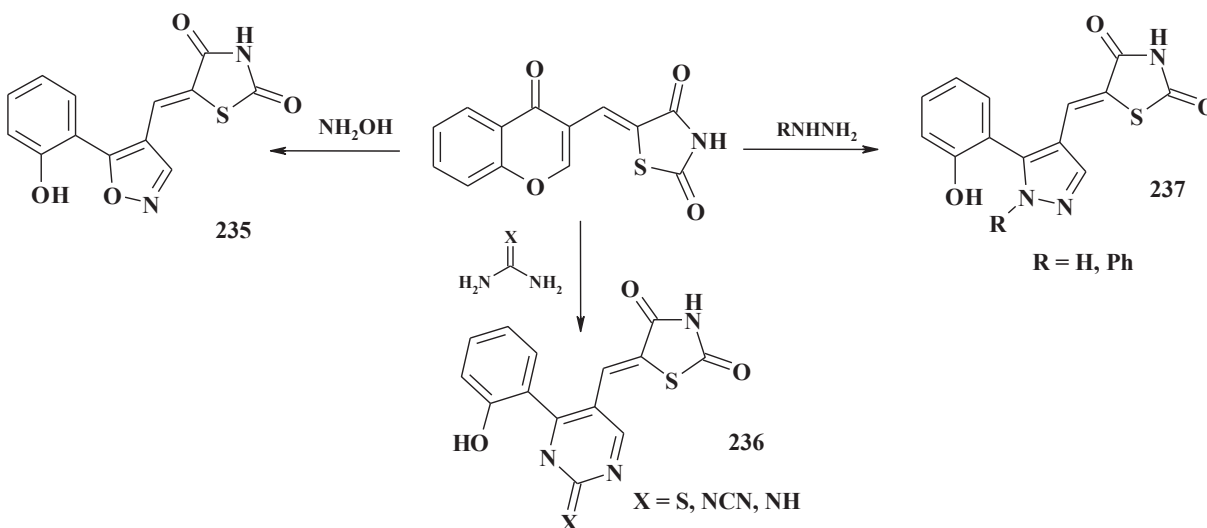
Interesting results were described when 5-benzylidenerhodanines with substituent in *ortho*-position in phenyl ring were utilized in such type of reactions. The reactions of the latter and crotonic acid, its anhydride or 4-chlorophenylamide, cinnamic acids [490], acrylic acid and its ester involved tandem *hetero*-Diels–Alder and acylation processes, affording tetracyclic fused heterocycles (chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazoles) **241** (Scheme 116).

Similar 2-hydroxybenzylidene rhodanine derivatives reacted with malononitrile to give fused chromeno[4',3':4,5]pyrano[2,3-*d*]thiazol-6-ones **242**. Due to instability of rhodanines in basic medium at high temperatures the yields of the cyclocondensation products are low [458] (Scheme 117).

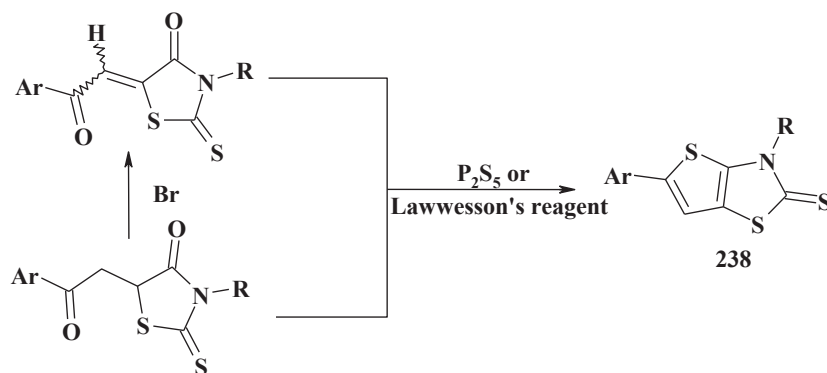
5-Ene-4-thiazolidinones are often the intermediates in the above mentioned tandem reactions involving the *hetero*-Diels–Alder reaction [67,69,483,484,490] (Scheme 118).

Rare are the reports about the utilization of 2-imino-4-thiazolidinones [491] and rhodanine derivatives in the *hetero*-Diels–Alder reaction. For example, in the reaction of 2-imino-4-thiazolidinones and norbornene fused thiopyranthiazole derivatives are formed **244** (Scheme 119).

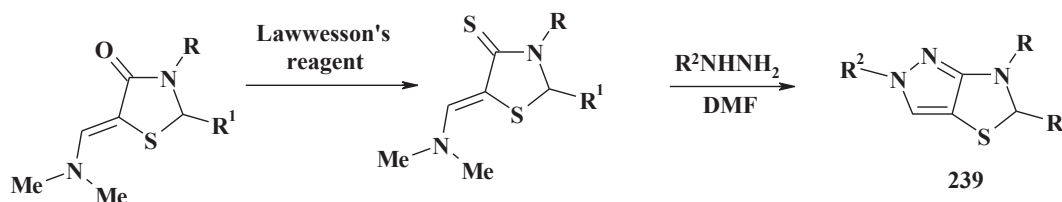
The reactions of arylidenerhodanines with maleic anhydride, *N*-phenylmaleimide, and DMAD were performed under MW irradiation and have led to pyrano[2,3-*d*][1,3]thiazoles formation [492].



**Scheme 112.** Examples of the reactions leading to introduction of bulky heterocyclic moieties into C5 of 4-thiazolidinone core.



**Scheme 113.** Synthesis of 2,3-dihydro-2-thioxothieno[2,3-*d*]thiazoles.



**Scheme 114.** Utilization of 5-ene-4-thioxothiazolidine in the reaction with hydrazines.

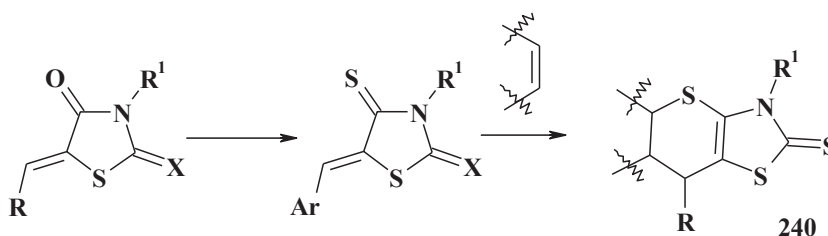
Besides 5-arylidene derivatives, other types of 5-ene-4-thioxothiazolidines were described. For instance, 5-ethoxy-4-thioxothiazolidines are starting materials for polycyclic systems **245–247** formation [64] (Scheme 120). The final product formation is accompanied by the elimination of alcohol molecule and oxidation in the case of **247**.

Rhodanine derivatives were successfully used as the dienophiles to react with the various 2,4-dienals in the asymmetric Diels-Alder reaction leading to the construction of structurally complex compounds **248** containing the rhodanine motif [493] (Scheme 121). The reaction is also diastereo- and enantioselective.

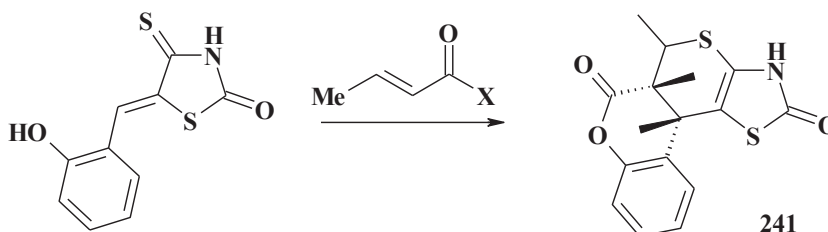
#### 4.4. Other cycloaddition reactions

Three-component 1,3-dipolar cycloaddition reaction of isatin, sarcosine and 5-arylidene-1,3-thiazolidine-2,4-dione or 5-arylidene-4-thioxo-1,3-thiazolidine-2-one in ethanol under ultrasound irradiation is an efficient protocol for the synthesis of dispiropyrridine derivatives **249** [494] (Scheme 122).

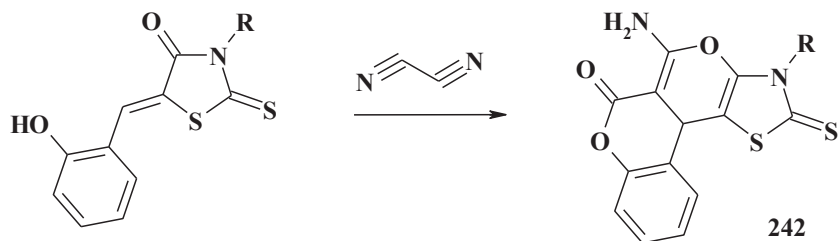
The analogues two step condensation reactions affording similar complex spiro derivatives **250** are described based on 5-arylidene-thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones which contain 'fixed' 5-arylidene-thiazolidinone fragment in their structure [495] (Scheme 122).



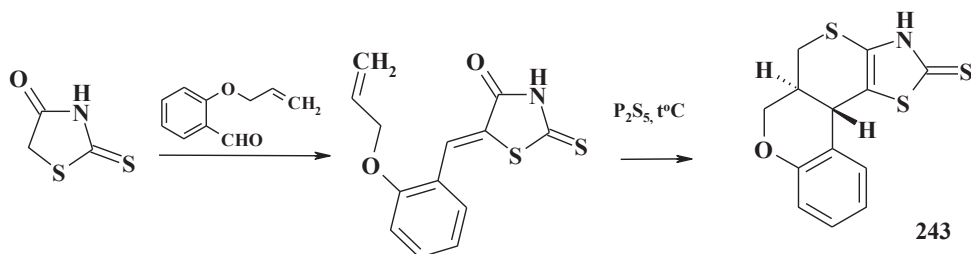
**Scheme 115.** Synthesis of fused thiopyranothiazole system.



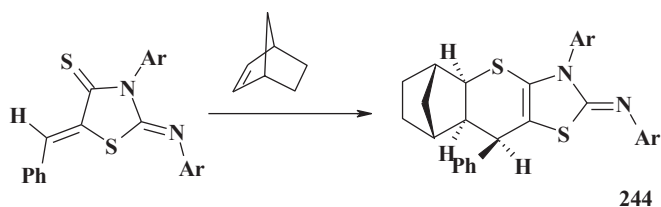
**Scheme 116.** Synthesis of chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazoles.



**Scheme 117.** Synthesis of chromeno[4',3':4,5]pyrano[2,3-d]thiazol-6-ones.



**Scheme 118.** Examples of 5-ene-4-thiazolidinones as intermediates in tandem reactions.



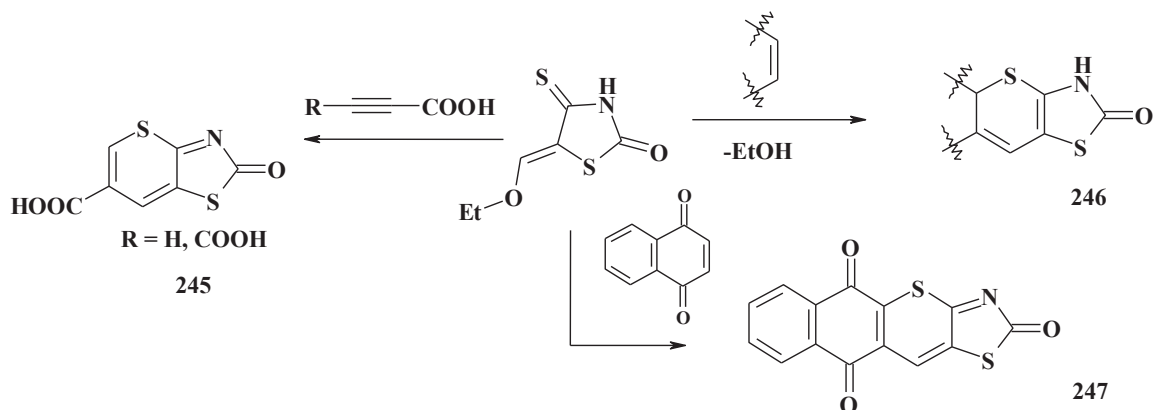
**Scheme 119.** Utilization of 2-imino-4-thiazolidinones in the *hetero*-Diels-Alder reaction.

Related dispiroindole-[3,3'-pyrrolidine-[4',5''-1,3]thiazolidine]-2,4''(1*H*)-diones **251** were synthesized starting from isatin-thiazolidinone conjugates in cyclocondensation reaction (Scheme 123). Mentioned compounds were formed as racemic mixture of two enantiomers resulting from the addition of azomethine ylide (the reaction proceeded diastereoselectively – following NMR data [496].

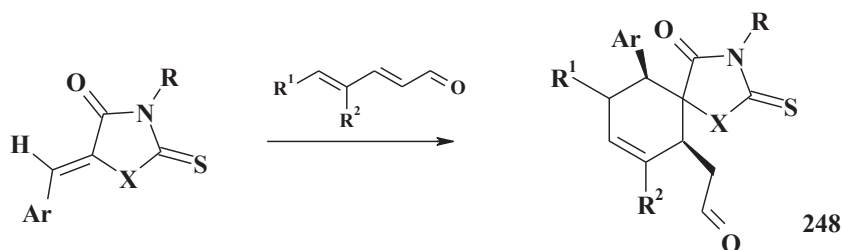
The 5-arylidene-4-thiazolidinones in the Michael reaction with 5-aminopyrazole in acetic acid afforded fused heterocyclic systems **252** containing anazolone moiety. The reaction involved the intramolecular cyclization of the appropriate intermediates and oxidative aromatization [497] (Scheme 124).

## 5. Conclusions

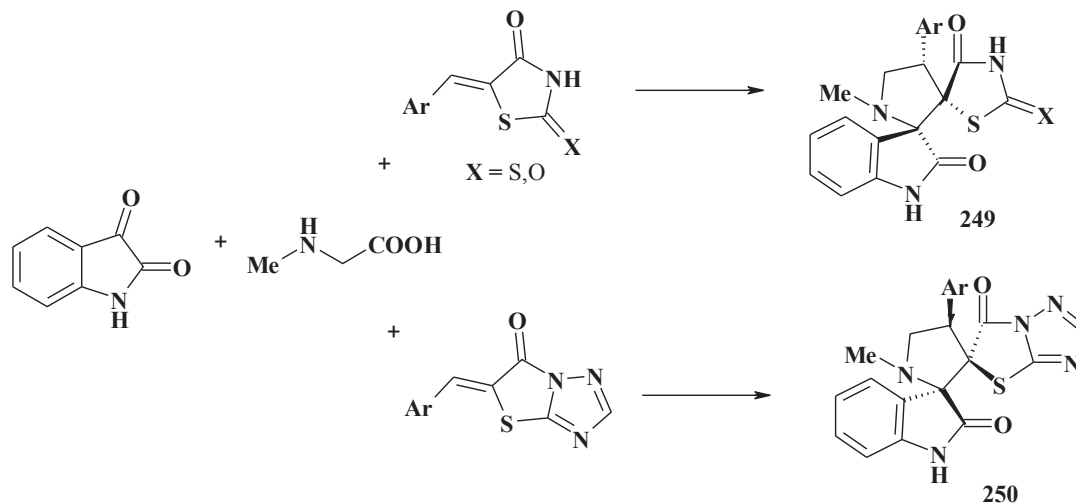
Class of 5-ene-thiazolidinones is an illustrative example of the so-called privileged heterocycles in modern medicinal chemistry, possessing wide range of pharmacological activities. The major achievements in their study have been related to antitumor, hypoglycemic, antiviral and antimicrobial activities. Despite 5-ene-4-thiazolidinone derivatives are assigned as pan-assay interference compounds (with possible low affinity to several biotargets and not sufficient selectivity), their properties of Michael acceptors *in vivo* should be studied more precisely and objectively. The affinity toward different targets may be considered as an advantage and basis for further modification aiming to increase the selectivity. Another



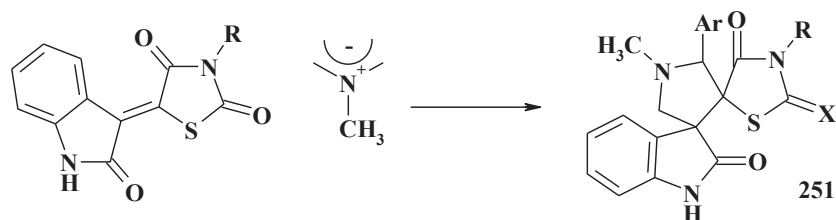
**Scheme 120.** Synthesis of polycyclic molecules based on 5-ene-4-thioxothiazolidines.



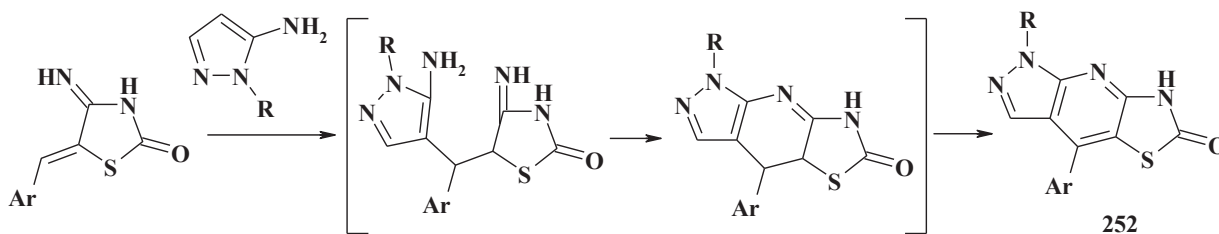
**Scheme 121.** Rhodanine derivatives as dienophiles in the Diels-Alder reaction.



**Scheme 122.** One-pot approach for the synthesis of spiro compounds using 5-arylidene-thiazolidinones.



**Scheme 123.** Synthesis of dispiroindole-[3,3'-pyrrolidine-[4',5''-1,3]thiazolidine]-2,4''(1H)-diones.



**Scheme 124.** Example of 5-arylidene-4-thiazolidinones utilization in Michael reaction.

benefit of the described compounds is relative simplicity of their synthesis – sufficiently important argument for the needs of medicinal chemistry. A lot of data indicates saving the biological activity of 5-ene-4-thiazolidinones in the molecules synthesized on their basis. Thereby, polyfunctional 5-ene-4-thiazolidinones are useful starting building blocks for the synthesis of complex

pharmacologically attractive heterocyclic systems. Given the data presented in the article, 5-ene-thiazolidinone scaffolds are the powerful tool in medicinal chemistry and undoubtedly should not be regarded as problematic compounds *per se*.

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