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Synthesis and biological activity of rhodanine-furan conjugates: A review

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A B S T R A C T

Rhodanines are recognized as privileged heterocycles in medicinal chemistry. The main achievements include the development of drug-like molecules with numerous biological activities as well as approved drugs. The Furan nucleus is considered one of the promising heterocyclic cores in medicinal chemistry that showed numerous ranges of activity. The combination of several heterocycles in a one molecule commonly provides much more interest in the enhanced activity profile of its analogs than their parent separate constituents. Such conjugates are promising objects for modern medicinal chemistry. In this review paper recent advances in the synthesis and biological activities rhodanine-furan conjugates which its application in the different field of drug discovery.

1. Introduction

Today, the main task of medicinal chemistry is the creation of effective and low-toxic medicinal products. Their search is carried out among various classes of compounds, in particular 4-thiazolidone derivatives. Among these compounds, many highly active agents with a wide spectrum of biological activity were found. Lead compounds with antimicrobial, antituberculosis, antiviral, antidiabetic, anti-inflammatory, antitumor, anticonvulsant and other activities have been identified. In this regard, the 4-thiazolidone ring is considered a privileged structure in medicinal chemistry.[1-3]

Due to their unique physicochemical, chemical and biological properties, furan derivatives have found application in various fields of chemistry and technology, and in particular, in pharmacy.[4-7] First of all, it should be noted the wide spectrum of biological activity of natural and synthetic derivatives of furan, as well as its condensed analogs (benzo[b]furan, naphthofurans, anthrafurans, etc.). All this determines the significant interest of scientists in the use of this heterocycle as an important "building block" in the creation of medicinal products.[4-7]

The combination of furan and rhodanine heterocycles in one molecule leads to the appearance of valuable pharmacological properties, which can lead to the creation of innovative medicines. The purpose of previously published reviews was to demonstrate the latest advances in the chemistry and biology of rhodanine derivatives with substituents of various natures.[1-3, 8-21] In contrast it this review aimed to provide an overview on literature data related to the synthesis and biological activity of conjugates, which include two heterocyclic systems - furan and rhodanine. This review is focused on

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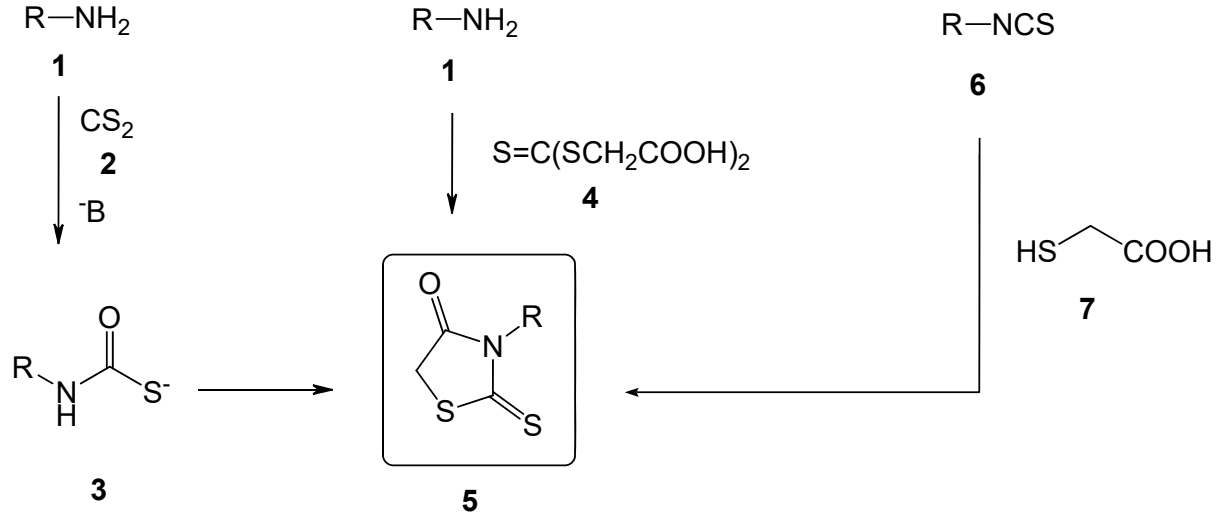
recent scientific reports on the biological activity of furanrhodanine hybrids, published mostly in the last two decades.The advantages of such strategies were reported in the article.[22]

2. Results and Discussion

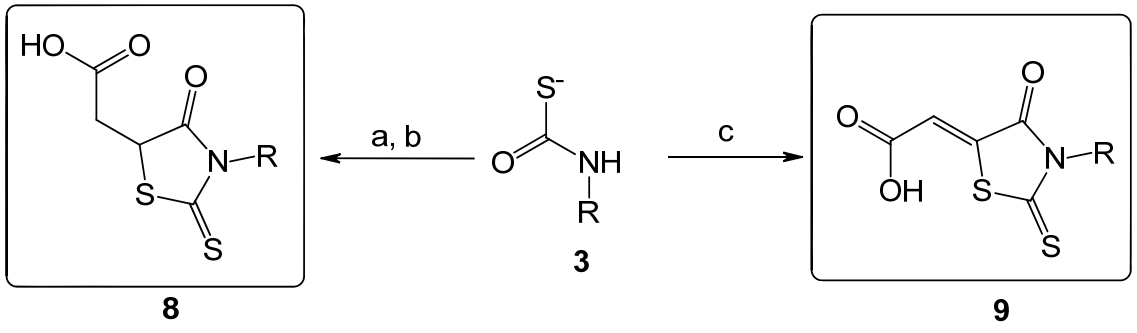
2.1 Methods of construction of the rhodanine (2-thioxothiazolidin-4-one) ring and 5-furan-2-ylmethylene-2-thioxothiazolidin-4-one derivatives

To date, there are three methods for constructing of a rhodanine cycle (**Scheme 1**). The first two methods are based on the use of primary amines, hydrazine derivatives and other compounds containing a primary amino group **1**. This type of compounds, when interacting with carbon disulfide **2**, forms carbamine salts **3**. The resulting compounds, when interacting with chloroacetic acid and their derivatives, cyclize into the target compounds [1-3, 23] Alternative method for converting aminogroup into rhodanine cycle **5** includs the reaction of aminocompounds with acid **4**.[1-3] Rhodanine derivatives **5** are also formed by the raction of isothiocyanates **6** with mercaptoacetic acid **7**.[1-3]



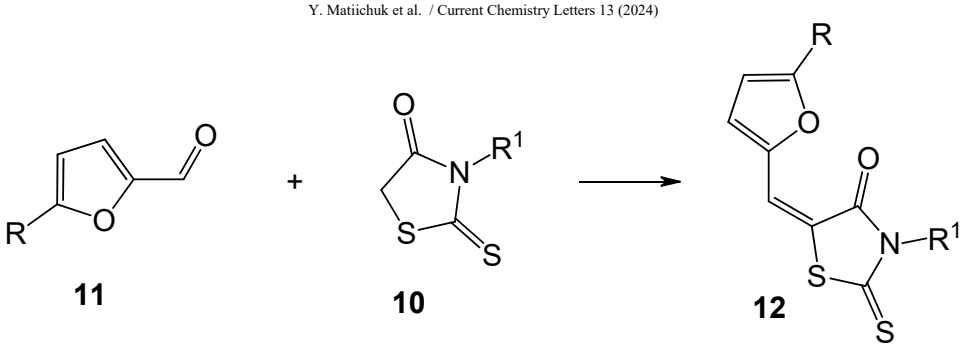
Scheme 1. Methods for constructing of a rhodanine cycle.

In the first case, other halogen-containing acids and mercapto acids can be used. This makes it possible to obtain (3-R-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-yl)acetic acid **8**, (2*Z*)-(3-R-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-ylidene)acetic acid **9** (**Scheme 2**). Good cyclizing reagents are also maleic **a**, fumaric **b** or acetylenedicarboxylic **c** acid and their derivatives. The use of these acids makes it possible to obtain the corresponding rhodanines.[1-3]



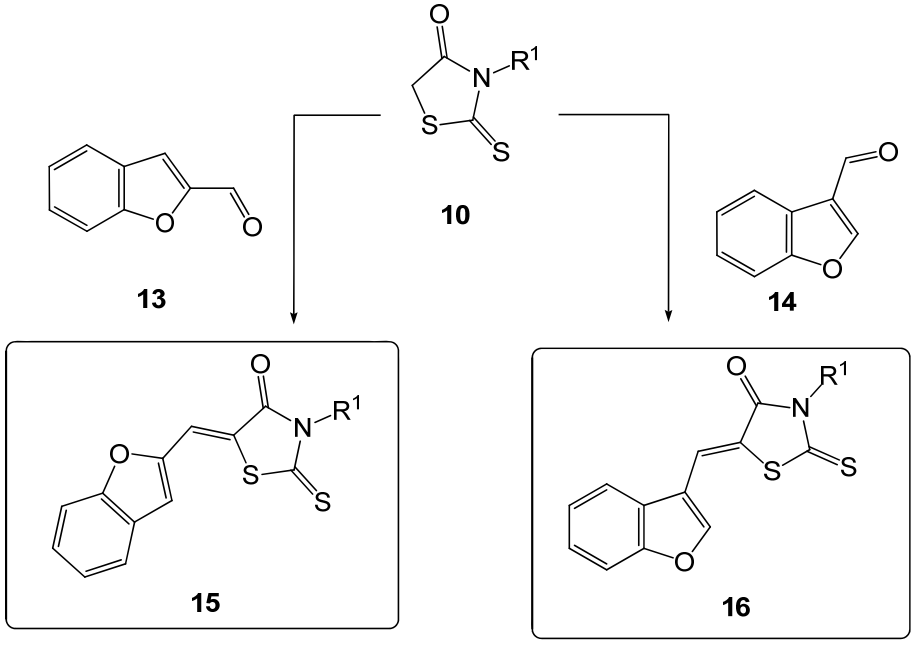
Scheme 2. Synthetic pathway to (3-R-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-yl/ ylidene)acetic acid.

The main attention in the design of furan-rhodanine conjugates was given to the synthesis and study of the biological activity of 5-furfurylidene rhodanines. The methylene group in rhodanine derivatives **10** is highly active and, upon interaction with furfural and its substituted derivatives **11** in the presence of basic catalysis, easily forms the target (5*E*)-3-R^1-5-[(5-R-furan-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-ones **12** (**Scheme 3**).[1-3, 23-26]



Scheme 3. Synthesis of (5*E*)-3-R[1]-5-[(5-R-furan-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-ones.

The 1-benzofuran-2-carbaldehyde **13** and 1-benzofuran-3-carbaldehyde **14** interact in a similar way (**Scheme 4**).[27,28]



Scheme 4. Synthesis of (5*Z*)-5-[(1-benzofuran-2-yl)methylidene]-3-R[1]-2-sulfanylidene-1,3-thiazolidin-4-one **15** and (5*Z*)-5-[(1-benzofuran-3-yl)methylidene]-3-R[1]-2-sulfanylidene-1,3-thiazolidin-4-one **16**.

The geometric placement of substituents at the 5-th position of the rhodanine ring of the above compounds has not been studied separately. However, by analogy with other 5-arylidenerhodanines, it can be argued that this is the Z-configuration[1-3].

2.2 Biological activity of 5-furfurylidenerhodanines

Derivatives of (5*Z*)-5-[(furan-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **17** (**Fig. 1**) are characterized by a wide spectrum of biological activity. Zvarec et al. reported that their simplest representative has antibacterial activity against gram-positive bacteria *Staphylococcus aureus ATCC 31890*, *Staphylococcus epidermidis* with a MIC value of 16–32 mg/ml. With respect to *Bacillus subtilis ATCC 6633*, this effect was not observed.[28]

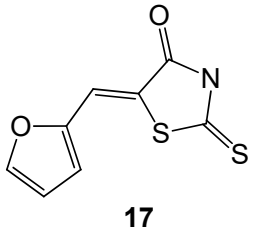


Fig.1. Structure of (5*Z*)-5-[(furan-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **17**.

In the work of Mendgen et al.[29] the inhibitory activity of compounds **17** and **18** (**Fig. 2**) four different enzymatic targets was determined: the NS2B-NS3 protease of Dengue virus (serine protease), thrombin from bovine plasma (Thr), bacterial transferase (*E. coli MurA*), and a metalloprotease (*E .coli MetAP*). Considering the two serine proteases (NS2B-NS3 and thrombin) in the panel, the SAR of the aromatic FMMHs appears quite ″flat”. The substituent at the α-carbon has only a minor influence on the activity. For the other two enzymes, the SAR landscape appears considerably more rugged, with the α-substituent having a pronounced influence on the activity. In the case of the bacterial transferase *E. coli MurA*, considerable activities and selectivitiescan be observed for derivatives of all types of heterocycles.

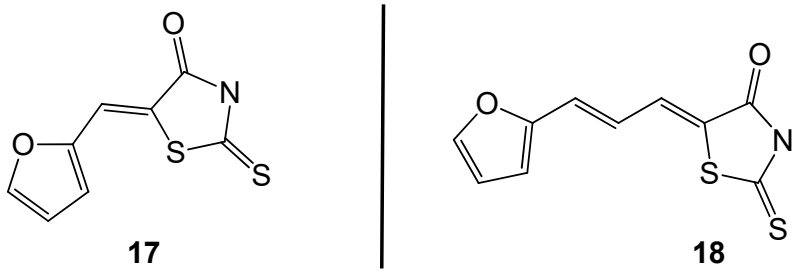


Fig. 2. Structure of (5*Z*)-5-[(furan-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **17** and (5*Z*)-5-[(2*E*)-3-(furan-2-yl)prop-2-en-1-ylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **18**.

The synthesis of hybrids of 4-aminoquinoline and rhodanine was reported by Chauhan et al.[30] This work describes compounds of general formula **19** (**Fig. 3**). These compounds were tested for *in vitro* antimalarial activity against chloroquine-resistant (K1) and chloroquine-sensitive (3D7) strains of Plasmodium falciparum. Their cytotoxicity against the VERO cell line was also investigated. For the corresponding 5-furfurylidene derivative **20** (**Fig. 3**), the concentration inhibiting parasite growth by 50% was IC_{50} = 35.0 μM in the case of chloroquine-sensitive strains 3D7 and 151.4 μM in the case of chloroquine-resistant strains, which was slightly higher. Anti-tuberculosis activity has also been investigated for this compound. However, the anti-tuberculosis effect was significantly lower than in the case of Isoniazid and rifampicin.

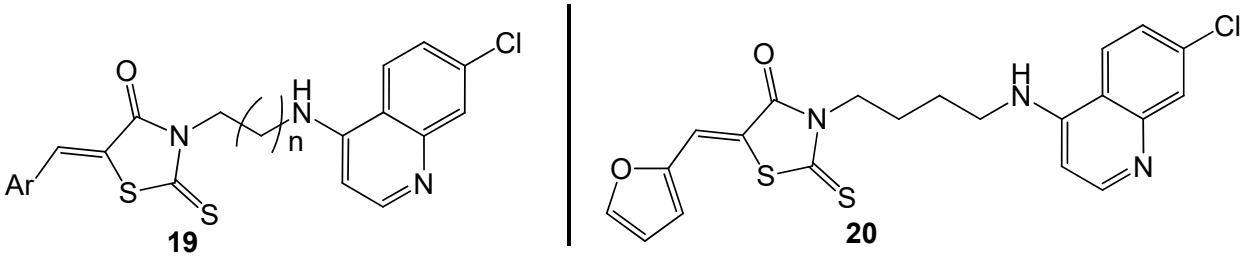
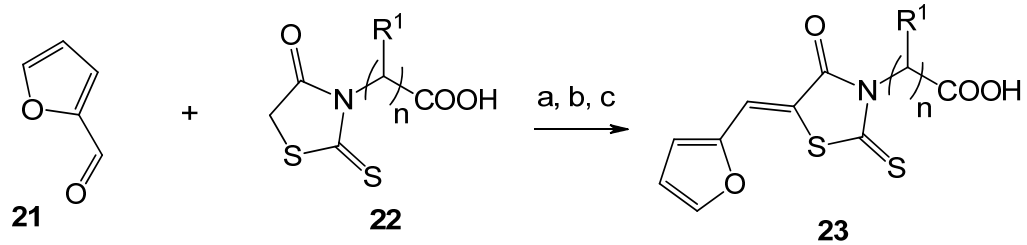


Fig. 3. Structure of (5*Z*)-3-{4-[(7-chloroquinolin-4-yl)amino]alkyl}-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one **19** and (5*Z*)-3-{4-[(7-chloroquinolin-4-yl)amino]butyl}-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one **20**.

The interaction of furan-2-carbaldehyde **21** with (4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl)alkancarboxylic acid **22** yielded a series of furfurylidene derivatives **23** (**Scheme 5**). They have antimicrobial[31] and antidiabetic[32, 33] properties.



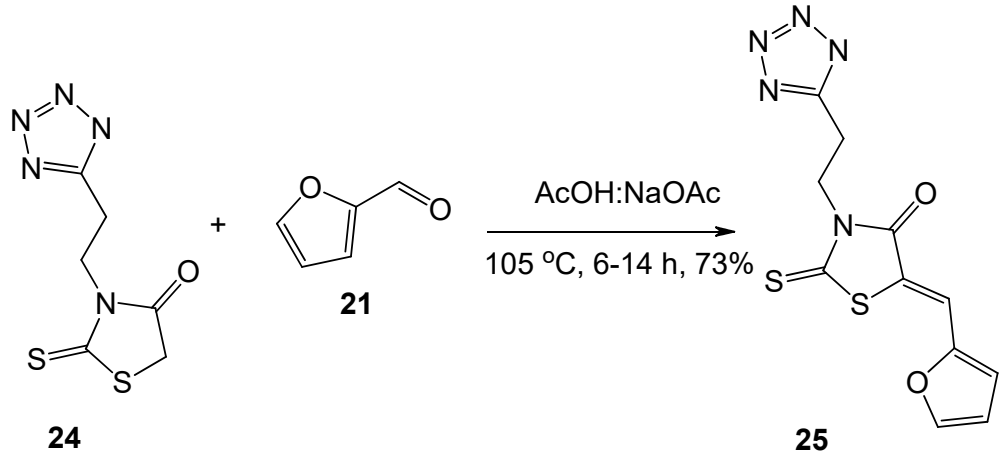
a: AcOH:NaOAc,105 °C, 6-14 h, 47-87%[31]

b: dry toluene, N-methyl piperazine, ammonium acetate, 110 °C, 15 h, 64%[32]

c: ethanol, piperidinium acetate, reflux[33]

Scheme 5. Synthesis of 3-{(5*Z*)-5-[(furan-2-yl)methylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl} alkancarboxylic acid.

Similar products **25** were obtained using furan-2-carbaldehyde **21** and 2-sulfanylidene-3-[2-(1H-tetrazol-5-yl)ethyl]-1,3-thiazolidin-4-one with tetrazole bioisosteric carboxylic group **24** (**Scheme 6**).[31] The resulting compound **25** showed antimicrobial properties.



Scheme 6. The reaction of 2-sulfanylidene-3-[2-(1*H*-tetrazol-5-yl)ethyl]-1,3-thiazolidin-4-one **24** with furan-2-carbaldehyde **21**.

Kumar et al. reported that acid **26** (**Fig. 4**) was investigated for their in vitro glucose uptake activity using rat-hemidiaphragm, both in presence and absence of insulin.[32] For it, the glucose uptake value was 9.04 ± 0.93 mg/g/45 min in the absence of insulin and 26.16 ± 1.18 mg/g/45 min in its presence. A comparative analysis of molecular similarity indices was also carried out for this compound and a number of similar ones.

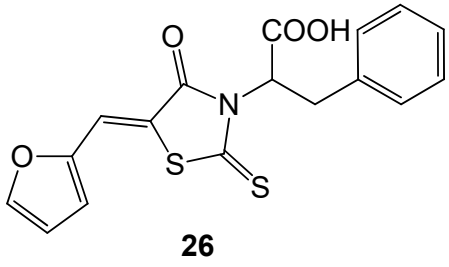


Fig. 4. Structure of 2-[(5*Z*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-3-phenylpropanoic acid **26**.

Liang et al.[31] designed inhibitors of the Pseudomonas aeruginosa heme oxygenase (pa-HemO) based on 3-(4-oxo-2-thioxothiazolidin-3-yl)propanoic acid. 3-{(5*Z*)-5-[(furan-2-yl)methylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl}propanoic acid **27** (**Fig. 5**) was found to exhibit insignificant activity with Ligand Grid Free Energy LGFE = 22.7 and Ligand Efficiency LE = 1.26. For this compound, the KD value calculated from three independent experiments was 38 ± 10mM.

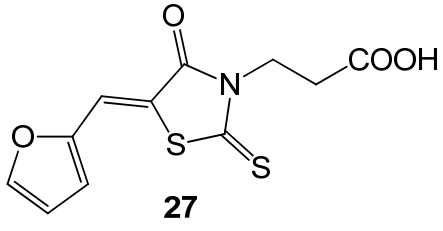
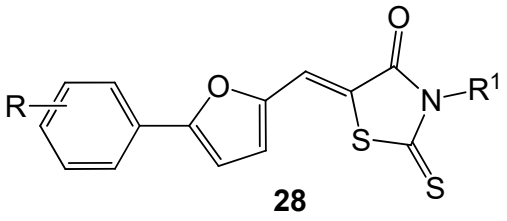


Fig. 5. Structure of 3-{(5*Z*)-5-[(furan-2-yl)methylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl}propanoic acid **27**.

2.3 Biological activity of 5\4-arylfurfurylidenerhodanines

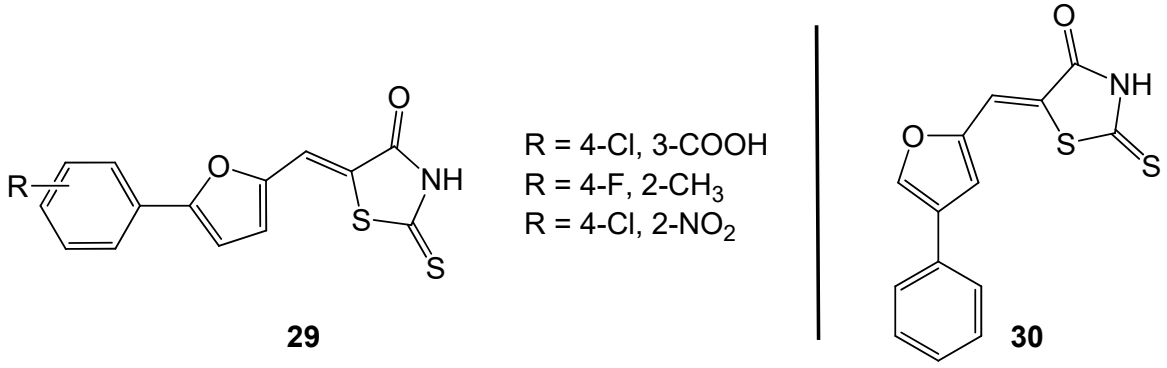
Among the derivatives of 5-furfurylidenerhodanine, the most studied are compounds containing an aryl substituent in the 5-th position of the 5\4-arylfuran cycle **28** (**Fig. 6**).



28

Fig. 6. Structure of (5Z)-3-R^1-5-[(5-arylfuran-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **28**.

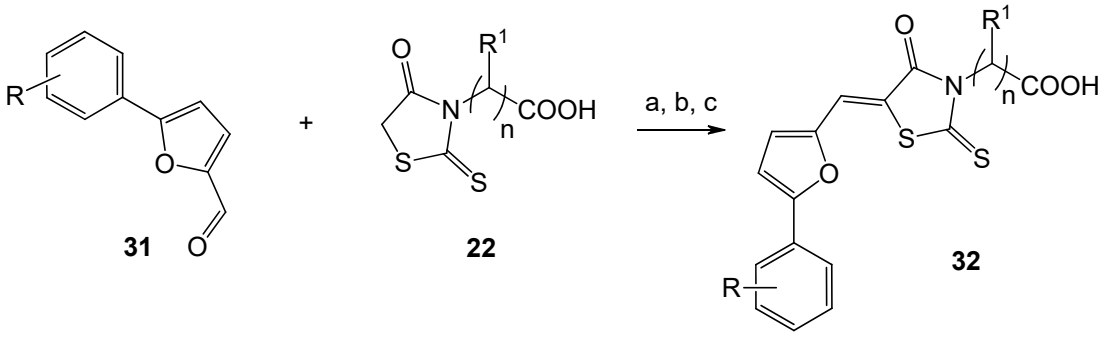
Vance et al. reported that a series of covalent antimicrobial inhibitors **29** and **30** (**Fig. 7**) targeting glutamate-racemase was identified using virtual screening.[34] Compounds from this series of inhibitors have antimicrobial activity compatible with β-lactam antibiotics, with significant activity against methicillin-resistant strains of *S. aureus*. These studies provide a platform for the development of antimicrobial agents with a novel mechanism of action against targets involved in bacterial cell wall biosynthesis. The results of these studies correlate with the data of work[35] regarding the antimicrobial activity of 5-isostructural arylfuryl isoxazoles.



29 **30**

Fig. 7. Structure of (5*Z*)-5-[(5-arylfuran-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **29** and (5*Z*)-5-[(4-phenylfuran-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-4-one **30**.

Similarly, by the interaction of 5-arylfuran-2-carbaldehydes **31** with rhodanine acetic acid, both under classical conditions and upon microwave activation, derivatives of {(5*Z*)-4-oxo-5-[(5-arylfuran-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-3-yl}alkancarboxylic acid **32** were obtained (**Scheme 7**). They are Anthrax Lethal Factor Protease inhibitors,[36] signal-regulating kinase inhibitors,[37] tyrosinephosphatase inhibitors and have antitumor[38,39] and antibacterial[40-42] properties. Also, authors proposed the use of such compounds in the treatment of Alzheimer's disease.[43]



31 **22** **32**

a: glacial acetic acid, anhydrous sodium acetate, 76-90%[38, 39]
piperidine and 10 drops glacial acetic acid in ethanol, 87-90%[40]
piperidine and 10 drops glacial acetic acid in ethanol, 35-49%[42]
b: ethanol (piperidine), 64-78%[37]
c: DMF in the microwave where it underwent four cycles of 1 min heating (140 °C, 1000W), 97%[36]

Scheme 7. The reaction of 5-arylfuran-2-carbaldehydes **31** with (4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl)alkancarboxylic acid **22**.

In particular, in the already mentioned work of Liang et al.,[31] the inhibitory ability of Pseudomonas aeruginosa heme oxygenase (pa-HemO) was also studied for compounds of general formula **33** (**Fig. 8**). It has been found that the introduction of an aryl substituent increases the activity. The best activity was observed for derivative **34** with a hydroxyl group in the aryl fragment (**Fig. 8**).

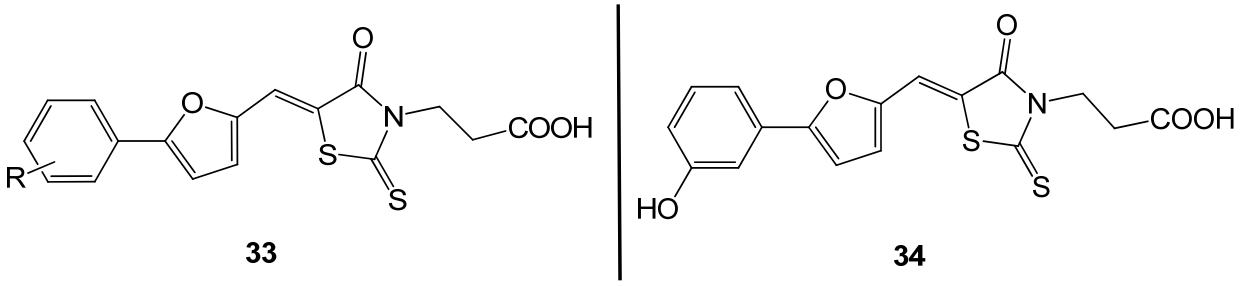
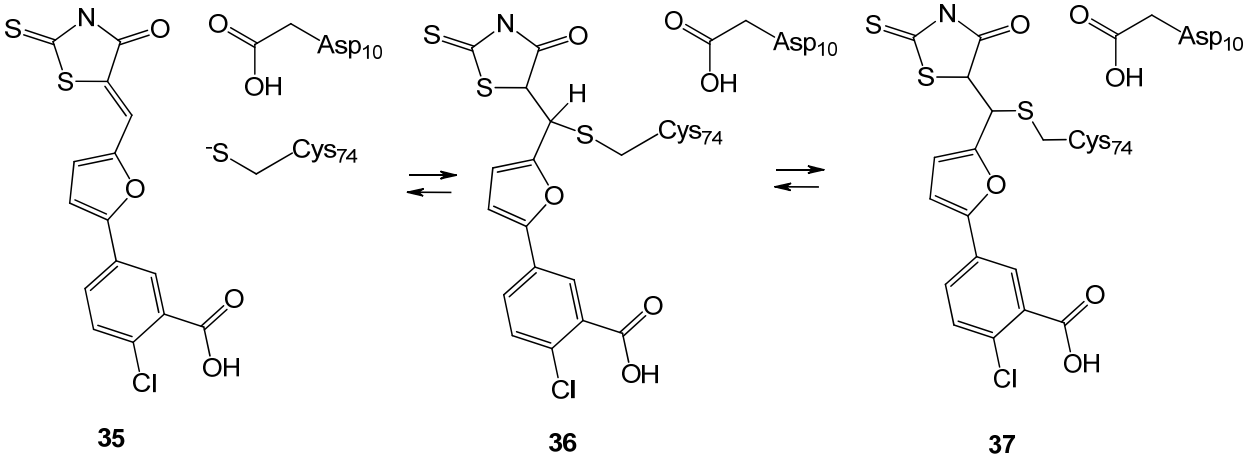


Fig. 8. Structure of 3-{(5Z)-4-oxo-5-[(5-aryl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-3-yl}propanoic acids **33** and 3-((5Z)-5-{[5-(3-hydroxyphenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid **34**.

A combination of enzyme kinetics studies, mass spectrometry data, and surface plasmon resonance experiments made it possible to establish the mechanism of ligand-target interaction. One of its manifestations is the nucleophilic 1,4-addition of the mercapto group of glutamate-racemase cysteine at the double bond in the 5-[th] position of rhodanine **35-37** (**Scheme 8**).



Scheme 8. The interaction of the mercapto group of glutamate-racemase cysteine and 5-arylfurfurylidenerhodanines.

In the studies of Rajamaki et al.,[44] among 5-arylfurfurylidenerhodanines, a new class of HIV-1 IN inhibitors was identified that can affect the formation of the IN viral DNA complex with the ligand. The most active were compounds **38** and **39** (**Fig. 9**), which are considered as prototypes for further optimization.

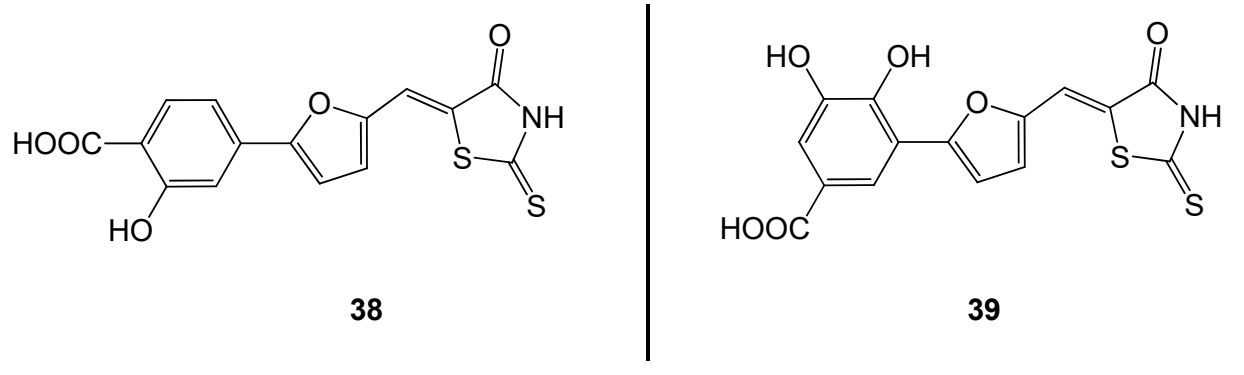


Fig. 9. Structure of 2-hydroxy-4-{5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid **38** and 3,4-dihydroxy-5-{5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid **39**.

On this topic, a new class of 2-thioxothiazolidin-4-ones has also been reported as potent inhibitors of lymphoid specific tyrosine phosphatase (Lyp).[45] This fact was established using high-throughput screenings. Chemical modification by incorporating known phosphotyrosine mimics (pTyr) led to the discovery of salicylate-based **40** (**Fig. 10**) inhibitors with submicromolar action .

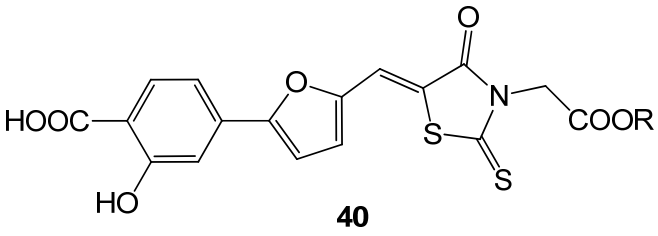


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Fig. 10. Structure of 2-hydroxy-4-(5-{(Z)-[3-(2-alcoxy-2-oxoethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid **40**.

A series of compounds that effectively inhibit anthrax lethal factor (LF) metallo-protease with micromolar and submicromolar activity is described by Johnson et al.[46] The best activity was shown by compound **41** (**Fig. 11**) with an IC_{50} value of 0.19 mM.

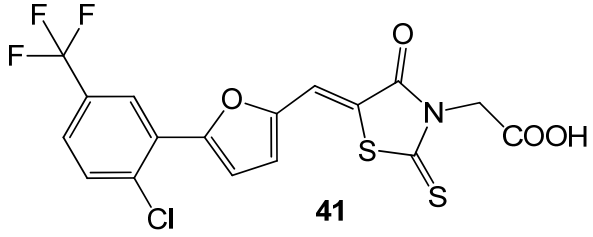

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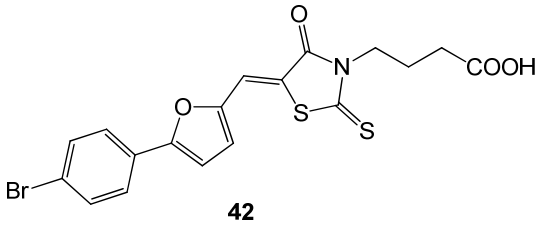
Fig. 11. Structure of [(5*Z*)-5-({5-[2-chloro-5-(trifluoromethyl)phenyl]-2-furyl}methylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]acetic acid **41**.

Volynets et al.[37] reported on a new class of ASK1 inhibitors, namely 5-(5-aryl-furan-2-ylmethylene)-2-thioxothiazolidin-4-one-3-alkylcarboxylic acids, which was identified using a virtual screening and biochemical tests. Increased activity of apoptosis signal regulating kinase 1 (ASK1) is associated with a number of diseases, and ASK1 inhibitors may become important compounds for pharmaceutical use. It was found that the most active compounds 4-((5Z)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo1,3-thiazolidin-3-yl)butanoic acid **42** and 6-((5Z)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)hexanoic acid **43** (**Fig. 12**) inhibit ASK1 from IC50 0.2 mM.



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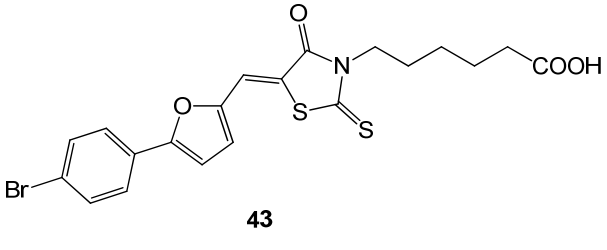

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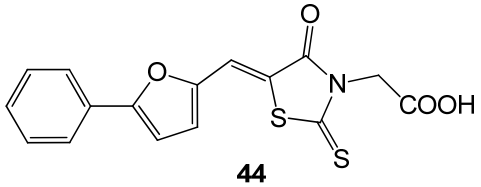
Fig. 12. Structure of 4-((5Z)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo1,3-thiazolidin-3-yl)butanoic acid **42** and 6-((5Z)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)hexanoic acid **43**.

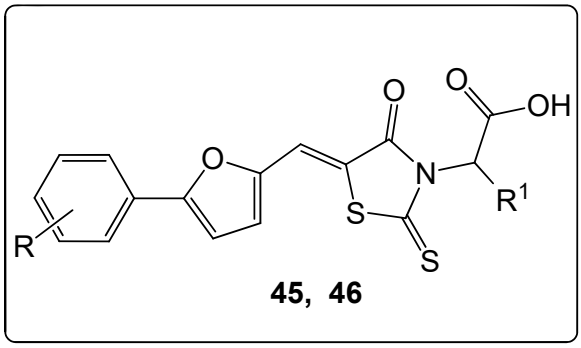


44

Fig. 13. Structure of {(5Z)-4-oxo-5-[(5-phenylfuran-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-3-yl}acetic acid **44**.

{(5Z)-4-oxo-5-[(5-phenylfuran-2-yl)methylidene]-2-sulfanylidene-1,3-thiazolidin-3-yl}acetic acid **44**[43] (**Fig. 13**) was considered as a promising tool for imaging neurofibrillary tangles (NFTs) in the diagnosis of Alzheimer's disease. However, it has been found to exhibit significantly lower activity than other 5-heterylidene rhodanines.

In the work of Jian Che et al.[40] two series of arylfuran derivatives **45** and **46** (**Fig. 14**) containing a rhodanine fragment were synthesized and their antibacterial activity was studied. Most of these compounds have shown high inhibitory activity against various Gram-positive bacteria, including multidrug-resistant strains with minimum inhibitory concentration (MIC) values ranging from 2–16 μg/ml. In particular, the compound with R = 2,5-Cl_2 turned out to be the most potent inhibitor of the synthesized compounds against multidrug-resistant strains, with an MIC value of 2 or 4 μg/ml. None of the tested compounds showed activity against the gram-negative bacteria Escherichia coli 1356 at 64 mg/ml. The study of the cytotoxicity of these compounds showed that they show a low level of toxicity against HeLa cells.[40]



45, 46

45: R^1 = $CH(CH_3)CH_2CH_3$

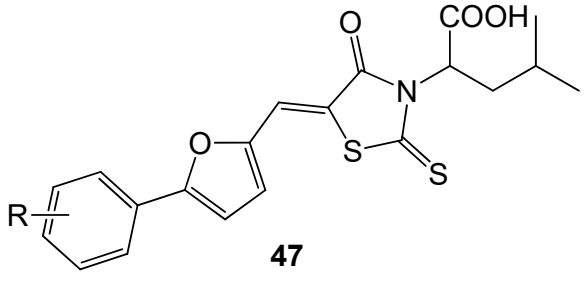
R = 4-CH_3; 4-OCH_3; 3-Cl,4-F; H; phenyl(3,4-fused); 4-Br; 4-Cl; 3-Cl; 2-Cl; 2-CH_3; 2-F; 2,5-Cl_2

46: R^1 = $CH_2C_6H_5$

R = 3-Cl,4-F; 4-OCF_3; 4-Br; 2-Cl; 3-Cl; 4-Cl; 2-F; H; phenyl(3,4-fused); 4-CH_3; 2-CH_3; 2,5-Cl_2

Fig. 14. Structure of {(5Z)-4-oxo-5-[(5-aryl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-3-yl} alkancarboxylic acids **45**, **46**.

The series (S,Z)-4-methyl-2-(4-oxo-5-((5-arylfuran-2-yl)methylene)-2-thioxothiazolidin-3-yl)pentanoic acid **47a-h** (**Fig. 15**) was synthesized using the Knowevagel reaction.[42] For them, *in vitro* antibacterial activity was studied. This test showed that all synthesized compounds have good antibacterial activity against Gram-positive bacteria (including multidrug-resistant clinical isolates) with minimum inhibitory concentrations (MICs) in the range of 2-4 μg/mL. Especially compounds **47c**, **47d**, **47e** and **47f** were the most potent, with MIC values of 2 μg/ml against four Gram-positive bacterial strains.

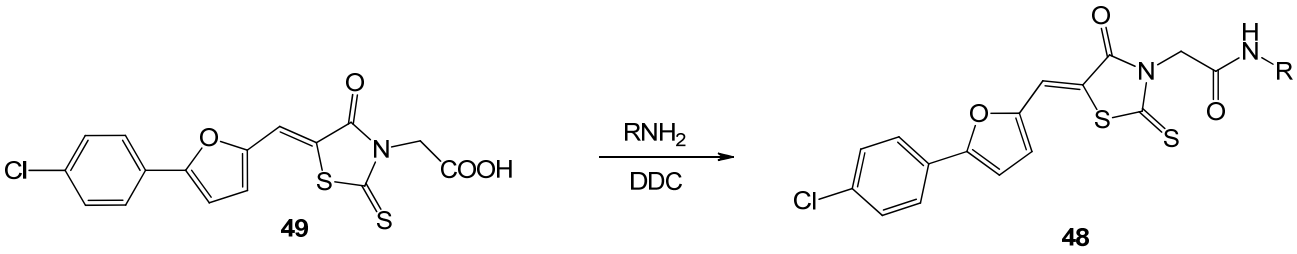


47

47: R = 2,5-Cl_2(**a**), 2-Cl(**b**), 3-Cl(**c**), 4-Cl(**d**), 3-Cl, 4F(**e**), 4-Br(**f**), 2-F(**g**) 4-CF_3O(**h**)

Fig. 15. Structure of (*S*,*Z*)-4-methyl-2-(4-oxo-5-((5-arylfuran-2-yl)methylene)-2-thioxothiazolidin-3-yl)pentanoic acids **47a-h**.

The antitumor properties of 2-((5*Z*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-R-acetamide **48** were studied by Chandrappa et al.[38, 39] They were synthesized by the condensation of various amines, both aliphatic and aromatic or heterocyclic in nature, with ((5*Z*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid **49** (**Scheme 9**). The authors of these works argue that these compounds may be candidates for antitumor therapy with the ability to inhibit tumor angiogenesis and tumor cell proliferation.



Scheme 9. Synthesis of 2-((5*Z*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-R-acetamide **48**.

In work[47] was described the design and synthesis of a series of (Z)-2-(5-benzylidene-4-oxo-2-thioxothiazolidin-3-yl)-N-phenylacetamide derivatives (**Fig. 16**) and evaluation of their microtubule-modulating and anticancer activities *in vitro*. Proliferation assays identified the potent of the antiproliferative compounds, with 50% inhibitory concentrations ranging from 7.0 to 20.3 μM with A549, PC-3, and HepG2 human cancer cell lines.

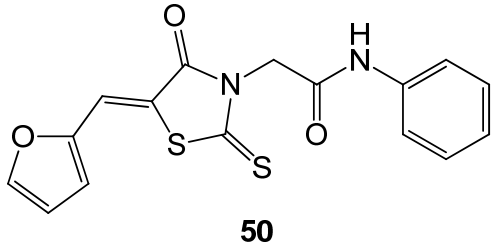
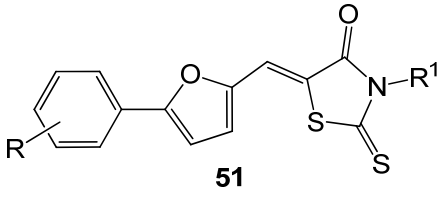


Fig. 16. Structure of 2-[(5*Z*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-N-phenylacetamide **50**.

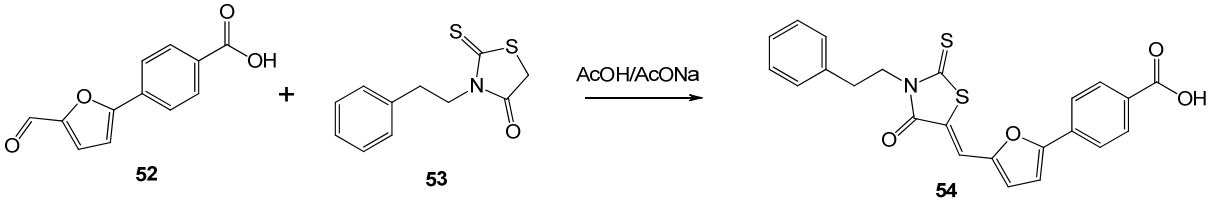
It should be noted that structurally related 2-indolinone derivatives demonstrated a similar profile of anticancer activity.[48]

Using phqarmacological screening Suree et al., it was possible to identify compounds **51** (**Fig. 17**) that inhibit the enzymatic activity of the *S.aureus SrtA sortase.*[49] Compounds that inhibit SrtA may function as potent anti-infective agents, as this enzyme is responsible for cell wall virulence factors.



R^1 = Me; Et; Pr; Allyl; $PhCH_2$

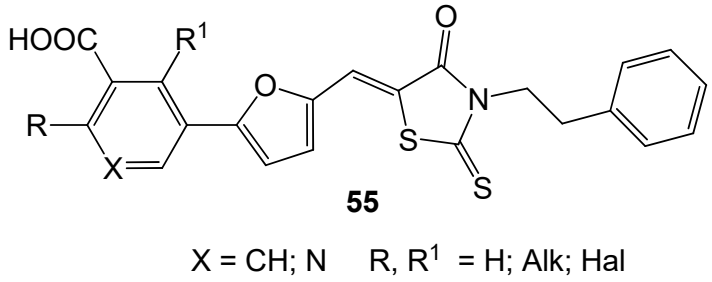
Fig. 17. Structure of (5*Z*)-3-R^1-5-[(5-aryl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-ones **51**.



Scheme 10. Synthesis of 4-(5-{(Z)-[4-oxo-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid **54**.

In study[50] potential fusion intermediates inhibitors based on the rhodanine structure were synthetized. The obtained derivatives were tested for cytotoxicity and for antiviral activity in human cells infected with HHV6. Among the synthetized derivatives, compound **54** (**Scheme 10**) showed a significative inhibitory effect on viral replication that lasted over 7 days, probably attributable to the particular combination of hydrophilic and hydrophobic substituents to the rhodanine moiety.

A series of 5-(5-{(*Z*)-[4-oxo-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic/nicotinic acids **55** (**Fig. 18**) was investigated for anti-HIV-1 activity and cytotoxicity on MT-2 cells.[51] All of them were found to have high anti-HIV-1 activity, and some of them showed inhibitory activity against HIV-1IIIB and 94UG103 replication in the <100 nM range, suggesting that these compounds may serve for the development of new HIV fusion inhibitors with small molecules.

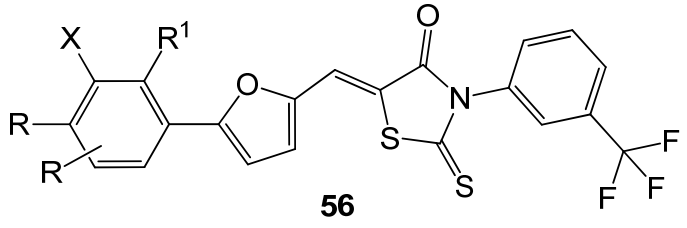


55

X = CH; N R, R^1 = H; Alk; Hal

Fig. 18. Structure of 5-(5-{(*Z*)-[4-oxo-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic/nicotinic acids **55**.

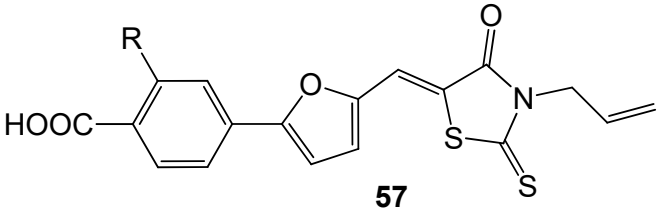
The work of Jiang et al.[52] reported the synthesis of (5*Z*)-5-[(5-aryl-2-furyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-ones **56** (**Fig. 19**). The presented compounds effectively inhibited HIV infection against both laboratory-adapted and primary HIV-1 strains and blocked HIV-1-mediated cell-cell fusion and gp41 six-helix bundle formation.



56

Fig. 19. Structure of (5*Z*)-5-[(5-aryl-2-furyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-ones **56**.

Villain-Guillot et al.[53] studied the relationship between the structure and activity of a series of phenylfuranylrhodanines as antibacterial inhibitors of RNA polymerase. The molecules were evaluated for their ability to repress transcription and influence the growth of live bacteria in suspension or biofilm. Also, this paper presents the propensity of these compounds to interact with albumin, which is a critical parameter for the discovery of antibacterial drugs. The most active of these compounds of general formula **57** (**Fig. 20**) inhibited the transcription of Escherichia coli RNA polymerase at concentrations of 1^{-10} M and have a promising effect against various gram-positive pathogens, including Staphylococcus epidermidis biofilms, which are the main cause of nosocomial infection.



57

R = H; Cl

Fig. 20. Structure of 4-{5-[(*Z*)-(3-allyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}-2-R-benzoic acid **57**.

Esterification of the carboxylic group in these compounds led to a complete loss of biological activity.[54] A similar effect was observed in the case of compounds where the strategy of bioisosteric transformation of the carboxyl group was used (compounds **58** and **59** (**Fig. 21**)).[53]

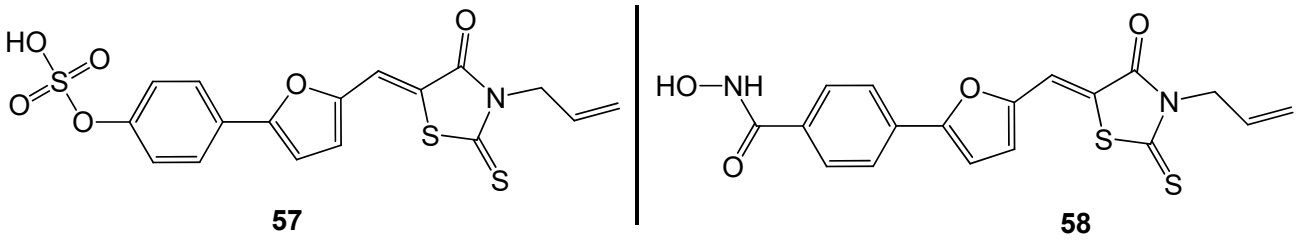


Fig. 21. Structure of 4-{5-[(*Z*)-(3-allyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}phenyl hydrogen sulfate **57** and 4-{5-[(*Z*)-(3-allyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}-*N*-hydroxybenzamide **58**.

In their work on this topic, Song et al. synthesized a small library of compounds of this class.[55] Also, the same authors investigated the antitumor activity of these compounds against breast cancer cells MCF-7, colon cancer HT-29 and Ramos Human Caucasian Burkitt's Lymphoma cells. Compounds **59** and **60** (**Fig. 22**) were found to show low IC_{50} values for MCF-7 cells.

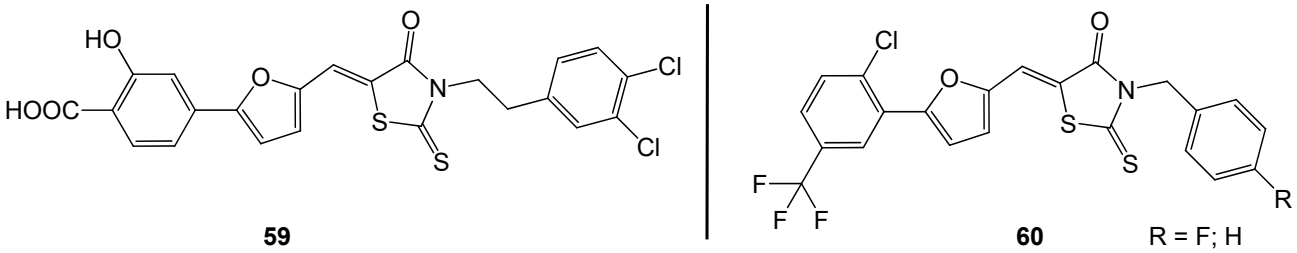


Fig. 22. Structure of 4-[5-((Z)-{3-[2-(3,4-dichlorophenyl)ethyl]-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene}methyl)-2-furyl]-2-hydroxybenzoic acid **59** and (5Z)-3-(4-R-benzyl)-5-({5-[2-chloro-5-(trifluoromethyl)phenyl]-2-furyl}methylene)-2-thioxo-1,3-thiazolidin-4-one **60**.

Regulation of NF-jB activation by inhibition of IKKb has been identified as a promising target for the treatment of inflammatory and autoimmune diseases such.[55] In order to develop new IKKb inhibitors, a high throughput screen of about 8000 library compounds was carried out. During the research, compounds **61** and **62** (**Fig. 23**) were identified, which have a blocking effect on NF-jB activation and TNFa production in the cell, as well as inhibitory activity against IKKb. Among these compounds there are also derivatives of 5-furfurylidene rhodanine.

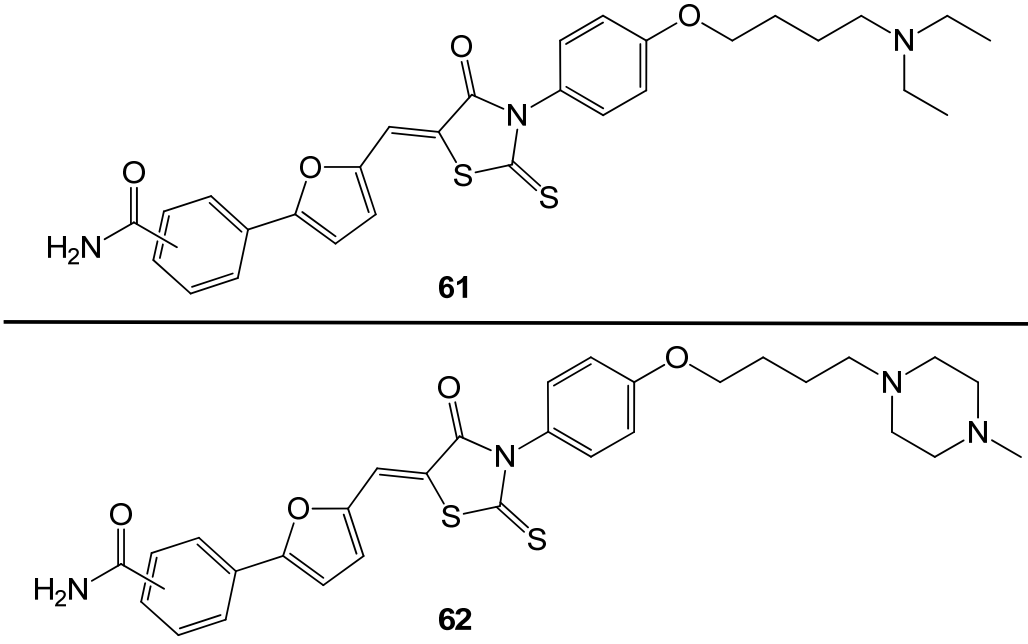
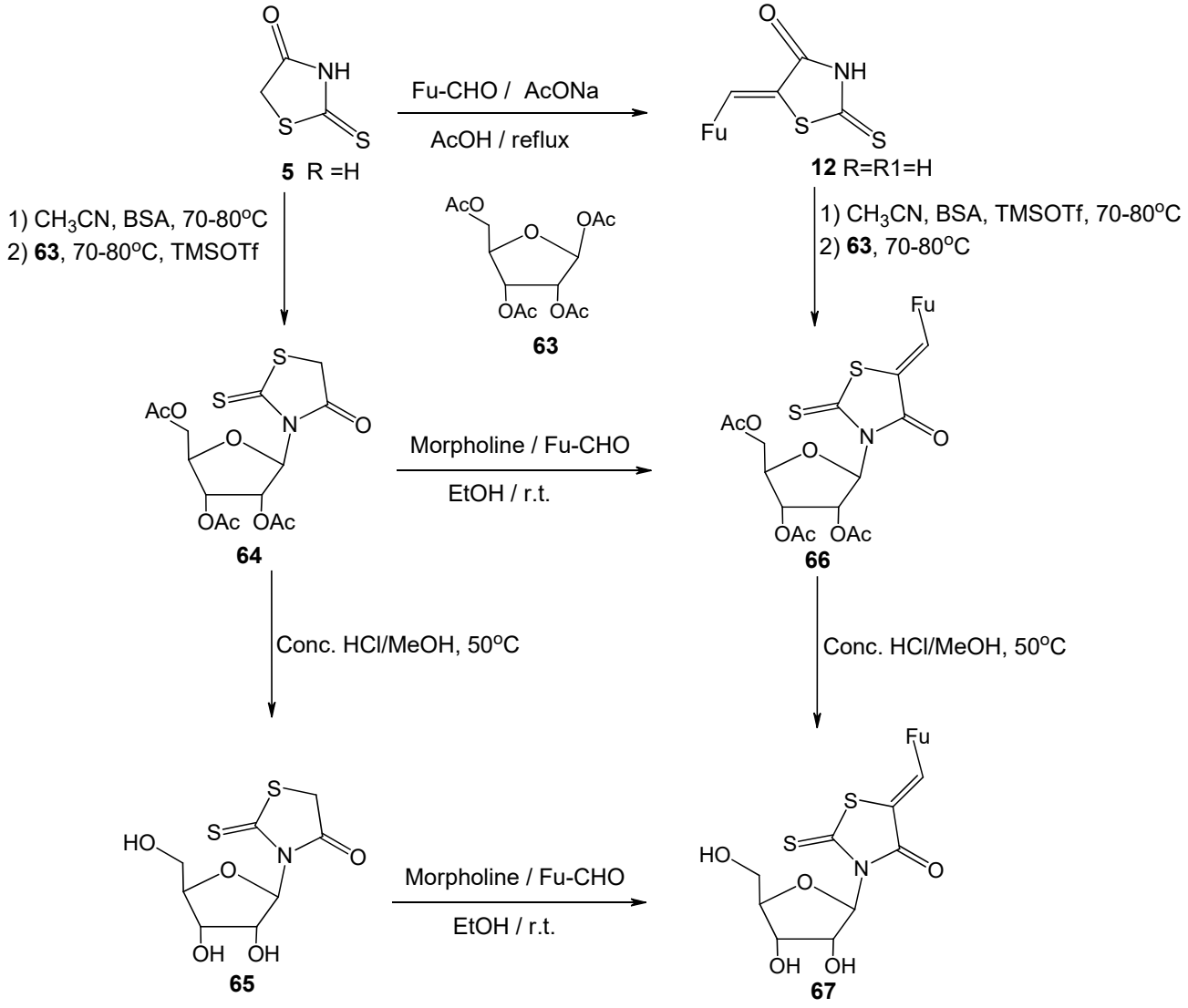


Fig. 23. Structure of 3/4-{5-[(*Z*)-(3-{4-[4-(diethylamino)butoxy]phenyl}-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzamide **61** and 3/4-{5-[(*Z*)-(3-{4-[4-(diethylamino)butoxy]phenyl}-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzamide **62**.

N-ribosylation and N-mannosylation compounds have a great role in compounds activity as anticancer. The reaction of 2-thioxo-4-thiazolidinone (rhodanine) derivatives, as aglycon part, was done with ribofuranose and mannopyranose sugars (glycone part) followed by deacetylation without cleavage of the rhodanine under acidic medium. All final the new deprotected nucleoside **67** (**Scheme 11**) was screened against leukemia 1210, and was found to be considerably less potent (IC_{50}% 6.3 μM) than doxorubicin (IC_{50}% 0.02 μM). Thiophene bioisoster has better activity (IC_{50}% 1.6 μM).[5]



Scheme 11. Synthesis of 5-((*Z*)-2-furylidene)-3-(*β*-*D*-ribofuranosyl)-2-thioxo-4-thiazolidinone **67**.

Summarizing the above, in addition to the wide spectrum of biological activity of rhodanine-furan conjugates, it should be noted that many bioisosteric structures are known for both the rhodanine and furan cycles, which expands the prospects for using this class of conjugates in drug design.[57,58] As a rule, good pharmacokinetic parameters are predicted for this class of compounds.[59]

3. Conclusions

Rhodanine and furan are an important class of organic compounds for drug development; they constitute an essential class of lead compounds to develop new pharmacevtical substances for treatment various disease with such a diverse range of biological activities, they have attracted much attention from researchers focusing on synthesizing different to developing novel and more potent drugs. Chemically, rhodanine can be easily synthesized from the commercially available furan precursor. It allows to quickly create a variety of combinatorial libraries of this type of compounds. This information in our review will guide medical scientists to purposefully influence the design of new organic compounds for the treatment of various diseases.

Acknowledgements

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