PART- IV

STUDIES ON RHODANINE Derivatives

Introduction

Last decade’s problem of chemistry and pharmacology of 4-thiazolidones and related heterocyclic systems that have been of interest for the pharmaceutical science since the beginning of 20th century, is in principle now undergoing new development. A series of fundamental reviews have been dedicated to 4-thiazolidones. It is worth to mention, that during last years the interest in 2, 4-thiazolidimidione derivatives has been heightened markedly, because of their development as a new class of antidiabetic (insulin-sensitizing) drugs (troglitazone, pioglitazone and darglitazone). These drugs are currently used for the treatment of type 2 Diabetes Mellitus. The 2-thioxo-4-thiazolidone (rhodanine) derivatives- epalrestat- is a highly active aldose reductase inhibitor, which possesses a perspective for the treatment of diabetic complications (cataract, nephropathy, and neuropathy).

4-Oxo-thiazolidines are the derivatives of thiazolidines which belong to an important group of heterocyclic compounds. Thiazolidinones with carbonyl group at positions 2, 4, and 5 have been the subject of extensive study in the recent past. Numerous reports which appeared in the literature have highlighted their chemistry and uses. Brown F C \(^1\) in 1961 gave a comprehensive review on 4-thiazolidines. Later on, Zolotorewa K A et al \(^3\) in 1966 prepared an article which deals with the use of thiazolidinones derivatives as stabilizers for polymeric materials. After this Danila G \(^4\) in 1979 published a review on the preparation of rhodanines (2-thiono-4-thiazolidinones) and their uses as intermediates in organic synthesis.

Diverse biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anti-inflammatory, antithyroidal, anaesthetic\(^5\)\(^6\), analgesic\(^7\), hypnotic\(^8\), sedative\(^9\), anticonvulsant\(^10\), antitubercular\(^11\), spasmpreventive\(^12\) etc. have been found to be associated with thiazolidinone derivatives.

A row of 5-arylidene-4-thiazolidones (phospholipase A2 inhibitors and dual COX2/5-LOX inhibitors) is under clinical trials as potential anti-inflammatory drugs.
Some original 4-thiazolidones are undergoing different stages of clinical trials as thyromimetic, antimicrobial, antiviral, anti-ischaemic, and cardiovascular, anticancer, thrombolytic drugs. The availability of recent material on chemistry, pharmacology and some aspects of clinical use of 4-thiazolidones, prompted us to select the research target. Accordingly to actuality for modern medicinal chemistry we have paid attention to 2, 4-thiazolidinedione, rhodanines and 2 imino/amino-4-thiazolidones derivatives. Some of thiazolidinones are employed in the synthesis of merocyanine dyes which are used in photographic film industries.¹³

Thiazolidine (i) with a carbonyl group at 4-position is known as 4-thiazolidinone (ii) or 4-oxo-thiazolidines (ii). Substituents at position 2, 3 and 5 are known and such a group can form alkyl, aryl or aryl-alkyl thiazolidinone (iii). The oxygen attached to C-2 would make 2, 4-thiazolidinone(iv). Sulphur atom attached at C-2 makes rhodanine (v) and imino group from 2-imino-4 thiazolidinediones (vi), which is known as pseudothiohydantoin.

\[
\begin{array}{c}
\text{(i)} \\
\text{(ii)} \\
\text{(iii)} \\
\text{(iv)} \\
\text{(v)} \\
\text{(vi)}
\end{array}
\]

2-Sulfanyl acetic acid has been recognized as a primary product of hydrolysis of 3- phenyl-2-phenylimino-4-thiazolidinone¹⁴.

**Methods of 4-thiazolidone cycle construction**

The synthetic methods leading to the 4-thiazolidone ring can be divided into three groups:

a) [2+3] cyclocondensation,

b) Synthesis of 4-thiazolidones from similar heterocycles

c) Ring transformation of some heterocycles into the 4-thiazolidone ring.
A classical approach, which is effectively used for construction of the 4-thiazolidone ring, is the [2+3]-cyclocondensation. Various derivatives of α-halogenated carboxylic acids, maleic acid derivatives, aroylacrylic acids have been used as equivalent of dielectrophilic synthon \([C_2]_2^+\) in reactions with N, S-nucleophiles. Dithiocarbamimates as precursors (Scheme-I) to rhodanines (1) represents one variant of this approach.\(^{15-17}\) In an analogy of mentioned method the substitution of CS\(_2\) to COS yields 2, 4-thiazolidinedione (1) derivatives.\(^{18}\) Krus and co-workers\(^{19}\) have applied the dithiocarbamate method of rhodanines synthesis (2) using chloroacetyl chloride, which reacted with N-alkyl (aryl) dithiocarbaminic acid salts in the presence of triethylamine. Use of unsaturated carboxylic acids derivatives instead of chloroacetic acids derivatives in the last step is an interesting modification of this method. Reaction of maleimides\(^{20}\)
or aroylacrylic acids \(^{21-22}\) with dithiocarbaminates yields amides of rhodanine-5-acetic acids (3) and 5-aroylmethylen rhodanines (4) accordingly.

\[
\begin{align*}
\text{Thiosemicarbazones} & \\
\text{Scheme-2} & \\
\text{Where, } R_3 = R_4 = H, \text{ Ar, Alk., etc} & \\
\end{align*}
\]

Reaction of chloroacetamides and potassium ethyl xanthogenate in the system CS\(_2\) - sodium tert-butylate in DMF at \(-10^\circ\text{C}\) yields the corresponding 3-alkyl rhodanines \(^{23}\)

2, 4-thiazolidinediones are synthesized by the condensation of alkyl (aryl) thiocarbamates (xanthogenamides) with \(\alpha\)-halogenated carboxylic acids in EtOH or acetic anhydride. \(^{24-25}\)

Various thioureas and thiosemicarbazones as N, S-nucleophiles are used for the synthesis of 2-imino-4-thiazolidones (pseudothiohydantoines) derivatives (5a/5b). As mentioned above reaction \(\alpha\)-halogenated carboxylic acids, \(^{26-29}\) ethyl (3-aryl-2-bromo) propionates, \(^{30}\) maleic anhydride and maleimides, \(^{31-33}\) aroylacrylic acids \(^{34}\) were proposed as equivalent of the dielectrophilic synthon [C\(_2\)]\(^+\) (Scheme-2). 3-Nonsubstituted 2-arylamino-4-thiazolidones display prototropic amino-imino tautomerism (Scheme-3) that was confirmed by their IR and \(^1\)H-NMR-spectra. \(^{35}\)
The approach mentioned has been successfully used for the synthesis fused heterocyclic systems with a pseudothiohydantoine scaffold on the base of the cyclic ureas. For example, the reaction with octahydro-2-quinazolin-ethiones with aliphatic or aromatic amides of chloroacetic acid or iodoacetamide will lead to thiazolo [2, 3-b] quinazoline-3-ones.\textsuperscript{36}

Some epoxy acids (6) (cis- and trans-epoxysuccinic, 2, 3-epoxybutyric and methyl –cis-epoxysuccinic acids) constitute another equivalent of the dielectrophilic synthon \([\text{C}_2\text{H}_2]^+\) in \([2+3]\)-cyclocondensation with thiourea (Scheme-4) for obtaining 5-substituted pseudothiohydantoin (7) and 2, 4-thiazolidinedione (8).\textsuperscript{37}

For the synthesis of rhodanine derivatives (10) based on aromatic amines and hydrazides of aromatic carboxylic acids, the Holmberg method is more effective. This approach is based on the reaction between thiocarbonyl-bis-thioglycolic acid (9) and amino derivatives in ethanol or ethanol-water medium. (Scheme-5).\textsuperscript{38}
Reaction of α-halogenated carboxylic acid with rhodanines ammonium or alkali salts is an important method of 3-non-substituted 4-thiazolidones (Scheme-6). This reaction was suggested by M. Nencki for rhodanines synthesis. Later Grishchuk A. P. and Baranov S. M. developed this method and expanded its synthetic possibilities, especially for obtaining of 5-substituted rhodanines (11). 2, 4-Thiazolidinediones (12) can be obtained in good yields by condensation of α-mercaptocarboxylic acids with cyanates. Various 4-thiazolidine-5-acetic acid have been synthesized by reacting mercaptosuccinic acid with compounds containing cyano groups. 2, 4-Thiazolidinediones is a product of heterocyclisation of rodanacetic (thiocyanocetic) acid or its methyl ester in the presence of hydrochloric acid.

Amides of α-diethoxyphosphoryl-α-thiocyanopropionic acid undergo cyclisation under basic catalysis to the corresponding 2-iminothiazolidones-4, that can be hydrolyzed to the following thiazolidinediones by heating in mixture 10% HCl and EtOH. In one-
step the hydrolysis of rodanacetate in the presence of aromatic aldehydes will give 5-arylidene-2, 4-thiazolidinediones in good yields. 47-48

Scheme-7

J. Pirki and J. Podstat have synthesized 3-allylrhodanine (13) using the thiocyanate method following the reaction of thioglycolic acid with potassium thiocyanate and allyl bromide. 49 2, 4-Thiazolidinediones (14) have been obtained following the reaction of thioglycolic with isocyanates. 50 (Scheme-7)

Reactions of rhodanines

The methylene carbon atom at position-5 of thiazolidinone is active and it possesses nucleophilic activity and attacks an electrophilic centre. 51-54

(i) Friedel-Craft reaction

Heating of 5-arylidenerhodanines (15) with dimethylsulphate without solvent and further hydrolysis by dilute ethanol (Scheme-8) is effective for the preparation of 5-arylidene-2, 4-thiazolidinediones (17). 55-61 Another variant of 2, 4-thiazolidinediones (19) syntheses depend on rhodanines (18) alkylation by chloroacetic acid. Chloroacetic acid acts both as alkylation and hydrolyzing agent. 62 3, 5-Disubstituted 2, 4-thiazolidinediones can be obtained from the corresponding rhodanines derivatives following the action of oxidizing agents. Rhodanines (20) oxidation by perchlorobenzoic acid in ether or acetone yields to corresponding thione-S-oxides (21), which by oxidation by KHSO₅ in the presence of 18-crown-6 are converted to 2,4-thiazolidinediones (22). 63
(ii) **Ring cleavage with alkali.**

Granacher\(^{64-65}\) has shown the applicability of rhodanine to organic syntheses. Its active methylene group permits reactions with aldehydes yielding stable condensation products. These are easily cleaved with alkali to thioketo acids (24) which are believed to exist in equilibrium with the tautomeric sulfhydryl forms since they give a deep green color with ferric chloride. Oximino acid (25), produced by the action of hydroxyl amine on the thioketo acids, can be converted to $\alpha$-substituted acetic acid (26) with acetic anhydride followed by the action of alcoholic KOH. Oximino acid (25), can be converted to aryl ethylamine (28) with acetic acid followed by reduction with Palladium\(^{66}\). Thioketo acid can be converted with sodium amalgam to amino acids (27).\(^{67}\)\((\text{Scheme-9})\)
(iii) Reaction of Grignard Reagent (R'MgX)

Grignard reagents add to the double bond of the lateral chain. Rhodanine having less tendency for tautomerization, proved to be stable towards the action of phenylmagnesium bromide. Thus showing the stability of the hetero ring towards the action of Grignard reagents.⁶⁸ (Scheme 10)
Effect of substituent at 3-position.

The synthesis of 5-(5-nitrofurylidene) rhodanine was reported by Sasaki \(^{69}\) in 1954. Owing to its poor water solubility appeared to lack promise as an antibacterial agent. Later, however, Koschucharoff \(^{70}\) found it to be the most active of a series of 5-nitrofurylidene derivatives tested against a variety of fungi, including *Candida albicans*, *Trichophyton*, *Epidermophyton* and *Microspore*. Parent Rhodanine derivatives was one of the more active compounds tested, exhibiting good antibacterial, antifungal and antiprotozoal activity. N-alkylation appeared to decrease antibacterial activity progressively in the rhodanine series as the size of the alkyl group increased. Introduction of hydrophilic groups in the N-alkyl substituent also resulted in greatly decreased activity, suggesting that solubility and aq-lipid partitioning are not the only factors responsible for reduction of activity resulting from N-substitution. This view is further supported by the high bacteriostatic activity observed for the N-phenyl derivatives. Thio tautomerism quite likely as in unsubstituted 3-position, but impossible in 3-substituted derivatives is also excluded as an important factor. Generally aldehyde condensed with rhodanine in the presence of basic catalysts. Some time basic catalyst had to be avoid because of the instability of this compound to alkaline condition. \(^{71}\)

Methods of 4-thiazolidone cycle modification

The most reactive positions in 4-thiazolidone's molecule are 3 and 5, which determine the major directions of heterocycle modification.

Approach to the synthesis of 3,5-disubstituted 4-thiazolidones in general include 2 groups of methods: a) synthesis of 3,5-disubstituted 4-thiazolidones by reactions in position 3 of the thiazolidone cycle and b) synthesis of 3,5-disubstituted 4-thiazolidones by reactions in position 5 of the thiazolidone cycle. In 5-position of 4-thiazolidones the methylene group is active enough, \(^{72-73}\) which is why one of the most studied reactions of 4-thiazolidones modification of the mentioned position.
It is worthy to estimate, that Knoevenagel condensation of the C-5 active methylene of 4-thiazolidones with oxo compounds under basic catalysis yielding of 5-arylidene derivatives constitute an efficient way to new biologically active substances. 5-Arylidene-4-thiazolidones (29) display a wide spectrum of pharmacological properties. It is known, that such reactions can be promoted by sodium hydroxide,\textsuperscript{74-75} sodium acetate in the presence of acetic acid and its anhydride,\textsuperscript{76-82} sodium acetate at 140-190°C, ammonium hydroxide or its mixture of methylamine with acetic acid,\textsuperscript{83} morpholine with acetic acid.\textsuperscript{84} In this reaction pyridine,\textsuperscript{85} piperidine,\textsuperscript{86-89} piperidinium acetate or benzoate in alcohol,\textsuperscript{90} piperidinium benzoate in toluene,\textsuperscript{91-96} piperidine and acetic acid in toluene have been studied.\textsuperscript{97} It was determined, that pyridine as a catalyst will result in low yields.\textsuperscript{84} Some authors have proposed as a route to 5-arylidene-3-R-rhodanines to use DMF and K\textsubscript{2}CO\textsubscript{3}, DMSO and K\textsubscript{2}CO\textsubscript{3} or mixture of DMF, acetic acid and sodium acetate,\textsuperscript{98} toluene and ammonium acetate,\textsuperscript{99} methanol and ethylenediammonium diacetate,\textsuperscript{100} mixture of ethanol and 25\% solution of ammonium hydroxide,\textsuperscript{101} mixture of ethanol and catalytic amount of piperidine,\textsuperscript{102} mixture of ethanol, NH\textsubscript{4}OH and NH\textsubscript{4}Cl, toluene and piperidine as well as dichloromethane using of molecular sieves 4A.\textsuperscript{102} Various bases have been tried,\textsuperscript{103-108} out of which sodium ethoxide in ethanol, sodium acetate in benzene, acetic acid or ethanol are frequently giving good yield.\textsuperscript{109-110}

For solid-phase combinational synthesis of 5-arylidenerhodanines, toluene as a solvent has been used during the cleavage step. Indicated reaction with aromatic aldehydes proceeded very smoothly to completion in toluene by heating only, whereas, with aromatic ketones the reaction proceeds only in the presence of ammonium acetate while heating. Heating at 110°C was essential to ensure complete condensation.

\begin{center}
\textbf{Scheme-11}
\end{center}
was therefore chosen for its relatively high boiling point and its good swelling property.  

D. Villemin and co-workers have synthesized the 5-arylidenederivatives by reacting 3-methyl rhodanine (30) with aromatic aldehydes on a surface of KF/Al₂O₃ in CH₂Cl₂ under microwave irradiation (Scheme-12). The same authors synthesized the original phosphonothiazolidones (31) under analogous conditions.

Scheme-12

Many aromatic aldehydes have been used in the Knoevenagel reaction and ¹H-NMR data (1 signal CH= at ~7.6δ) were almost independent of the aldehyde used and only the trans isomer was obtained.  

5-Arylidene derivatives, obtained by Knoevenagel reaction, are semi-products of some hypoglycemic thiazolidinediones. By reduction of 5-Arylidene-2, 4-thiazolidinediones by hydrogen at 10% Pd/C catalysis or Mg in methanol a series of drugs can be obtained, e.g. Pioglitazone, Rosiglitazone, and Enoglitazone. For the reduction of double bond of 5-arylidene-3-carboxymethylrhodanines Ohishi Yoshitaka and co-workers have used NaBH₄ in DMF. Ogawa Kazuo and Honna Takagi have carried out hydrogenation in aqueous medium in the presence of 10% Pd/C and NaHCO₃ under pressure of hydrogen.

To obtain 3,5-disubstituted rhodanines Ohishi Yoshitaka and co-workers have synthesized the ethyl ester of 5-(β-chloroethylidene)-3-carboxymethylrhodanine (34) by condensation of the ethyl ester of 3-carboxymethylrhodanine (32) and ClCH₂CHO in mixture of ether-water in the presence of NaHCO₃ following treatment of the intermediate (33) with TsOH (Scheme-13)
During condensation of thiazolidinedione or rhodanine and diethyl oxalate in alcohol in the presence of sodium alkoxide one ethoxy group reacts giving 2, 4-thiazolidinedione with glyoxalic acid residues in 5 positions. When performing this reaction in methanol in the presence of MeONa transesterification takes place.\(^{117}\)

During reaction of 4-thiazolidone-5-glyoxalic acids and their derivatives with aromatic aldehydes, nitroso compounds and diazonium salts substitution of glyoxalic residue is observed, classic 5-arylidene, 5-arylmino- and 5-arylazo derivatives will be obtained. Labile atom in position 5 of rhodanine molecule was the cause of reaction with carboxylic acid ortho esters.\(^{118}\) Thus 3-carboxymethylrhodanine (35) reacts with orthoformate ester in acetic anhydride leading to 3-carboxymethyl-5-ethoxymethylidenerhodanine (36). Following reaction of this substance with primary and secondary amines in alcohol results in 5-aminomethylidene derivatives of 3-carboxymethylrhodanine (37).\(^{119}\) (Scheme-14)

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**Scheme-13**

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**Scheme-14**

Reaction of 5-non-substituted rhodanine (38) derivatives with substituted isothiocyanates and isothiocyanates in anhydrous THF in the presence of diazabicyclo [4,3,0] didecene (Scheme-15) yields 5-carbamoyl rhodanines (39).\(^{120}\)
Reaction of 3-R-rhodanines with NaN$_2$ in acetic acid will yield 5-isonitroso-3-R-rhodanines. Unlike rhodanine and pseudothiohydantoin direct nitrosation of 2, 4-thiazolidinedione has not been successful, because of insufficient activity of its methylene group. 5-Isonitroso-2, 4-thiazolidinediones have been synthesized from the corresponding rhodanine and pseudothiohydantoin derivatives.\textsuperscript{121} Difficulty accessible 5-amino-rhodanines have been synthesized from 5-isonitroso-rhodanine by electrochemical reduction.\textsuperscript{122} Reaction of 3-(4-R-phenyl)-5-isonitrosorhodanines which upon reaction with aromatic amines will yield aryliminoethylideneamine derivatives.\textsuperscript{123} 3-Ethylrhodanine and 5-methyl-3-ethylrhodanine (40) upon reaction with acid chlorides of aromatic carboxylic acids in the presence of calcium hydroxide (Scheme-16) produced 5-aroyl substituted (41) in high yields.\textsuperscript{124}
reaction with methyl p-toluenesulfonate at 120°C and the product (44) with an activated position 2 was obtained. Treatment of (44) with 1, 2- or 1, 4-dimethyl-pyridinium p-toluenesulfonate in the presence of triethylamine provided rhodacyanines (45).¹²⁵

Scheme-17

Kandeel Maymona¹²⁶ has provided an example of a classical approach to the synthesis of 5-substituted rhodanine derivatives by utilizing the methylene group in position 5. Heteryl substituted rhodanine derivatives, obtained by the dithicarbaminate method on the base of 2-amino-6-(4-nitrophenylthio) benzothiazole, and were converted in to 5-arylidene derivatives. Subsequent bromination in chloroform gave dibromo derivatives, which were condensed with o-aminophenol. Reaction of the precursor with 4-diethylaminonitrosobenzene in ethanol gave the 5-arylimino derivatives. Condensation of this substance with acyl chloride in benzene gave 5-acetyl-3-R-rhodanine. The same author also has synthesized some products by condensation with diazonium salts.
Dimerisation of 3-carboxyalkylrhodanines \((46)\) under the action of thionyl chloride to crude acid chlorides of bis-rhodanine \((47)\) can be viewed as a consequence of the reactivity of the methylene group in position 5 (Scheme-18). Original esters and amides \((48)\) were synthesized on the basis of the acid chlorides \(^{127}\) mentioned. Short-term heating of 3-alkyl(aryl)rhodanines \((49)\) with bis-(trimethylsilyl)formamide also lead to dimerisation and formation of bis-(3-R-rhodaninyl-5)methinoxynes \((50)\).\(^{128}\) Some related 5, 5-bicyclic 4-thiazolidone derivatives have been synthesized by another route using 5-methoxycarbonylmethylidene-4-thiazolidones \((51)\) as a starting substance (Scheme-19). Addition of dithiocarbamates and thiocarbamates to the double bond in 4-thiazolidones resulted in spontaneous heterocyclisation to non-educted intermediates \((52)\) \((5,5'\text{-di-4-thiazolidones})\), which were oxidized in the presence of the triethylamine to compounds \((53)\). 5, 5'-Di-4-thiazolidones \((52)\) have been synthesized by reduction of \((52)\) using Zn in acetic acid. Following reaction of 5-methoxycarbonylmethylidene-4-thiazolidones \((51)\) with \(\alpha\)-aminothiophenol in methanol produced 2-R-3-R\(_1\)-5-(3-oxo-2,3-dihydro-4-H-1,4-benzothiazinyl-2)-4-thiazolidones \((54)\), which underwent dehydrogenation in the presence of triethylamine in DMF to \((55)\).\(^{129-130}\)
Ambident nucleophiles:

The nucleophiles which have been more than one (generally two) suitable atoms through which they can attack the substrate are known as ambient nucleophiles, e.g., \(-\text{CN}, \text{DMSO}, \text{-SCN}, \text{-NO}_2\) etc.

In rhodanine, \(-\text{CONHS}\) is ambident nucleophiles owing to the presence of \(\text{O}, \text{N}\) and \(\text{S}\) with unshared pairs of electrons. On methylation of rhodanine with MeI gives three isomers, form O-alkylation, N-alkylation and S-alkylation. Within a period of the periodic table, nucleophilicity decreases with increasing atomic number of the atom having negative charge. \(\text{R}_2\text{N}^-\) In contrast, within a group, nucleophilicity increases with increasing atomic number.

Methylation of 5-aryliden-erhodanines (56) using diazomethane also leads to 3-methyl derivatives. But, besides direct N-alkylation (57) S-alkylation (58) to can occur depending on the thione-thiole tautomerism in the crude rhodanine (Scheme-20). In polar
solvents N-methyl derivatives were generally obtained, but increase of SH-acidity of the starting substance will promote formation of S-methyl derivatives.\textsuperscript{131}

The method of alkylation for synthesis of 5-non-substituted 3-R-rhodanines has limitations as a result of ambiguity of alkylation and in most cases 2-substituted derivatives\textsuperscript{132-133} are obtained. Alkylation of 5-arylidenerhodanines generally gave mixtures of 2-and 3-substituted isomers. Some technological procedures support selective alkylation in position 3 of thiazolidine cycle (Scheme-21). For example,
3-phenacylrhodanines (59) have been synthesized following the reaction of 5-arylidenerhodanines with bromoacetophenones in the presence of sodium ethanoate in ethanol\textsuperscript{134} and esters of 5-arylidenerhodanine-3-alkancarboxylic acids (60) were obtained by reaction of potassium salts of corresponding heterocycles with ethyl or phenyl halogenecarboxylates in acetone.\textsuperscript{135} Following the reaction of 6-R\textsubscript{1}-8-R\textsubscript{2}-chloroquinazolines (a) with 5-arylidenerhodanines in pyridine also lead to 3, 5-disubstituted rhodanines (61).\textsuperscript{136}

**Pharmacological features of 4-thiazolidones and possible aspects of their clinical applications**

4-Thiazolidone derivatives are powerful sources of biologically active substances as potential drugs. Even the simplest representatives, such as 2,4-thiazolidinedione, are recommended to be used as radioprotective agents.\textsuperscript{137} Modification of the 2,4-thiazolidinedione ring leads to various kinds of pharmacological activity. Among them antidiabetic activity is currently typical. Scientists of Takeda and Sankyo companies were the first to uncover thiazolidinediones as endogenous insulin stimulants. In 1982 research scientists at Takeda\textsuperscript{138} reported a series of 5-(4-alkoxybenzyl)-2, 4-thiazolidinediones as a hyperglycemic agent of a new type, which reduced insulin resistance in genetically obese and diabetic animal models. Later in 1997, following efforts at Sanyo, troglitazone was put on the pharmaceutical market in the USA and Japan. In 1996 the Takeda company introduced pioglitazone for clinical use in Japan and a little bit later- in the USA. Rosiglitazone (SmithKline Beecham) was adopted for clinical use in the USA and Englitasone (Pfizer), GI262570 (Glaxo Wellcom), JTT-501 (JT) and MCC-55 (Mitsubishi) are undergoing the II Phase of clinical trials.\textsuperscript{139-140} (Chart 1)

Another aspect of application of rhodanine and 2,4-thiazolidinediones derivatives in medicine may be their use for treatment of diabetes complications. Progression of chronic diabetes complications such as cataractogenesis and microangiopathy including nephropathy, retinopathy and neuropathy are thought to be linked to excess of free glucose in the corresponding tissues and leading to increase flux of glucose through the polyl pathway. Numerous observations have provided evidence of aldose reductase
implication in diabetic complications. Inhibition of aldose reductase, the first enzyme of the polyol pathway, is therefore a useful strategy for prevention and treatment of complications of chronic diabetes. Considerable effort in this search led to the discovery of several aldose reductase inhibitors (ARI). Among ARI rhodanine and thiazolidinedione derivatives form the separate group. Rhodanine derivatives (Epalrestat) are a highly active aldose reductase inhibitor, discovered by scientists of ONO pharmaceuticals in 1982.

Another prospective direction of medicinal chemistry of 4-thiazolidone derivatives involves study of anti-inflammatory activity. 4-Thiazolidone derivative-Darbufelone- has been selected. The moiety of darbufelone imparts antioxidant property, supposed to be responsible for their anti-inflammatory potency and their low ulcerogenic potential. During search for novel immunomodulating compounds, 4-thiazolidone with potent antiarthritic activity in rat adjuvant arthritis were discovered. These derivatives possessed high potency in suppressing chronic inflammation and joint destruction in this experimental model. The compound CGP 52608 exhibits antiarthritic activity and was shown to specifically activate the retinoid Z receptor / retinoid acid receptor related orphan receptor α (RZR/ROR α) in low nanomolar concentrations. CGP is a potential drug for the treatment of rheumatoid arthritis.

During pharmacological screening of anti-inflammatory activity paw Oedema test model on white rat, some potent 4-thiazolidone derivatives were selected for the search for potential NSAIDs. It was established, that the character of the substituent in position 5 of the 4-thiazolidones significantly influences the anti-inflammatory activity. In early work there were data about antimicrobial activity of 4-thiazolidones, which were mainly explained by the authors on the basis structural similarity of substances to antibiotics of the penicillin type. Modern investigations and structural-activity mechanisms might change this opinion. Recently it was established that benzylidene rhodanines are novel inhibitors of the UDP N-acetylmuramate/L-alanine ligase. They showed selective whole-cell activity against the Gram-positive meticillin-resistant Staphylococcus aureus (MRSA) and have promise for realization of new strategy in discovery of original antimicrobial drugs. Some derivatives of 2,4-thiazolidinedione (Chart 2) also showed some antimicrobial activity. Some conclusions of structural
activity, were determined: a) having an NH at the 3-position of the five-membered ring is a minimum requirement for activity, b) a heteroatom at the 1 position of the five-membered ring is also needed for antibacterial activity, sulphur or nitrogen atom appears to confer slightly better antibacterial activity than oxygen at that position. \(^{96}\)

Recently, various thiazolidine derivatives have been synthesized as candidate antidiabetes drugs, and some of them have been proven to and activate PPARs (peroxisome proliferation activated receptors).

The rhodacyanine dye MKT-077 has been developed as novel anticancer drugs, and it has been subjected for further clinical investigation for the treatment of solid tumours. Also this, compound was found to possess strong in vitro activity against Plasmodium falciparum coupled with low toxicity. A related derivative to MKT-077 was found to display high antimalarial activity and a significantly good selective toxicity. \(^{125}\)

During biological anticancer assays in National Cancer Institute of combinatorial library of 4-thiazolidone derivatives and related heterocycles, synthesized in Lviv National Medical University, group of active compounds with low cytotoxicity were selected. \(^{150-152}\) The most interesting anticancer 4-thiazolidones are present in (Chart 2). Type of activity characterized above is not the last in variety of pharmacological features of 4-thiazolidones that is why the chosen class of substances is prospective for further research. Different possibilities of heterocycles modifications with wide spectrum of pharmacological properties are the most important grounds for investigations of this interesting class of heterocyclic compounds.
Chart 1
Clinically available drugs based on thiazolidinones cycle
New chemical entities as potential anticancer drugs

As discussed in the literature survey rhodanine derivatives are potent antibacterial and anti fungal agents. This inspired us for designing and synthesis of following hodanine derivatives have been discussed in part IV.

Section 1: 2-substituted-4-y1-5-(4-pyridylmethylene)-1,3-thiazolin-4-ones
Section 2: 2-substituted-4-y1-5-(indol-3-ylmethylene)-1,3-thiazolin-4-ones
Section 3: 5-[(aryl)methylene]-2-[(2-indol-3-ylethyl)amino]-1,3-thiazolin-4-ones

Spectroscopic analysis and biological activities are discussed in Part-V
**PREPARATION OF RHODANINE**

\[
\begin{align*}
CS_2 + NH_3 &\rightarrow NH_2SCSNH_2 \\
(A) \\
NH_2SCSNH_2 (A) + CH_2COONa &\rightarrow ONa \quad H_2N \quad S \quad S \\
(B) \\
\quad ONa \quad H_2N \quad S \quad S + HCl &\rightarrow ONa \quad H_2N \quad S \quad S + NaCl + H_2O
\end{align*}
\]

(A) **Preparation of Ammonium dithiocarbamate.**

Gaseous ammonia was passed into 250 ml of 95% of ethanol contained in a 500 ml Erlenmeyer flask immersed in ice bath for 3 h to gain in weight was 39 g (2.3 mol). To this cooled solution mixture of 76 g (1 mol) of carbon disulfide and 200 ml of ether was added and allow to remain in the ice bath for 3 to 4 h and then at room temperature overnight. The mixture was cooled in an ice bath or refrigerator, and the crystals were collected by filtration, and washed it twice with 50 ml ether. 86 g lemon-yellow solid product was obtained.

(B) **Preparation of Rhodanine.**

A solution of sodium chloroacetate was prepared by dissolving 71 g, (0.75 mol) of chloroacetic acid in 150 ml of water, and neutralizing the acid with 40 g, (0.38 mol) of anhydrous sodium carbonate while stirring the solution mechanically. This solution was cooled in an ice bath and ammonium dithiocarbamate was added during 5 minutes with continual stirring. After all the dithiocarbamate has been added, the ice bath was removed and stirring was discontinued. The solution was allowed to stand for 20-30 minutes further.

This solution was poured with stirring to boiled solution of 400 ml 6N hydrochloric acid. Heating is continued until the solution has attained a temperature of 90-95 °C, after which the solution was allowed to cool slowly to room temperature. The rhodanine separated as nearly colorless long blades which were collected by filtration, washed well with water, and dried. The product obtained was 89% in yield. Recrystallization from boiling acetic acid. m.p.- 168-9 °C.
SECTION-1

PREPARATION OF
2-PIPERAZINY1-5-(4-PYRIDYLMETHYLENE) -1,3-THIAZOLIDIN-4-ONES

\[
\text{(I) } + \text{CHO} \xrightarrow{\text{CH}_3\text{COONa, EtOH, Reflux}} \text{(III)}
\]

\[
\text{NH}_2 \xrightarrow{\text{EthOH, NEt}_3/\text{CH}_3\text{I, 0-5 °C}} \text{(IV)}
\]

Where, \(X = \text{O, S, -NH, -N-CH}_3, -\text{CH}_2\text{, etc.}\)

Synthetic Scheme :- 10
TABLE: 10
PHYSICAL CONSTANTS OF
2-PIPERAZINYL-5-(4-PYRIDYL METHYLENE)-1,3-THIAZOLIDIN-4-ONES

Where, X = O, S, -NH, -N-CH₃, -CH₂, etc.

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</table>
EXPERIMENTAL PROCEDURE

Preparation of 5-(4-pyridylmethylene)-2-thioxo-1,3-thiazolidin-4-one (III)

A mixture of Pyridine-4-carbaldehyde (II) (0.01 mole), rhodanine (I) (0.01 mole), freshly fused sodium acetate (0.01 mole) and 150 ml of ethanol was heated on a steam bath with stirring for 3 hrs. After cooling, the mixture was poured on ice. The resulting yellow crystalline powder was filtered, washed well with water and cold ether and finally with cold ethanol and dried to give 82% of the compound (III). This was recrystallized from dry DMF and washed with water, m.p. 180 °C, yield-82%, Ana. Obs.: C-48.62%, N-12.60%; Calc. for C9H6N2O2S2: C-48.17%, N-12.26%.

Preparation of 2-methylthio-5-(4-pyridylmethylene)-1,3-thiazolidin-4-one (IV)

Compound (III) (0.01 mole) was taken in 20 ml of absolute alcohol in flat bottom flask placed on magnetic stirrer and the temperature of the mixture was maintained between 0 to 5 °C. Triethylamine (0.015 mole) was added to the reaction mixture keeping temperature below 5 °C and stirred for half an hour. Methyl iodide was added portion wise to the mixture between 0-5 °C and the reaction was stirred for 4 hrs. at the same temperature. The mixture was poured onto ice; the solid mass was separated out, filtered with suction and washed with cold water and cold ethanol. The solid product was recrystallized from rectified spirit. Compound (IV) obtained in yield 77%, m.p. 189 °C. Ana. Obs.: C-50.28%, N-11.89%; Calc. for C10H10N2O2S: C-50.39%, N-11.75%.

Preparation of 2-piperazinyl-5-(4-pyridylmethylene)-1,3-thiazolidin-4-one (V) (DMX-01)

Compound (IV) (0.01 mole) was taken in 30 ml of ethanol in flat bottom flask placed on magnetic stirrer. Piperazinyl (cyclic secondary base) (0.01 mole), was added drop wise with stirring to the reaction mass for 4 hrs. at room temperature and the solvent was removed under reduced pressure. The resulting crystalline powder was shaken well with cold ether, filtered, washed well cold ether and finally with cold ethanol and dried to give the compound (V). Recrystallized from absolute alcohol. Product obtained 67% after recrystallization. m.p. 196 °C, Ana. Obs.: C-56.98%, N-20. 62%; Calc. for C13H14N4OS: C- 56.91%, N-20.42%.

The completion of the reaction and the purity of compound (III), (IV) and (V) were checked on TLC aluminium sheet silica gel 60 F254 (E.Merck) using benzene-ethanol (5 : 5 V/V) and hexane-ethyl acetate (7.5 : 2.5 V/V) as irrigator and was developed in iodine chamber.

Other compounds of the series (DMX-02 to 12) were prepared by using a similar method and their physical data are recorded in Table-10.
SECTION- 2

PREPARATION OF
2-PIPERAZINYL-5-(4-PYRIDYLMETHYLENE)-1, 3-THIAZOLIDIN-4-ONES

\[
\text{(I)} \quad \text{EtOH, Reflux} \quad \text{CH}_3\text{COONa} \quad \text{NH} \\
\text{(II)} \quad \text{EtOH} \quad \text{NEt}_3 / \text{CH}_3\text{OH} \quad 0-5^\circ\text{C} \quad \text{NH} \\
\text{(III)} \quad \text{EtOH} \quad \text{RT} \quad \text{NH} \\
\text{(IV)} \quad \text{EtOH} \quad \text{RT} \quad \text{NH} \\
\text{(V)} \quad \text{Where, } X = O, S, -\text{NH}, -\text{N-CH}_3, -\text{CH}_2, \text{etc.}
\]

Synthetic Scheme :: 11
TABLE: 11

PHYSICAL CONSTANTS OF
2-PIPERAZINYL-5-(4-PYRIDYMETHYLENE)-1, 3-THIAZOLIDIN-4-ONES

Where, X = -CH₂, O, -NH, -N-CH₃, etc.

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<th>% Yield</th>
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</table>
EXPERIMENTAL PROCEDURE

Preparation of 5-(indol-3-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one (III)

A mixture of indol-3-carbaldehyde (II) (0.01 mole), rhodanine (I) (0.01 mole), freshly fused sodium acetate (0.01 mole) and 150 ml of ethanol was heated on a steam bath with stirring for 3 hrs. After cooling, the mixture was poured on ice. The resulting yellow crystalline powder was filtered, washed well with water and cold ether and finally with cold ethanol and dried to give 81% of the compound (III). This was recrystallized from dry DMF and washed with water, m.p. 179 °C, yield-80%, Ana. Obs.: C-55.10%, N-10.93%; Calc. for C_{12}H_{10}N_{2}O_{2}S_{2}: C- 54.93%, N-10.67%.

Preparation of 5-(indol-3-ylmethyl)-2-methylthio-1,3-thiazolidin-4-one (IV)

Compound (III) (0.01 mole) was taken in 20 ml of absolute alcohol in flat bottom flask placed on magnetic stirrer and the temperature of the mixture was maintained between 0 to 5 °C. Triethylamine (0.015 mole) was added to the reaction mixture keeping temperature below 5 °C and stirred for half an hr. Methyl iodide was added portion wise to the mixture between 0-5 °C and the reaction was stirred for 4 hrs. at the same temperature. The mixture was poured onto ice; the solid mass was separated out, filtered with suction and washed with cold water and cold ethanol. The solid product was recrystallized from rectified spirit. Compound (IV) obtained in yield 73%, m.p. 189 °C. Ana. Obs.: C-56.48%, N-10.11%; Calc. for C_{13}H_{14}N_{2}O_{2}S_{2}: C- 56.08%, N-10.06%.

Preparation of 5-(indol-3-ylmethyl)-2-morpholin-4-yl-1,3-thiazolin-4-one (V) (DMxl-01)

Compound (IV) (0.01 mole) was taken in 30 ml of ethanol in flat bottom flask placed on magnetic stirrer. Morpholine (cyclic secondary base) (0.01 mole), was added drop wise with stirring to the reaction mass for 4 hrs. at room temperature and the solvent was removed under reduced pressure. The resulting crystalline powder was shaken well with cold ether, filtered, washed well cold ether and finally with cold ethanol and dried to give the compound (V). Recrystallized from absolute alcohol. Product obtained 78% after recrystallization. m.p. 180°C, Ana. Obs.: C-60.68%, N-13.22%; Calc. for C_{16}H_{17}N_{3}O_{2}S: C- 60.93%, N-13.32%.

The completion of the reaction and the purity of compound (III), (IV) and (V) were checked on TLC hexane-ethyl acetate (7.5 : 2.5 V/V) as irrigator and was developed in iodine chamber.

Other compounds of the series (DMxl-02 to 12) were prepared by using a similar method and their physical data are recorded in Table-11.
SECTION-3

PREPARATION OF
5-[(ARYL)METHYLENE]-2-[(2-INDOL-3-YLETHYL)
AMINO]-1,3-THIAZOLIN-4-ONE

\[
\begin{align*}
\text{(I)} & \quad \text{CHO} + \text{(II)} & \quad \text{Reflux} & \quad \text{CH}_3\text{COONa} \\
\text{(III)} & \quad \text{R} & \quad \text{EtOH} \\
\text{(IV)} & \quad \text{R} & \quad \text{EtOH} \\
\text{(V)} & \quad \text{R} & \quad \text{EtOH} \\
\end{align*}
\]

Where, \( R = \) Different groups

Synthetic Scheme :- 12
TABLE: 12

PHYSICAL CONSTANTS OF
5-[(ARYL)METHYLENE]-2-[(2-INDOL-3-YLETYL)AMINO]-1,3-THIAZOLIN-4-ONE

Where, R= Different groups

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EXPERIMENTAL PROCEDURE

Preparation of 5-(phenylmethylene)-2-thioxo-1,3-thiazolidin-4-one (III)
A mixture of benzaldehyde (aromatic aldehydes) (I) (0.01 mole), rhodanine (II) (0.01 mole), freshly fused sodium acetate (0.01 mole) and 150 ml of ethanol was heated on the steam bath with stirring for 3 hrs. After cooling, the mixture was poured on ice. The resulting yellow crystalline powder was filtered, washed well with water and cold ether and finally with cold ethanol and dried to give 81% of the compound (III). This was recrystallized from dry DMF and washed with water, m.p. 165°C, yield-85%, Ana. Obs.: C-54.40%, N-6.53%; Calc. for C_{10}H_{7}NOS_{2}: C- 54.27%, N-6.32%.

Preparation of 2-methylthio-5-(phenylmethylene)-1,3-thiazolidin-4-one (IV)
Compound (III) (0.01 mole) was taken in 20 ml of absolute alcohol in flat bottom flask placed on magnetic stirrer and the temperature of the mixture was maintained between 0 to 5°C. Triethylamine (0.015 mole) was added to the reaction mixture keeping temperature below 5°C and stirred for half an hrs. Methyl iodide was added portion wise to the mixture between 0-5°C and the reaction was stirred for 4 hrs. at the same temperature. The mixture was poured onto ice; the solid mass was separated out, filtered with suction and washed with cold water and cold ethanol. The solid product was recrystallized from rectified spirit. Compound (IV) obtained in yield 78%, m.p. 210°C. Ana. Obs.: C-55.88%, N-5.91%; Calc. for C_{11}H_{11}NOS_{2}: C- 55.66%, N-5.90%.

Preparation of 2-[(2-indol-3-ylethyl)amino]-5-(phenylmethylene)-1,3-thiazolin-4-one (V) (DMxHII-01)
Compound (IV) (0.01 mole) was taken in 30 ml of ethanol in flat bottom flask placed on magnetic stirrer. 2-indol-3-ylethylamine (0.01 mole), was added drop wise with stirring to the reaction mass for 4 h at room temperature and the solvent was removed under reduced pressure. The resulting crystalline powder was shaken well with cold ether, filtered, washed well cold ether and finally with cold ethanol and dried to give the compound (V). Recrystallized from absolute alcohol. Product obtained 82% after recrystallization. m.p. 174°C, Ana. Obs.: C-69.22%, N-12.22%; Calc. for C_{20}H_{17}N_{3}OS: C- 69.14%, N-12.09%.

The completion of the reaction and the purity of compound (III), (IV) and (V) were checked on TLC hexane-ethyl acetate (7.5 : 2.5 V/V) as irrigator and was developed in iodine chamber.

Other compounds of the series (DMxHII-02 to 12) were prepared by using a similar method and their physical data are recorded in Table-12.
References

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44. Wheeler H & Barnes B, J Am Chem, 24, 1900, 76.
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