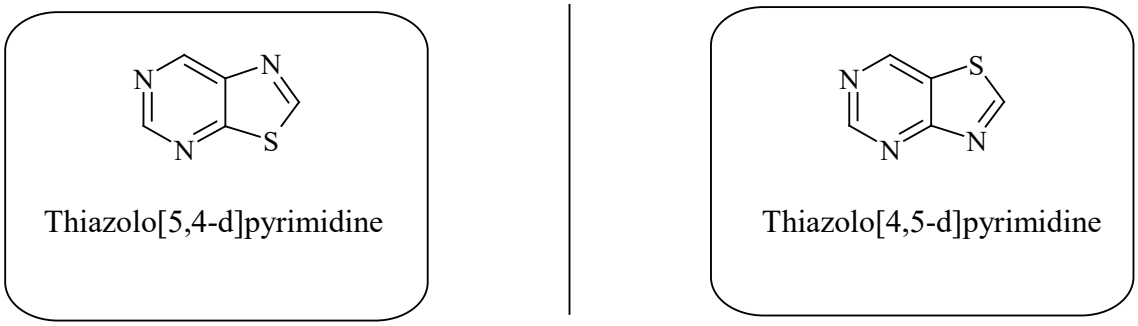
THIAZOLO[5,4-*D*]PYRIMIDINES AND THIAZOLO[4,5-*D*] PYRIMIDINES: A REVIEW ON SYNTHESIS AND PHARMACOLOGICAL IMPORTANCE OF THEIR DERIVATIVES

Taras Chaban[1*], Olena Klenina[1], Ihor Chaban[2], Volodymyr Ogurtsov[1], Stefan Harkov[3], & Maryan Lelyukh[2]

[1]Department of General, Bioinorganic, Physical and Colloidal Chemistry
Danylo Halytsky Lviv National Medical University, Ukraine
Pekarska 69, Lviv, 79010, Ukraine
[2]Department of Pharmaceutical Chemistry FPGE
Danylo Halytsky Lviv National Medical University, Ukraine
Pekarska 69, Lviv, 79010, Ukraine
[3]Department of Pharmacy
Medical College of Burgas University "Prof. Dr. Asen Zlatarov"
St. Stambolov 69 Blv., Burgas, 8000, Bulgaria

Abstract. Thiazolopyrimidine scaffold is important pharmacophore in compounds which have shown various biological activities. The objective of this review is to compile the literature concerning existing approaches applied for these fused heterocycles construction with an emphasis on recent developments. This paper also reviews the current literature references with regard of prospects and challenges of condensed thiazolopyrimidine derivatives application for the directed synthesis of biologically active substances and analysis of recent advances in pharmacology screening of this heterocyclic compounds.

Graphical abstract



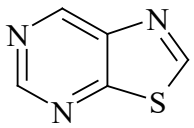
Keywords: fused heterocycles, thiazolopyrimidines, organic synthesis, pharmacological activity.

Introduction

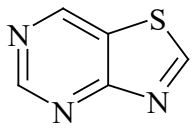
The chemistry of thiazole and most of its derivatives has been well studied. However, the chemistry of condensed thiazoles is still essentially in the development stage. The number of review and original articles within the development of 4-thiazolidinone derivatives efficient preparation methods and their biological activity evaluations as novel chemotherapeutical agents is quite limited, while almost all of them were published over the last three decades [1-5].

4-Azolidone is widely used in modern medical chemistry as a scaffold for molecular rational design of drug candidates. The thiazolidinone core imparts an important function in medicinal chemistry and serves as a powerful biophore template for the rational design of ”drug-like” molecules as the prototypes of variour therapeutical agents development. Condensed bicyclic systems with thiazolidine core being annulated to pyrimidine one occupy prominent place in medicinal chemistry because of their broad spectrum of pharmacological activities. The combination of these heterocyclic systems into a bicyclic scaffold commonly provides much more interest in the enhanced activity profile of its analogs than their parent monocyclic constituents. Thiazolopyrimidine scaffold is important pharmacophores in compounds which have shown various biological activities. They are fused heterocyclic ring-systems that can be viewed at the first glance as purine isosteres. Because of the structural resemblance to adenine and guanine and their related derivatives as adenosine, guanosine, cAMP, cGMP and similar biomolecules, many thiazolopyrimidines scaffold were developed and utilized by medicinal chemists to design novel therapeutics.

In the present review we highlight recent advances in the fast growing research area of thiazolopyrimidines chemistry summarizing the existing literature information with respect of condensed, thiazolopyrimidines construction synthetic approaches (thiazolo[5,4-*d*]pyrimidines and thiazolo[4,5-*d*]pyrimidines):



Thiazolo[5,4-d]pyrimidine

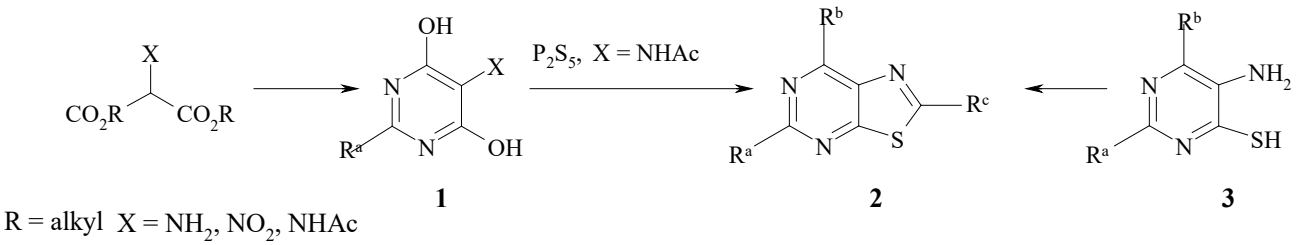


Thiazolo[4,5-d]pyrimidine

The review is also aimed to report the biological activities evaluation of thiazolopyrimidines during past years.

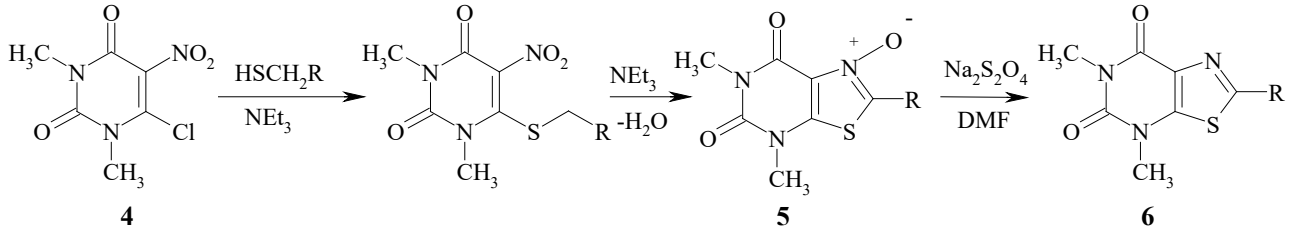
Synthesis of Thiazolopyrimidines

One of the most facile routes of thiazolo[5,4-*d*]pyrimidines **2** synthesis is based on pyrimidine derivatives utilization with nitrogen containing substituents in C^5 position of the fused heterocyclic scaffold, *e.g.* 5-nitro- or 5-aminopyrimidines. The above-mentioned precursors are afforded by amino-, nitro- or acetylamino derivatives of diethyl ester treatment with thiourea [6], urea [7], guanidine [8] or amidine [9] in alkaline medium. 4,6-Dihydroxypyrimidines **1** prepared in this way are then introduced into thionation reaction with phosphorus pentasulfide or Lawesson’s reagent in pyridine medium resulted in thiazole ring construction. 5-Amino-6-mercaptopyrimidine **3** treatment with phosgene [10], formic acid [11] or acetic anhydride [12] also leaded to thiazolo[5,4-*d*]pyrimidine scaffold generation (Scheme 1).



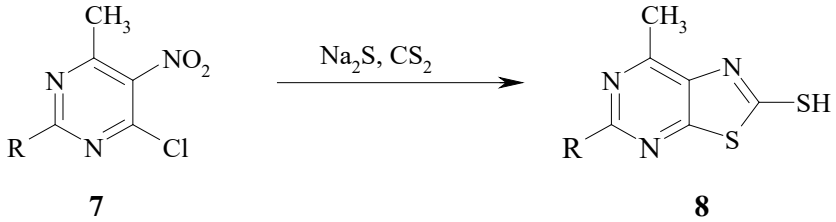
Scheme 1. Synthesis of thiazolo[5,4-*d*]pyrimidine scaffold based on pyrimidine derivatives utilization with nitrogen containing substituents.

6-Chloro-1,3-dimethyl-5-nitropyrimidinone **4** and mercaptans ($HSCH_2R$) employment affords the synthesis of thiazolopyrimidine oxides **5** which can be transformed into thiazolo[5,4-*d*]pyrimidines **6** under the reaction of reductive deoxygenation with sodium dithionite treatment or under the reaction of oxidative deoxygenation in boiling dimethylformamide [13] (Scheme 2).



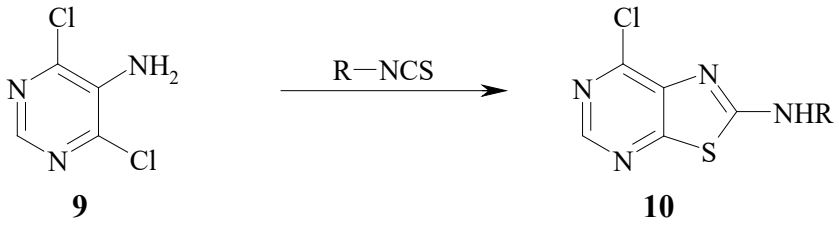
Scheme 2. Synthesis of thiazolo[5,4-*d*]pyrimidine under the reaction of reductive deoxygenation.

2-Mercaptothiazolo[4,5-*d*]pyrimidines **8** can be achieved by 6-chloro-5-nitropyrimidines **7** utilization in the reaction with sodium sulfide and carbon disulfide [14] (Scheme 3).



Scheme 3. Synthesis of 2-mercaptothiazolo[4,5-*d*]pyrimidines.

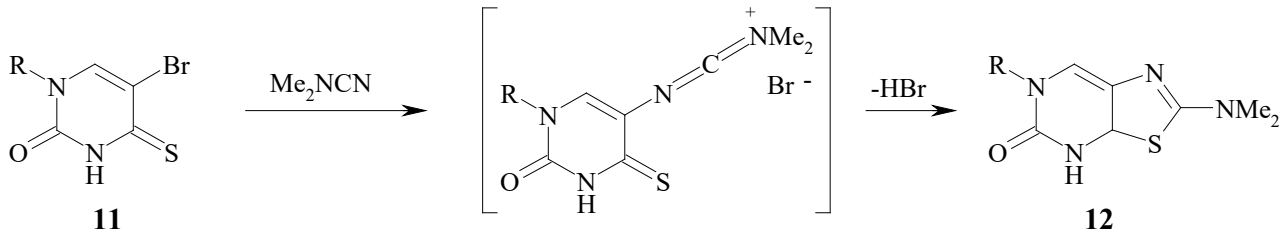
The efficient method of thiazolo[5,4-*d*]pyrimidines synthesis was reported based on 5-amino-4,6-dichloropyrimidine **9** utilization as the precursor [15]. Its treatment with isothiocyanates afforded 2-amino-7-chlorothiazolo[5,4-*d*]pyrimidines **10** generation (Scheme 4).



9 **10**

Scheme 4. Synthesis of 2-amino-7-chlorothiazolo[5,4-*d*]pyrimidines based on 5-amino-4,6-dichloropyrimidine utilization as the precursor.

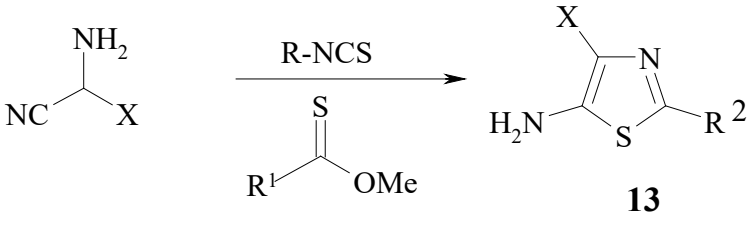
A.F.S. Ahmed reported thiazolo[5,4-*d*]pyrimidines **12** synthetic approach as pyrimidine derivatives utilization without 5-amino or 5-nitro substituents. In the proposed strategy 5-bromo-4-thioxopyrimidine-2-ones **11** were firstly treated with N,N-dimethylcyanamide resulted in the intermediate carbodiimide formation. On the next stage thiazole ring construction appeared to proceed *via* the carbodiimide intermolecular cyclization [16] (Scheme 5).



11 **12**

Scheme 5. Synthesis of thiazolo[5,4-*d*]pyrimidines synthetic approach as pyrimidine derivatives utilization without 5-amino or 5-nitro substituents.

Thiazolo[5,4-*d*]pyrimidines can be also accessed starting with 5-aminothiazole derivatives **13** which in their turn are yielded by aminomalononitrile (or its appropriate derivativatives) and isothianates [17] or thio esters [18] employing (Scheme 6).

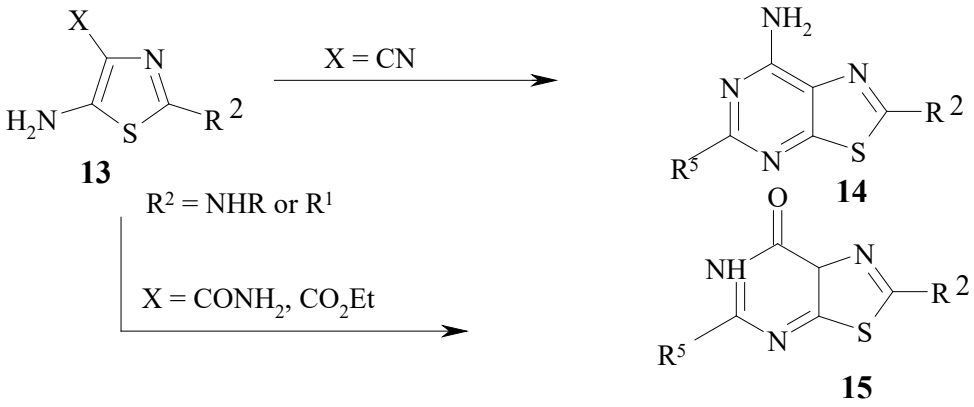


13

X = CN, $CONH_2$, CO_2Et R^2 = NHR or R^1

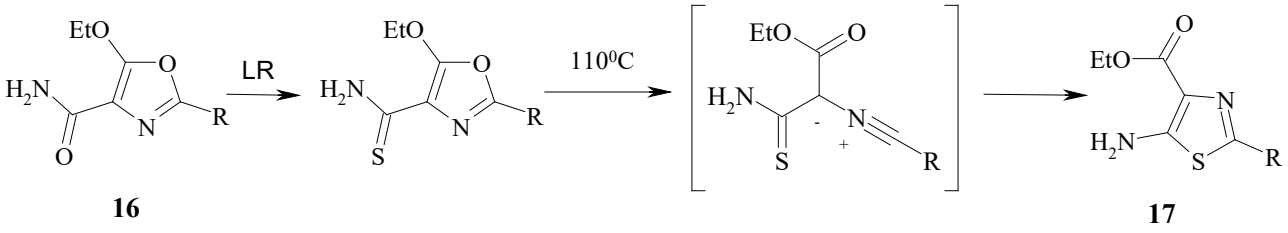
Scheme 6. Synthesis of thiazolo[5,4-*d*]pyrimidines based on 5-aminothiazole derivatives.

The presence of amino substituent in C^5 position of thiazole ring and cyano, carboxamide or ester moieties in its C^4 position provides the facile possibility for pyrimidine core annelation to thiazole ring affording the fused heterocyclic scaffold construction. 5-Amino-4-cyanothiazoles, ortho esters and amidines employment [19,20] results in aminothiazolo[4,5-*d*]pyrimidines **14** preparation while 5-amino-4-carboxamido- (or carboxylate-) thiazole treatment with ortho esters [17], formamide [20] and ethyl chloroformate [21] leads to 6*H*-thiazolo[5,4-*d*]pyrimidine-7-ones **15** yielding (Scheme 7).



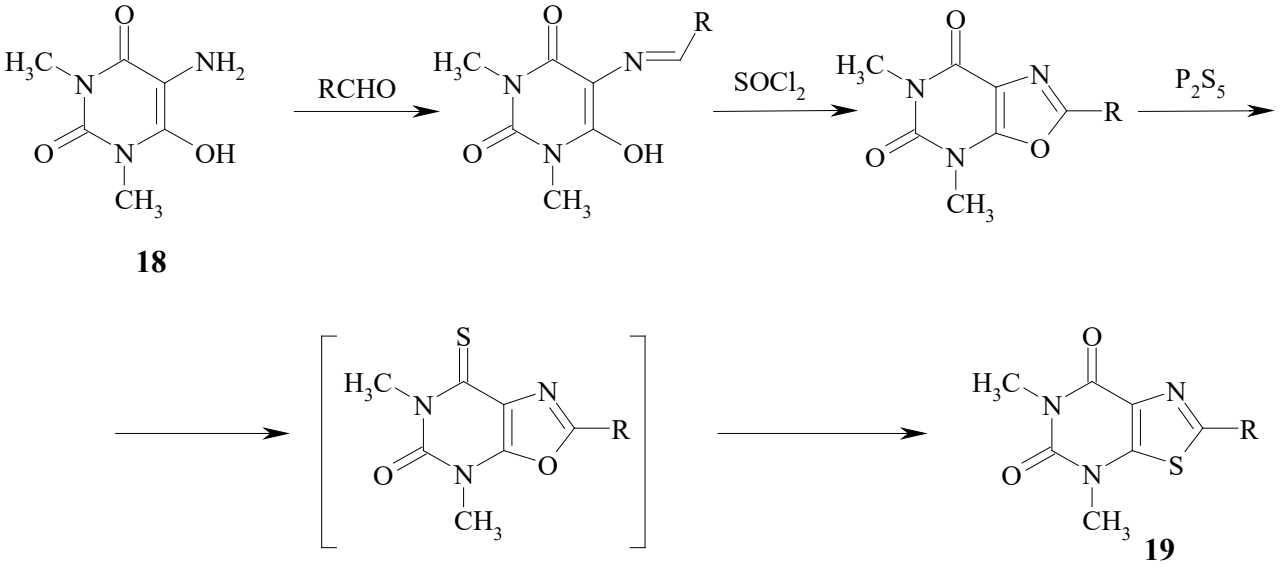
Scheme 7. Synthesis of aminothiazolo[4,5-*d*]pyrimidines and 6*H*-thiazolo[5,4-*d*]pyrimidine-7-ones.

The appropriate oxazol pyrimidines also may be employed to yield thiazolo[5,4-*d*]pyrimidines. This technique is based on 1,3-oxazole ring transformation into 1,3-thiazole one proceeded as the thermal rearrangement. Oxazole derivatives with thioamide moiety **16** are afforded from the appropriate amides by their treatment with Lawesson's reagent. Thioamide derivatives heating to 110°C results in oxasole ring opening followed by 1,3-thiazole ring formation **17** [22] (Scheme 8).



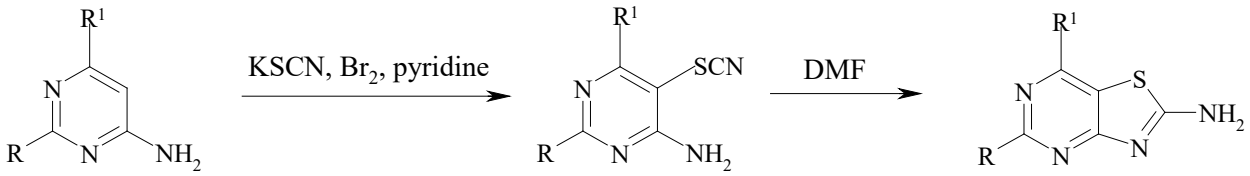
Scheme 8. Synthesis of thiazolo[5,4-*d*]pyrimidines based on 1,3-oxazole ring transformation into 1,3-thiazole.

Scheme 9 illustrates the example of oxothiazolo[5,4-*d*]pyrimidines transformation into thiazolo[5,4-*d*]pyrimidines. Oxothiazolo[5,4-*d*]pyrimidines are accessed in the reaction of 5-aminobarbituric acid **18** with aldehydes and the product further treatment with thionyl chloride. Thiazolo[5,4-*d*]pyrimidines construction appears to proceed *via* initial oxazol pyrimidinedithiones generation followed by oxazole transformation into thiazole **19** [23] (Scheme 9).



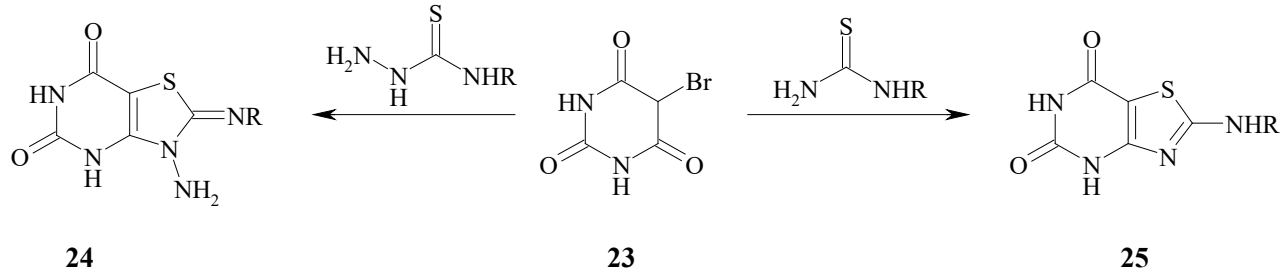
Scheme 9. Transformation of oxothiazolo[5,4-*d*]pyrimidines into thiazolo[5,4-*d*]pyrimidines.

6-Aminopyrimidines are used as presursors in thiazolo[4,5-*d*]pyrimidines synthesis. Firstly 5-isothiocyanate-6-aminopyrimidines **21** are accessed by 6-aminopyrimidines **20** treatment with potassium rhodanine, bromine and pyridine. Further cyclization of the products leads to 2-aminothiazolo[4,5-*d*]pyrimidines **22** generation [24] (Scheme 10).



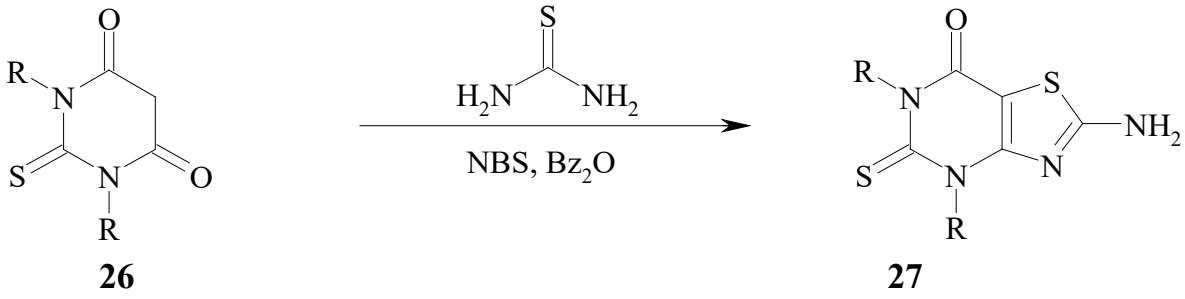
Scheme 10. Synthesis of 2-aminothiazolo[4,5-*d*]pyrimidines based on 6-aminopyrimidines.

5-Bromobarbituric acid **23** condensation with thiosemicarbazide or thiourea derivatives leads to thiazolo[4,5-*d*]pyrimidines **24** and **25**, respectively, formation [25, 26] (Scheme 11):



Scheme 11. Synthesis of thiazolo[4,5-*d*]pyrimidines based on 5-bromobarbituric acid condensation with thiourea or thiosemicarbazide derivatives.

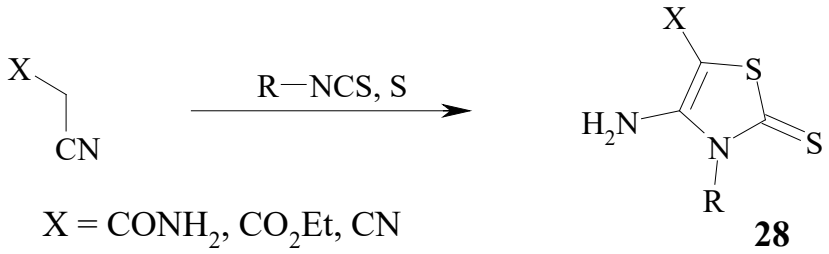
Additionally 2-thiobarbituric acid **26** treatment with thiourea and *N*-bromo cyccinimide (NBS) in the presence of benzoic anhydride (Bz_2O) is resulted in thiazolo[4,5-*d*]pyrimidines **27** formation [27] (Scheme 12).



26 **27**

Scheme 12. Synthesis of thiazolo[4,5-*d*]pyrimidines under the reactions of 2-thiobarbituric acid treatment with thiourea and *N*-bromocyccinimide (NBS) in the presence of benzoic anhydride.

Other method of thiazolo[4,5-*d*]pyrimidines generation includes 4-iminothiazoles synthesis as its first stage. 4-Iminothiazoles **28** may be yielded *via* Hewald reaction proceeding with isothiocyanates, sulfur and 2-cyanoacetamide employing (or 2-cyanoethylacetate and malononitrile employing) [28] (Scheme 13).



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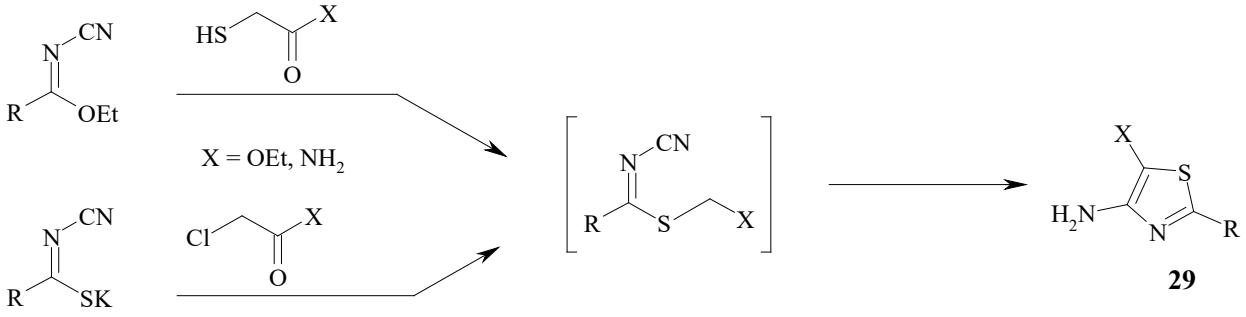
Scheme 13. Synthesis of 4-iminothiazoles yielded via Hewald reaction.

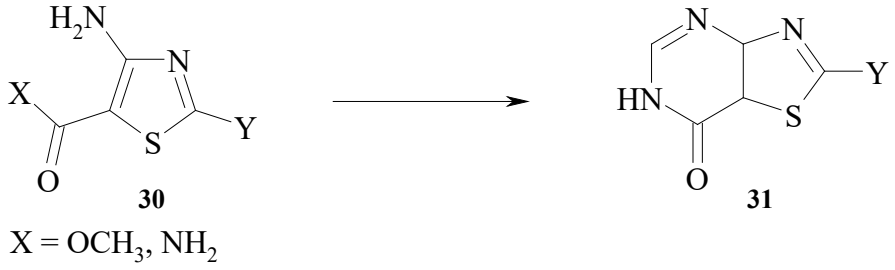
The intermediate alkylthio-*N*-cyanoimines introduction into Torp-Ziegler cyclization may lead to the formation of 4-aminothiazoles **29**. Two main strategies are applicable for these versatile intermediates employment in 4-iminothiazoles preparation: *N*-cyanoimidates may be treated with α-mercaptocarbonyl compounds in the presence of bases [29, 30] or *N*-cyanoimidothiolates treatment with α-carbonyl halides in basic medium conditions [31] (Scheme 14).



29

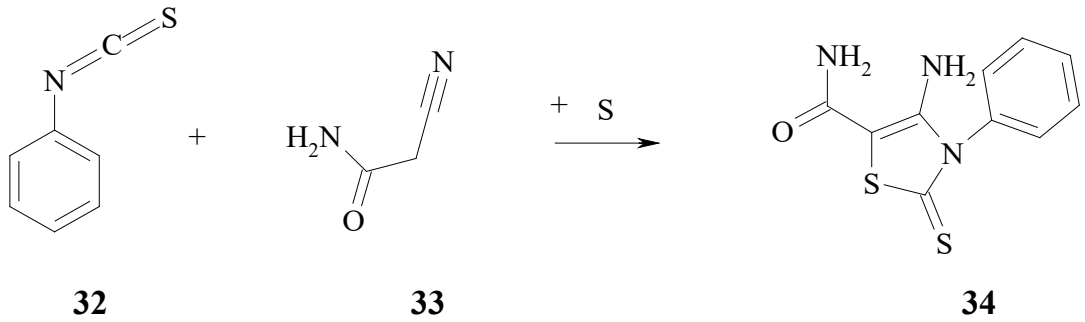
Scheme 14. The intermediate alkylthio-N-cyanoimines introduction into Torp-Ziegler cyclization.

The procedure used for thiazolo[5,4-*d*]pyrimidines **31** preparation starting with 5-aminothiazole may be successfully utilized to acces the same product yielding by employing substituted 4-aminothiazoles **30** and ortho esters [32], amidines [18], appropriate acids anhydrides and chloroanhydrides [33] and carbon disulfide (Scheme 15).



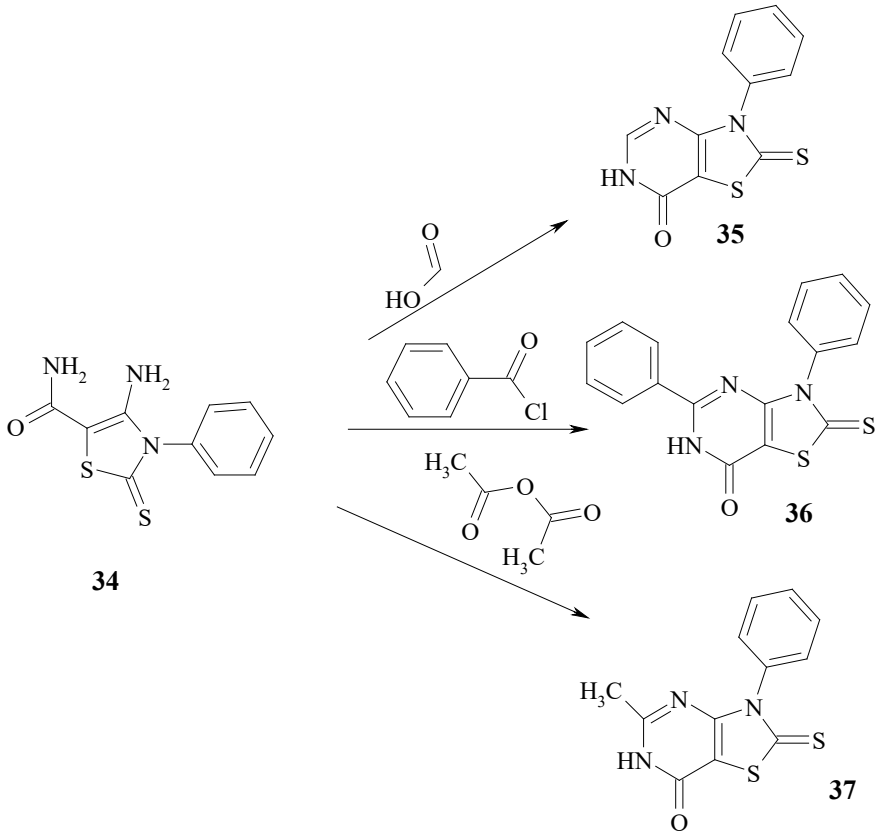
Scheme 15. Synthesis of thiazolo[5,4-*d*]pyrimidines by employing substituted 4-aminothiazoles.

The employment of phenyl isothiocyanate **32** treatment with 2-cyanoacetamide **33** leaded to 4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxylic acid amide **34** formation [34] (Scheme 16) which in its turn is the convenient precursor for thiazolo[4,5-*d*]pyrimidines construction.



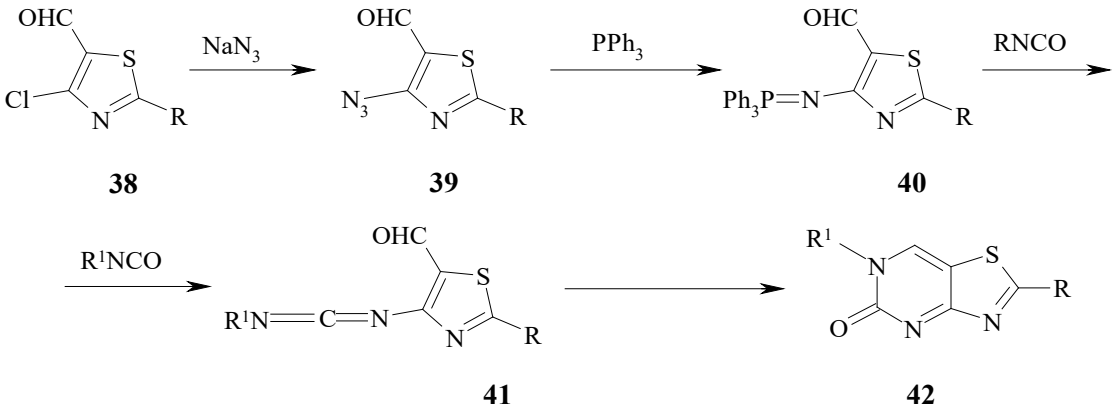
Scheme 16. Synthesis of thiazolo[4,5-*d*]pyrimidines based of 4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxylic acid amide.

4-Amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxylic acid amide **34** treatment with the appropriate binucleophiles (formic acid, benzoic acid chloroanhydride, acetic anhydride *etc.*) resulted in various thiazolo[4,5-*d*]pyrimidines **35-37** [35, 36] obtaining (Scheme 17):



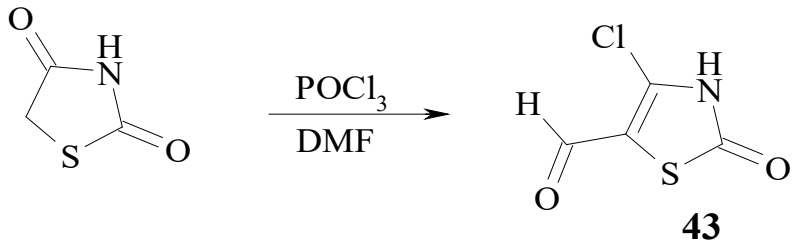
Scheme 17. Synthesis of thiazolo[4,5-*d*]pyrimidines under the reactions of 4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxylic acid amide with the appropriate binucleophiles.

Another approach afforded the synthesis of thiazolo[4,5-*d*]pyrimidines starting with thiazole **38** is based on aza-Wittig reaction [37-39]. Iminophosphoranes as the intermediates of this rearrangement are forming at 5-formyl-4-chlorothiazole **39-40** treatment with sodium azide and triphenylphosphine (Staudinger reaction). Carbodiimides **41** generated by iminophosphoranes coupling with isocyanides provides a facile route for the ring construction at heating. Finally thiazolo[4,5-*d*]pyrimidine scaffold **42** construction is accessed via Dimroth rearrangement [40] (Scheme 18).



Scheme 18. Synthesis of thiazolo[4,5-*d*]pyrimidine based of Dimroth rearrangement.

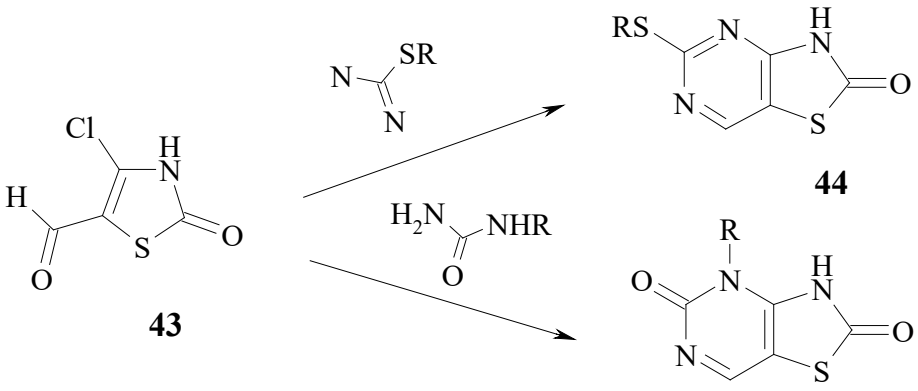
Thiazolidines also may be utilized in the Vilsmeier–Haack reaction [41] leading to 2-oxo-4-chloro-2,3-dihydrothiazole-5-carbaldehyde **43** formation (Scheme 19).



43

Scheme 19. Synthesis of 2-oxo-4-chloro-2,3-dihydrothiazole-5-carbaldehyde under the Vilsmeier–Haack reaction.

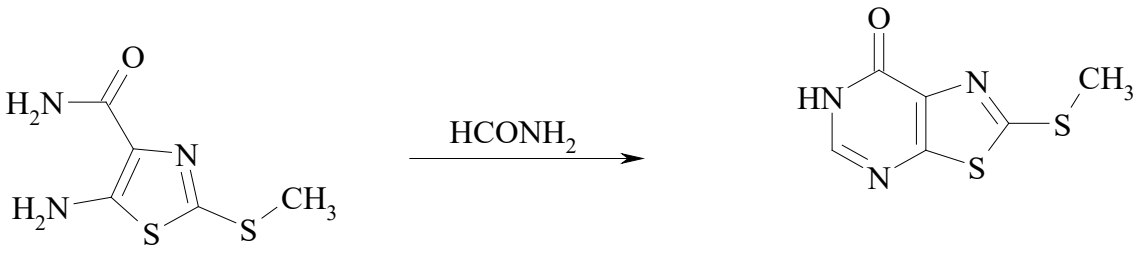
The latest one can be easily transformed into betains of the thiazolydine series which are especially convenient for various condensed heterocyclic systems with thiazolidine ring design. Thiazoles annulated with pyrimidine ring **44-45** [42-44] were furnished in this way (Scheme 20).



43 **44** **45**

Scheme 20. Synthesis of thiazolo[4,5-*d*]pyrimidine based of 2-oxo-4-chloro-2,3-dihydrothiazole-5-carbaldehyde.

One more approach used to generate thiazolo[4,5-*d*]pyrimidines **47** is based on 5-amino-2-methylsulfanylthiazolo-4-carboxylic acid amide **46** utilization as the precursor [45] as it is depicted on Scheme 21.



46 **47**

Scheme 21. Synthesis of thiazolo[4,5-*d*]pyrimidine based of 5-amino-2-methylsulfanylthiazolo-4-carboxylic acid amide.

The latest reacts with formamide by using a microwave-assisted reaction resulted in 2-methylsulfanyl-6*H*-thiazolo[5,4-*d*]pyrimidine-2-one obtaining.

Pharmacological Potential of Thiazolopyrimidines

The combination of combinatory chemistry and highly effective pharmacological screening has made possible the identification of a large group of cell biotargets. The above-mentioned fact leaded to more effective studying and understanding the details of the realization of pharmacological agent mechanism as well as the considerable expansion of chemical compounds as remedies. The application of the aforementioned strategy has become a key factor in the rapid development of the pharmacological potential of the condensed thiazole and thiazolidone derivatives and allowed to discover new pharmacological effects of the above-mentioned compounds as well as in the further development of the peculiarities of the mechanisms action on the "ligand –receptor" level, which had been revealed earlier due to the detailed elaboration.

Thiazolo[4,5-*d*]pyrimidines could be shown as structural analogues of purines, in which imidazole ring is replaced with 1,3-thiazole one.

Even through the chemistry of purine analogs has been the rather widly covered by review and original papers, the number of research articles, which describe the synthesis and biological activity of thiazolopyrimidines, remains limited. This fact shows that derivatives of thiazolopyrimidines are not commonly used as therapeutic agents.

According to pharmacological screening results of the recent years it was disclosed that in this group of chemical compounds some substances were detected which possess different types of biological activities. It was indentified *in vitro* that thiazolo[4,5-*d*]pyrimidine derivative (analogue of guanosine-5'-triphosphate) is active against DNA- and RNA viruses [46-48]. It also has antitumor and antimetastatic effects [49]. Thiazolopyrimidine derivatives which are structure analogues of guanine exhibited strong effect against human cytomegalovirus evaluated through *in vitro* testing [50]. Thiazolo[4,5-*d*]pyrimidine-5,7-diones act as anti-anflammaty agents owing to their TNF inhibition ability [51].

Some thiazolo[4,5-*d*]pyrimidines are CRHR1 receptor antagonists [52, 53]. 2-Th io-3-arylthiazolo[4,5-*d*]pyrimidines exhibit antitumor [54, 55], antimicrobial and anti-anflammatory activities [56, 57, 58]. It was revealed that 2-aminothiazolo[4,5-*d*]pyrimidines are CXCR2 receptor antagonists [59, 60]. 2,7-Substituted thiazolo[4,5-*b*]pyrimidines were evaluated as substances, which are ATP competitive inhibitors of kinase protein [61]. Among thiazolo[5,4-*d*]pyrimidine derivatives 2,5-diaminothiazolo[5,4-*d*]pyrimidine-7(6*H*)-ones were disclosed as weak inhibitors of purine

nucleoside phosphorylase (PNP) [62] while 7-diethylamino-5-metylthiazolo[4,5-*d*]pyrimidines have some vasodilating and hypertensive effects, they also can inhibit the aggregation of platelets and lower cholesterol level [63]. Numerous patents were issued on thiazolo[4,5-*d*]pyrimidine derivatives, which are caspase activators and apoptosis inductors [64], antiangiogenic agents [65], epidermal growth factor (EGF) receptors inhibitors [66], heat-shock proteins 90 (Hsp90) inhibitors [67] and xanthine oxidase (XO) inhibitors [68]. As one type of those heterocyclic rings, thiazolopyrimidines are considered a promising class of bioactive heterocyclic compounds encompassing a diverse range of biological activities such as antifungal [69], antibiofilm [70], antibacterial [70], antiviral [71], antioxidant [72-75], antitumor [76, 77], antitubercular [78, 79], 5-HT2a receptor antagonistic [80] and group II metabotropic glutamate receptor antagonist activities [81]. Thiazolo[5,4-*d*] pyrimidines are reported to act as immunosuppressive agents for treatment of autoimmune diseases and prevention of transplant rejection [82, 83], phosphatidylinositide 3-kinases (PI3K) inhibitors [84-88], agrochemicals and pesticides [89, 90], Tie-2 inhibitors [91], bronchodilators for asthma [92], RAF/vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors [93], anticancer agents [94], TRPV1 antagonist for the treatment of pain [95-97], thrombin inhibitor [98], xanthine oxidase (XOD) inhibitors [99], purine nucleoside phosphorylase (PNP) inhibitors [83]. Furthermore, the fact that they have been explored as purine antimetabolites and hence as anticancer agents has been previously recognized [100].

Conclusions

In the present review we performed the literature search and highlighted recent advances in the fast growing research area of thiazolopyrimidines chemistry. References obtained were considered to review and summarize the existing information with respect of condensed thiazolopyrimidines construction synthetic approaches and their pharmacological actions spectrum. Thus, broad synthetic possibilities of condensed thiazolopyrimidines generation and functionalization, their high pharmacological potential found a strong basis for the systematic research of these compounds.

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Corresponding author:
chabantaras@ukr.net (T. Chaban)
tel. +38 098 942-79-56
fax. +38 0322 75-77-34