Preparation and biological properties of 2-thio-containing pyrimidines and their condensed analogs

Oleksii Yu. Voskoboynik¹, Oleksandra S. Kolomoets¹, Galyna G. Berest¹, Inna S. Nosulenko¹, Yuliya V. Martynenko¹, Sergiy I. Kovalenko¹

¹ Zaporizhzhia State Medical University, 26 Mayakovskiy Ave, Zaporizhzhia 69035, Ukraine

e-mail: kovalenko sergey@gmail.com

The known methods for synthesis of thioxopyrimidines and their condensed analogs with exocyclic sulfur atom are summarized and discussed. The most popular approaches are based on [3+3], [4+2], [5+1] cyclization processes or domino reactions. The literature data analysis shows that the title compounds possess diverse biological activities, such as antioxidant, radioprotective, analgesic, anti-inflammatory, antihypertensive, anxiolytic, anamnestic, anticonvulsant, antimicrobial, fungicidal, herbicidal, antiviral, and anticancer.

Keywords: condensed pyrimidines, thioxopyrimidines, biological activity, synthesis.
Layeva\textsuperscript{25} used [3+3] heterocyclization to form the fluorine-containing compounds with thiopyrimidine fragment. 2,3,4,5-Tetrafluorobenzoyl chloride (4) and ethylcarbamimidothioate 5 were used as starting compounds (Scheme 2). Their condensation followed by cyclization of intermediate 6 led to the formation of 6,7,8-trifluoro-5H-dihydrofuro[3,2-d]pyrimidin-3(6H)-ylacetate (13) (Scheme 4).

Chowdhury and Shibata\textsuperscript{28} published results of the study in which they used a similar approach for pyrimidine derivative formation. Authors used 2-isothiocyanatoacetate (14) as electrophilic reagent and various \(\alpha\)-amino nitriles 15, 17–19 or \(\alpha\)-amino ester 16 as 1,4-binucleophiles (Scheme 5). In all cases the appropriate condensed pyrimidine derivatives 20–24 were obtained. It should be noted, that the interaction of 2-isothiocyanatoacetate (14) with 2-amino-4,5-dimethylfuran-3-carbonitrile (19) had some peculiarities: the involvement of the acetate chain in the cyclization lead to isolation of 8,9-dimethyl-5-thioxo-5,6-dihydrofuro[3,2-c]imidazo[1,2-c]pyrimidin-2(3H)-one (24) as the reaction product.

Weinstock et al.\textsuperscript{29} investigated products of the thermal cyclization of 8-trifluoromethylphenothiazine-1-carboxylic acid isothiocyanate (26) that was formed via interaction of compound 25 with potassium thiocyanate. It was shown that heating of compound 26 in diphenyl oxide leads to the formation of 1-thioxo-10-((trifluoromethyl)-1,2-di-hydro-1H-pyrimido-[5,6,1-kl]phenothiazin-3(2H)-one (27) (Scheme 6).
[5+1] Heterocyclization

Methods of the construction of 2-thioxopyrimidines based on [5+1] heterocyclization processes are more widespread. The first information about using of this method for the synthesis of compounds with thioxopyrimidine fragments appeared in patents published between 1967 and 1972. Ott\textsuperscript{30} claimed methods for preparation and chemical modification of substituted 5,8,9,13b-tetrahydro-6H-isoquinolino[2,1-c]quinazoline-6-thiones 29 by condensation of 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)anilines 28 with carbon disulfide (Scheme 7).

Scheme 7

\[
\begin{align*}
\text{Scheme 7} & \\
R^1, R^2 &= H, \text{OMe}; R^3 = H, \text{Cl} \\
\end{align*}
\]

A similar approach was used by Hardtmann\textsuperscript{31} for the synthesis of octahydro-1H-pyrido[1,2-c]pyrimidine-1-thione (31) by the reaction of an appropriate diamine 30 with carbon disulfide (Scheme 8).

Scheme 8

The same cyclization method was also used for the synthesis of pyrazolo[1,5-c]quinazoline-5(6H)-thione (33) from aniline derivative 32 (Scheme 9). The reaction proceeded with quantitative yield.\textsuperscript{32} Compound 33 was further alkylated by methyl iodide and the corresponding S-methyl derivative 34 was utilized in reactions with amines to synthesize pyrazolo[1,5-c]quinazolin-5-amines 35.

The investigation of Yip and colleagues\textsuperscript{33} was devoted to the synthesis of 2-substituted 1-N'-ethenoadenosides 37–39 which are fluorescent analogs of adenosine. (5-Amino-1H,1'1H-[2,4'-biimidazol]-1-yl)-\beta-D-ribofuranoside (36) was used as 1,5-binucleophilic starting material that interacted with carbon disulfide in pyridine medium.
forming compound 37 (Scheme 10). Alkylation and oxidation of compound 37 lead to nucleosides 38 and 39, respectively. Thiol–thione tautomerism was discussed and proven by comparative analysis of UV spectra of compound 37 and the product of its alkylation 38 in solutions of various pH.

A work published by Yamaji could be considered as a further development of the chemistry considered above and was dedicated to the synthesis of 2-substituted 1-N-6-etheno-adenosine-3',5'-cyclophosphates (Scheme 11). N-Glycoside of 1'-methyl-1H,1'H-[2,4'-biimidazol]-5'-amine 40 was used as the starting compound. Compounds 41–43 display fluorescence with emission maximum at 410–430 nm.

The interaction of substituted 4,5-dimethoxy-2-(1,2,3,4-tetrahydroquinolin-2-yl)anilines 44 with carbon disulfide in pyridine leads to the formation of the corresponding 7,11b,12,13-tetrahydro-6H-quinolino[1,2-c]quinazoline-6-thiones 45 (Scheme 12). Shishoo et al. investigated the reactivity of 2-amino-3-triazolylthiophenes 46 toward carbon disulfide in the alkaline alcoholic solutions. To the products was assigned the structure of thieno[3,2-e]1,2,4-triazolo[1,5-c]pyrimidine-5(6H)-thiones 47 (Scheme 13). The IR and mass spectra, but not NMR methods, were used to establish the structure of the obtained compounds. Thus, the assumption of existence of compounds 47 in the thiol form is debatable. Within this study, compound 47 were alkylated by dimethyl sulfate to yield methylsulfanyl derivatives 48.
The method of transformation of adenosine diphosphate (ADP, 49) into thioderivative 52 (Scheme 14) was described by Jefferson.\textsuperscript{37} The first stage of the synthesis was interaction of ADP with chloroacetaldehyde that led to the formation of imidazo[2,1-d]purine derivative 50. The subsequent alkaline hydrolysis of compound 50 allowed to obtain 1,5-binucleophile 51 which was then transformed into ribosylpyrophosphate 2-mercapto-1,4-dihydrobenzo[a]imidazol-2-yl)ethan-1-amine (Scheme 14)\textsuperscript{38} the reaction did not stop, after the nucleophilic addition and subsequent cyclization into 2-thioxo-pyrrolo[3,2-d]pyrimidine-1(2H)-thione (54) (Scheme 15). Alkylation of the latter with methyl iodide and subsequent alcoholsysis of the obtained methylsulfanyl derivative 57 with sodium methoxide lead to 6-benzoyl-3-ethyl-2-methoxy-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one (58).

An original method to access the [1,2,4]triazolo[3′,4′:2,3]pyrimido[1,6-a]benzimidazole system 62 that included the stage of formation and modification of partially hydrogenated 2-thioxopyrimidine fragment was presented in the work of Cherkaoui et al. (Scheme 16).\textsuperscript{39} The first step of the synthesis was the interaction of 2-(1H-benzimidazol-2-yl)ethan-1-amine (59) with carbon disulfide in basic medium. The resulting 3,4-dihydrobenzo[4,5]imidazo[1,2-c]pyrimidine-1(2H)-thione (60) was converted into the S-methylated derivative 61. Refluxing of compound 61 with acetic or benzoic acid hydrazides led to the mixtures of the tetracyclic compounds 62 and N′-(3,4-di-hydroxopyrimido[1,6-a]benzimidazol-1-yl)acet(o)benzo)hydrazides 63.

An interesting transformation was published by Gewald and his colleagues.\textsuperscript{40} They explored the reaction of 2-aminothiophene-3-carbonitrile and its substituted derivatives 64 with phenyl isocyanate (Scheme 17). It was established that unlike in some previously described similar cases (cf. Scheme 15)\textsuperscript{38} the reaction did not stop, after the nucleophilic addition and subsequent cyclization into 2-thioxopyrimidine moiety from the intermediate 65, at the formation of pyrrolo[3,2-d]pyrimidine 66, but proceeded as a tandem nucleophilic addition – nucleophilic substitution followed by formation of thiopyrimidine and imino-pyrimidine cycles. It should be noted that the structure of
the products 67 was proven both by a complex of physicochemical methods (1H, 13C NMR, IR spectra) and by alternative synthesis with thiophosgene as a reagent.

Sondhi et al. 41 performed the reaction of 3-isothiocyanatobutanal (68) with aromatic, heteroaromatic, and aliphatic diamines with the aim to find compounds with analgesic and anti-inflammatory activity. It was shown that structure of the products greatly depended on the type of diamine used (Scheme 18). The interaction of compound 68 with 3,4-disubstituted 1,2-phenylenediamines proceeded as a tandem reaction and resulted in the formation of pyrimidine and imidazole cycles. The authors of the cited study demonstrated that the reaction proceeds in a regioselective manner and led to the formation of 7,8-disubstituted 3-methyl-3,4,4a,5-tetrahydropyrimido[1,6-a]benzimidazole-1(2H)-thiones 69. Replacing 1,2-phenylenediamine with 2,3-diaminopyridine led to the formation of isolated pyrimidine cycle only (compound 70) in low yield. This fact could be explained by decreasing of amino group nucleophilicity due to the electron effect of pyridine nitrogen atom. Interaction of 3-isothiocyanatobutanal (68) with butane-1,4-diamine yielded bispyrimidine derivative 71.

Another good example of the [5+1] heterocyclization process involving carbon disulfide and 1,3-diamines 72 was demonstrated by Gößnitzer et al. 42 in the synthesis of 3-aryl-3,4-dihydropyrimido[1,6-a]benzimidazole-1(2H)-thiones 75 and products of their S-alkylation 76 (Scheme 20). 43

As a part of a study aimed to create new antiulcer drugs, a similar method, starting from benzimidazole derivatives 74 has been developed for the synthesis of 3-aryl-3,4-dihydropyrimido[1,6-a]benzimidazole-1(2H)-thiones 75 and products of their S-alkylation 76 (Scheme 20). 43
The formation of heterocycles by reactions of multifunctional compounds containing isothiocyanate and carbonyl groups has been systematically studied. It was found that the reaction of isothiocyanates containing aldehyde (compound 68) or ketone (compound 77) carbonyl group with 2-aminoacetonitrile hydrochloride (78) led to the formation of three alternative products 79, 80, or 81 (Scheme 21) depending on the reaction conditions and the structure of the carbonyl component.

Scheme 21

The reaction of compounds 68 and 77 with 2-amino-3-hydroxypyridine (82) was also described in the same paper (Scheme 22). Thus, 1-(3-hydroxypyridin-2-yl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione (83) was formed using isothiocyanate 77 and refluxing the starting compounds in methanol. In turn, conducting the reaction with compound 68 under the ambient temperature and increasing its duration to ten days resulted in the formation of 7,7-dimethyl-5a,6,7,8-tetrahydro-9H-imidazo[1,2-c]pyrazolo[4,3-c]pyrimidine-5-thione 86 (Scheme 23).

Another good example of the use of a heterocycle assembly was 1,5-dinucleophile by El-Essawy. It was shown that interaction of 2-(1H-imidazol-2-yl)-4,6-dimethylthieno[2,3-b]pyridin-3-amine (87) with carbon disulfide in pyridine led to 7,9-dimethylimidazo[1,2-c]pyrido[3',2';4,5]-thieno[2,3-e]pyrimidine-5(6H)-thione 88 (Scheme 24).

Kovalenko et al. published a series of papers devoted to the development of preparative methods and study of antibacterial and anticancer activity of 3-substituted potassium 2-oxo-2H-[1,2,4]triazino[2,3-c]quinoxaline-6-thiolates 90 and their S-alkylated derivatives 91, 92 (Scheme 25). The [5+1] heterocyclization of appropriate 3-(2-aminophenyl)-1,2,4-triazin-5(2H)-ones 89 with carbon disulfide or ethyl xanthogenate was used to form the target tricyclic system.

Scheme 23

7-substituted 2,3,6,7-tetrahydro-5H-imidazo[1,2-c]pyrazolo[4,3-c]pyrimidine-5-thione 86 (Scheme 23).

Scheme 24

Kovalenko et al. published a series of papers devoted to the development of preparative methods and study of antibacterial and anticancer activity of 3-substituted potassium 2-oxo-2H-[1,2,4]triazino[2,3-c]quinoxaline-6-thiolates 90 and their S-alkylated derivatives 91, 92 (Scheme 25). The [5+1] heterocyclization of appropriate 3-(2-aminophenyl)-1,2,4-triazin-5(2H)-ones 89 with carbon disulfide or ethyl xanthogenate was used to form the target tricyclic system.

Scheme 25

Farghaly and El-Kasser published a work that described a [5+1] heterocyclization in which 1,5-binucleophile 85 interacted with carbon disulfide and formed...
The introduction of microwave-assisted organic synthesis technology has affected also the area under review. From 2-(benzimidazol-2-yl)aniline (93) Soukri et al.\textsuperscript{51} have synthesized benzimidazo[1,2-c]quinazoline-6-thione (94) (Scheme 26). The irradiation of a mixture, absorbed on graphite, consisting of alkylation product 95 and an excess of an antranilic acid derivative led to a new heterocyclic system – 14-substituted 1H-benzimidazo[1,2-c]quinazolino[3,2-a]quinazolin-11-ones 96.

### Scheme 26

![Scheme 26](image)

Antypenko et al.\textsuperscript{52,53} showed a high potential of 2-(1H-tetrazol-5-yl)aniline (97) as the starting compound in [5+1] heterocyclizations. Thus, the interaction of compound 97 with carbon disulfide and potassium hydroxide in the ethanol or with potassium ethyl xanthogenate in isopropanol led to the formation of potassium tetrazolo[1,5-c]-quinazoline-5-thiolate 98 (Scheme 27). Furthermore, thiolate 98 and thione 99 were utilized in the alkylation reaction with various reagents (haloalkanes, haloalkylamines, halo ketones, halocarboxylic acids amides) to obtain S-substituted derivatives 100.

2-(1,2,4-Triazol-3-yl)phenylamines 101 also acted as 1,5-bineucleophiles in [5+1] heterocyclization with carbon disulfide in the presence of potassium hydroxide in ethanol or potassium ethyl xanthogenate in isopropanol.\textsuperscript{54,55} The possible pathways of the reaction were discussed, and potassium 2-hetaryl[1,2,4]triazolo[1,5-c]quinazolino-5-thiolates 102 and the respective thiones 103 were identified as products of the reaction. Subsequently, compounds 102 and 103 were used for the synthesis of S-substituted derivatives 104. Besides, authors conducted single-crystal X-ray analysis for one of the basic structures for indisputable determination of the cyclization direction.

### Tandem cyclizations

Some tandem reactions already were presented in previous sections, due to the fact that they were described within the scope of [4+2] and [5+1] cyclocondensations. In present section the most interesting domino-processes are considered.

One such domino reaction was developed by Sauter et al.\textsuperscript{27} The interaction of ethyl 2-isothiocyanatoacetate (14) with 2-amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-carbonitrile (105) led to the formation of condensed pyrimidine and imidazole fragments forming part of the 5-thioxo-6,8,10,11-tetrahydro-5H-imidazo[1,2-c]thiopyrano[4',3':4,5]-thieno[3,2-e]pyrimidin-2(3H)-one (106) molecule (Scheme 28). The reaction of nitrile 105 with ethyl 2-[[bis-(methylsulfanyl)methylidene]amino]acetate (12) was proceeding in a similar way forming 5-(methylsulfanyl)-10,11-dihydro-8H-imidazo[1,2-c]thiopyrano[4',3':4,5]thieno[3,2-e]-pyrimidin-2(3H)-one (107). The latter was also obtained by a direct alkylation of compound 106 with methyl iodide.

### Scheme 27

![Scheme 27](image)

### Scheme 28

![Scheme 28](image)

An interaction of 2-isothiocyanatobenzonitrile (108) with α-aminocetophenones was described by Bodtke and coworkers.\textsuperscript{56} The results of their research showed that the studied reaction yielded 2,3-disubstituted imidazo[1,2-c]-quinazoline-5(6H)-thiones 109 (Scheme 29). Formation of alternative products through the Dimroth rearrangement, such as 1,2-disubstituted imidazo[1,2-a]quinazoline-5(4H)-
thiones was disproven by NOESY experiment and X-ray diffraction analysis.

Synthesis and transformations of 6,10b-dihydropyrazolo[1,5-c]quinazoline-5(1H)-thiones 112 was described by Hull and Swain as a part of a series of works devoted to the study of the interaction of thiophosgene with heterocyclic compounds. o-Isothiocyanato-trans-cinnamic aldehydes 111 were obtained by a cleavage of quinoline cycle of compound 110 by thiophosgene in basic medium (Scheme 30). The interaction of aldehydes 111 with hydrazine hydrate in ethanol led to the formation of tricyclic compounds 112. The latter were reduced by sodium borohydride to the corresponding tetrahydro derivatives 113 that were used as starting compounds for the formation of 3-aryl-1,3,4,10b-tetrahydro-2H-thia-2a,2a1,6-triazaaceantrylen-3-ols 114. Besides, a possibility of alkylation or nucleophilic cleavage of compounds 112 was shown by obtaining compounds 115 and 116, respectively.

An original method of the construction of mercapto-pyrimidine fragment was offered by Yamazaki. It was shown that substituted alkyl N'-methylidenecarbamoylthiocarbamoylhydrazonothioates 117 readily interact with 2-(ethoxy-methylene)malononitrile (2) and form 2,2-disubstituted 5-alkylsulfanyl-2,3-dihydro[1,2,4]triazolo[1,5-c]pyrimidine-8-carbonitriles 119 (Scheme 31). The product of nucleophilic substitution 118 was proposed as an intermediate of this reaction.

The use of 2,4,6-triarylpyrimidinium perchlorate (120) in the synthesis of heterocyclic systems was described in works by Zvezdina et al. A thiosemicarbazide-mediated pyran ring opening in compounds 120 led to 3a-substituted 2,5-diphenyl-3a,6-dihydropyrazolo[1,5-c]pyrimidine-7(3H)-thiones 121 obtained together with pyridine derivatives 122 (Scheme 32). The alkylation of thiones 121 with methyl iodide provided new S-methyl derivatives 123.
possibility of tautomeric transformations of compounds 121 was studied by UV spectrometry method.

Francis et al. studied the synthesis and chemical modification of 5-thio-substituted 2-hetaryl[1,2,4]triazolo[1,5-c]quinazolines. Thus, it was found that the interaction of 5-chloro-2-isothiocyanatobenzonitrile (124) with furan-2-carboxyhydrazide (125) led to the formation of 2-(furan-2-yl)[1,2,4]triazolo[1,5-c]quinazoline-5(6H)-thione (126) (Scheme 33). The methylation of compound 126 led to the methylsulfanyl derivative 127. The SMe group in the molecule of compound 127 underwent substitution with ammonia yielding the corresponding amine 128.

Kranz et al. published a work describing the synthesis of 2,5-dimethylpyrazolo[1,5-c]pyrimidine-7(6H)-thione (130) via condensation of dehydroacetic acid (3-acetyl-2-hydroxy-6-methyl-4H-pyran-4-one) (129) with thiosemicarbazide (Scheme 34). Two alternative pathways of transformation were proposed. Considering the fact that the reaction of the proposed intermediate diacetylacetone (131) with thiosemicarbazide also yielded compound 130, the pathway B was accepted as more probable.

El-Ansary et al. described the synthesis and modification of 2-thioxopyrimidine-5-carbonitriles 135. The latter were obtained via three-component condensation of N-phenylurea (132), ethyl 2-cyanoacetate (133), and aromatic aldehyde 134 in ethanol (Scheme 35). Compounds 134 were used as starting materials for the synthesis of condensed heterocyclic systems containing 2-thioxopyrimidine moiety.

Louvel and coworkers published the results of their work aimed at the search for novel non-glycoside agonists of A1 adenosine receptors. 4-Amino-6-aryl-2-[hetaryl-methyl]sulfanyl]pyrimidine-5-carbonitriles 139 were selected as the target compounds and synthesized in two-step procedure that included a one-pot three-component
cyclocondensation of aromatic aldehyde 134, thiourea 137, and malonodinitrile 136 followed by the alkylation of the obtained 4-amino-6-aryl-2-mercaptopyrimidine-5-carbonitriles 138 (Scheme 36).

Pfeiffer et al. have developed an approach that could be successfully used for formation of 2-substituted 8,9,10,11-tetrahydro\[1\]benzothieno[3,2-e]\[1,2,4\]triazolo[1,5-c]pyrimidine-5(6H)-thiones 141a, as well as 2-substituted 8,9,10,11-tetrahydro\[1\]benzothieno[3,2-e]imidazo[1,5-c]pyrimidine-5(6H)-thiones 141b. The method was based on the interaction of 2-isothiocyanato-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (140) with hydrazides or aminocarbonyl compounds and allowed to obtain the target compounds with high yields (Scheme 37).

### Biological properties of 2-thiopyrimidines and their condensed derivatives

The study of biological activity of compounds containing 2-thiopyrimidine moiety began practically at the same time as systematic development of synthetic approaches toward this class of compounds. One of the first references to biological activities was found in a patent which discussed, along the methods of synthesis, the antiarthritic activity of 1-thioxo-10-(trifluoromethyl)-1,2-dihydro-1H-pyrimido-[5,6,1-kl]phenothiazin-3(2H)-one (27).

The work by Jefferson was one of the few early studies that described purposeful synthesis of compounds with the ability to initiate platelet aggregation. The main motivation of this study was the presence of such activity in adenosine-5'-diphosphate. An optimization of that molecule led to the synthesis of 2-[(3-aminopropyl)sulfanyl]-1,6-ethenoadenosine diphosphate (53) that showed a strong ability to initiate platelet aggregation.

El-Essawy reported the strong antifungal effect of compound 88 against Trichophyton rubrum and Chrysosporium tropicum along with moderate antimicrobial activity against Bacillus cereus.

The antitumor, antimicrobial, and fungicidal activity of S-substituted tetrazolo[1,5-c]quinazoline-5(6H)-thiones were described by Antypenko et al. It was shown, that 2-(tetrazolo[1,5-c]quinazolin-5-ylsulfanyl)ethanones 100c-g (Fig. 1) and 5-(3-chloropropylsulfanyl)tetrazolo[1,5-c]-quinazoline 100a inhibited growth of Candida albicans.
compound 100b inhibited growth of S. aureus and E. faecalis. Compounds 100c–g revealed moderate antitumor activity against standard NCI lines panel (Fig. 1).

Antitumor and antifungal activities of 2-hetaryl-[1,2,4]-triazolo[1,5-c]quinazoline-5(6H)-thiones were also observed by Billy et al.55 Thus, potassium 2-hetaryl-[1,2,4]-triazolo[1,5-c]quinazoline-5-thiolates with antibacterial activity. Research of leishmanicide activity was conducted on hamsters in dose 10 mg/kg. The authors established that among the investigated compounds was also effective against methicillin-resistant strains of S. aureus.

Ram's work67 was devoted to the search of leishmanicides and herbicides among pyrimidine derivatives and their condensed analogs. Research of leishmanicide activity was conducted on hamsters in dose 10 mg/kg. The authors established that among the investigated compounds S-substituted 2-mercaptopirimidine-5-carbonitriles 142a–c (Fig. 3) showed the highest activity.

Hericidal activity of the synthesized compounds was investigated against Echinochloa crus-galli, Lactuca sativa, and plants of subfamily Lemnoideae. It was established that the synthesized compounds exhibited a strong herbicidal activity against Lactuca sativa and plants of subfamily Lemnoideae and a reasonable activity against Echinochloa crus-galli.67

Within the work by Dianova et al.68 toxicity, anticancer, antiviral, and radioprotective activities of 2-[(7-amino-[1,2,4]triazolo[1,5-c]pyrimidin-5-yl)sulfanyl]acetic acid 143 and its derivatives 144, 145 (Fig. 4) were examined.

Breast adenocarcinoma AK-755, sarcoma 37 and 180 cell lines were used for anticancer tests. The abovementioned acid 143 showed low anticancer effect against cells of sarcoma 37 (growth inhibition 49 ± 3%) and low stimulating effect on the growth of breast adenocarcinoma AK-755, whereas its amide 145a inhibited the growth of both sarcoma 37 and carcinoma AK-755 (growth inhibition 35 ± 2.3%) and hydrazide 145d inhibited cell growth of AK-755 (35 ± 2.1%) and slightly stimulated growth of sarcoma 37; hydrazones 145e–g, unexpectedly, exhibited growth-stimulating effect (58–200%) against cells of sarcoma 37. None of the studied compounds showed activity against cell sarcoma 180. The investigation of the antiviral activity of all synthesized compounds referred in this study revealed that acid 143 exhibited a pronounced antiviral activity against influenza viruses type A and B (index protection 61 ± 8.5% for type A and 63 ± 9.2% for type B).

In Chern's work69 was described an antihypertensive effect and the ability to act as selective adrenoreceptor (AR) antagonists in the series of 2,3-dihydroimidazo[1,2-c]-quinazoline derivatives (Fig. 5), especially those (compounds 146) that contain thiopyrimidine moiety. The study was conducted on rats with hypertension using prazosin as a reference drug. The results showed, that the tested compounds reduced blood pressure (−33.9 ± 9.7% in 1 h and −22.5 ± 7.6% in 4 h after the administration).

**Figure 2.** Potassium 2-hetaryl-[1,2,4]triazolo[1,5-c]quinazoline-5-thiolates with antibacterial activity.

**Figure 3.** 2-Thiosubstituted pyrimidines with leishmanicidal activity.

**Figure 4.** 5-Sulfanyl derivatives of [1,2,4]triazolo[1,5-c]pyrimidines tested for anticancer and antiviral activity.

**Figure 5.** Adrenoreceptor antagonists with imidazo[1,2-c]-quinazoline moiety.

Chemistry of Heterocyclic Compounds 2017, 53(3), 256–272
In the work by Sondhi and his colleagues, antiviral activity against HIV virus was studied among pyrimido[1,6-a]benzimidazole derivatives. Unfortunately, the results of the study showed low activity of these compounds. The same research group also investigated anti-inflammatory, analgesic, and antiamebic activities of compounds that were similar to those described in the previous work. It was shown that the tested compounds (Fig. 6) exhibited anti-inflammatory effect in a range of 5–46% in dose 50 mg/kg. Among other compounds, only thione showed a moderate anti-inflammatory activity, while compound showed high antiamebic activity (IC_{50} 1.82 µM).

The same authors identified a related biheterocyclic compound that possessed anti-inflammatory and analgesic effects, as well as the ability to inhibit the activity of protein kinases CDK-1 (IC_{50} 5.0 µM) (Fig. 6). In another study, the same group reported anti-inflammatory and anticancer activities in the same fused pyrimidine series. The results showed that compounds that are S-substituted analogs of compounds (Fig. 6) had a moderate anti-inflammatory activity in dose 100 mg/kg. An investigation of anticancer activity showed that these compounds also inhibited cell growth of melanoma, prostate, colon, breast, ovarian cancer and cancer of CNS. Compound, an N-acylated analog of compounds, was the most active and inhibited by a half the growth of CNC cancer (U251) cells at concentration 5.02 µM.

Nalbandyan and his colleagues conducted a study of psychotropic properties of pyrano[4',3':4,5]furo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines and pyrano[4',3':4,5]furo[3,2-e]tetrazolo[1,5-c]pyrimidines (Fig. 7). It was shown that compounds of this series exhibited anxiolytic, antiamnestic, ataxic, and anticorazol activities.

Li and colleagues reported 2-[(aryloyl(phenylacetyl)methyl)sulfonyl]-1,6-ethenoadenosine triphosphates as promising nucleoside-based reverse transcriptase inhibitors (Fig. 8).

Bhuiyan and his colleagues reported on significant antimicrobial and antifungal activities of 5-methylsulfanyl-8,9-diphenylfuro[3,2-e]imidazo[1,2-c]pyrimidin-2(3H)-one (Fig. 9).
Lauria et al.\textsuperscript{75} presented a search for anticancer agents among thiopyrimidine moiety-containing annulated pyrrolopyrimidines 153 (Fig. 10) using the Virtual Lock-And-Key chemometric protocol.

El-Gazzar\textsuperscript{76} presented data on the antimicrobial activity of pyrimido[4,5-b]quinolines and pyrimido[2,3-d]pyrimidines. A moderate antimicrobial activity of compounds 154, 155 (Fig. 11) was discussed. The same research group\textsuperscript{77} continued the search for antioxidant, anti-inflammatory, and analgesic agents among azopyrimidoquinazolines. 5-Aryl-9-arylidene-2-thioxo-2,3,5,6,7,8,9,10-octahydroprymidine(4,5-b)quinolin-4(1H)-ones 156 were identified as compounds with the highest antioxidant activity. Thus, their ability to inhibit oxidative processes were comparable with ascorbic acid as the reference drug. The members of this class of compounds also were the most active anti-inflammatory agents in the carrageenan-induced paw edema model (protection percent 40.2 ± 1.05 to 62.4 ± 2.03).

Kovalenko et al.\textsuperscript{47–50,78–82} presented the results of biological activity study of 3-R-6-thio-substituted 1H-[1,2,4]-triazino[2,3-c]quinazolin-2-ones 91, 92 are most active against the following tumor cell lines: K-562 (pGI\textsubscript{50} 6.47), SR (pGI\textsubscript{50} 6.42) of leukemia; SNB-75 (pGI\textsubscript{50} 6.07) of CNS cancer; CAKI-1 (pGI\textsubscript{50} 5.94), A498 (pGI\textsubscript{50} 5.93–7.57) of renal cancer; NCI-H522 (pGI\textsubscript{50} 6.65) and HOP-92 (pGI\textsubscript{50} 6.01–6.20) of non-small lung cancer; HCT-116 (pGI\textsubscript{50} 5.93–6.35), HT29 (pGI\textsubscript{50} 5.96–6.39), COLO 205 (pGI\textsubscript{50} 6.30) and KM12 (pGI\textsubscript{50} 6.31) of colon cancer; MALME-3M (pGI\textsubscript{50} 6.28), SK-MEL-5 (pGI\textsubscript{50} 6.32) of melanoma; OVCAR-3 (pGI\textsubscript{50} 6.59) of ovarian cancer; MCF7 (pGI\textsubscript{50} 6.32), SK-MEL-5 (pGI\textsubscript{50} 6.31) of CNS cancer; 3-Ethylbicyclo[2.2.1]heptan-2-yl-2-[3-(4-methoxyphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl]-sulfanylacetamide (91a) (Fig. 13) was identified as lead compound with remarkable anticancer activity.\textsuperscript{77} The significant number of compounds tested for anticancer activity allowed to evaluate quantitative structure–activity relationships.\textsuperscript{82}
El-Ansary$^{63}$ and coworkers studied the anticancer activity of 2-thioxopyrimidine-5-carbonitrile 135 and their condensed analogs. The obtained data allowed to identify several compounds 135a, 157a,b, and 158 that showed cytotoxic activity against HepG2, PC3, MCF7 test lines (Fig. 14).

Compounds 9 combining 2-thiopyrimidine and steroid fragments were studied for their anabolic and androgenic activity, as well as acute toxicity.$^{26}$ It was shown that these compounds are almost nontoxic and are able to increase the muscle mass. The determining role of 2-thiopyrimidine moiety in respect to the biological activity was noted. It was suggested that the presence of pyrimidine cycle and thiol group conditioned the formation of hydrogen bonds with human androgen receptor hGR.

Abdelhafez and coauthors$^{83}$ described the results of the purposeful search of novel anticancer agents among compounds that contain benzofuran cycle, including substances in which the latter is combined with 2-thiopyrimidine moiety. It was shown that 6-aryl-4-(6-hydroxy-4-methoxy-1-benzofuran-5-yl)-5,6-dihydropyrimidine-2(1H)-thiones 159a,b (Fig. 15) possess VEGFR-2 inhibiting activity and suppress the growth of cancer cell lines both in vitro and in vivo. The results of docking studies were aimed to find the VEGFR-2 binding features of synthesized compounds and correlation between docking studies scores and their VEGFR-2 inhibiting and anticancer activity against lung carcinoma (NCI-H460), glioblastoma (SF268), and prostate cancer (PC-3).

The work by Al-Masoudi$^{84}$ was devoted to the synthesis and evaluation of antiviral and antimicrobial activity of 2-thioxopyrimidines and their complexes with platinum(II) and ruthenium(III). It was shown that among the obtained compounds only two, namely, 4-{[(6-amino-1,3-dimethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)diazeyl]-N-(4-methylpyrimidin-2-yl)benzenesulfonamide (160) and 6-amino-5-{[(4-chlorophenyldiazeyl]-1,3-dimethyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one complex with Pt(II)Cl2 (161), revealed any significant antiviral activity (Fig. 16). The former was also the only compound active against S. aureus and E. coli, which was quite predictable considering the presence of sulfamerazine fragment in its molecular structure.

Louvel$^{64}$ presented the results that identified S-substituted 4-amino-6-aryl-2-mercaptopyrimidine-5-carbonitriles 139 as agonists or partial agonists of A1 adenosine receptors. In the same paper, its authors discussed the kinetics of ligand–receptor binding. It was found that, depending on the nature of substituent, the binding period may vary in the range of 1.2–63.8 min. It was also shown that there were not any correlations between kinetic parameters of complexe dissociation and the effectiveness of synthesized compounds as A1 adenosine receptors agonists.

Piechowicz and coauthors$^{85}$ described the inhibiting activity of compounds in which pyrimidine and thiazole fragments were joined by thioacetamide linker toward Ca-dependent chloride channels TMEM16A/Ano1. Despite the fact that most of the synthesized compounds were inactive at 10 µM concentration authors isolated a molecule that may be identified as lead compound 162 (Fig. 17).
Santhoshi and coauthors\textsuperscript{86} showed that S-substituted 2-thiopyrimidine derivatives 163a,b (Fig. 18) containing 2-carboxy-3-arylpropene fragment possess COX-2 inhibiting activity.

2-Thiopyrimidines and their condensed analogs are a promising class of bioactive agents. Condensed derivatives of 2-thiopyrimidine, especially their biological activities, are comparatively less studied, but they nevertheless have also captured the attention of medicinal chemists. Among the possible synthetic pathways, the [5+1] heterocyclization is the most widely used method for 2-thiopyrimidine fragment formation.

References

1. Gabriel, S.; Colman, J. Ber. Dtsch. Chem. Ges. 1899, 32, 2921.
2. Angerstein, S. Ber. Dtsch. Chem. Ges. 1901, 34, 3956.
3. Schlenker, J. Ber. Dtsch. Chem. Ges. 1901, 34, 2812.
4. Gabriel, S.; Colman, J. Ber. Dtsch. Chem. Ges. 1902, 35, 1569.
5. Backer, H. J.; Grevenstuk, A. B. Rec. Trav. Chim. Pays-Bas. 1945, 64, 115.
6. Roblin, R.; Clapp, J. J. Am. Chem. Soc. 1950, 72, 4890.
7. English, J.; Leffler, E. J. Am. Chem. Soc. 1950, 72, 4324.
8. Boarland, M. P. V.; McOmie, J. F. W. J. Chem. Soc. 1951, 1218.
9. Boarland, M. P. V.; McOmie, J. F. W. J. Chem. Soc. 1952, 3722.
10. Marshall, J. R.; Walker, J. J. Chem. Soc. 1951, 1004.
11. Martin, R. H.; Mathieu, J. Tetrahedron. 1957, 1, 75.
12. Schmidt, C. L.; Townsend, L. B. J. Heterocycl. Chem. 1970, 7, 715.
13. Foye, W. O.; Abood, N.; Kauffman, J. M.; Kim, Y.-H.; Patel, B. R. Phosphorus, Sulfur Silicon Relat. Elem. 1980, 8, 205.
14. Hurst, D. T. Heterocycles 1984, 22, 79.
15. Cherny, Y.-J. Tetrahedron Lett. 2002, 58, 887.
16. Argüello, J. E.; Schmidt, L. C.; Peñãñory, A. B. Org. Lett. 2003, 5, 4133.
17. Furukubo, Sh.; Miyazaki, H. Eur. Patent 1956009.
18. Lee, J.; Kim, J. Y.; Choi, J.; Lee, S.-H.; Lee, J. Bioorg. Med. Chem. Lett. 2010, 20, 7046.
19. Zhang, X.; Zhang, N.; Chen, G.; Turpoff, A.; Ren, H.; Takasugi, J.; Morrill, C.; Zhu, J.; Li, C.; Lemnox, W.; Paget, S.; Liu, Y.; Almstead, N.; Njorge, G.; Gu, Z.; Komatsu, T.; Clausen, V.; Espiritu, C.; Graci, J.; Colacino, J.; Lahser, F.; Risher, N.; Weetall, M.; Nomeir, A.; Karp, G. Bioorg. Med. Chem. Lett. 2013, 23, 3947.
20. Benneche, T.; Gacek, M. J.; Undheim, K. US Patent 4423047.
21. Rodgers, J. D.; Shepard, S.; Arvanitis, A. G.; Wang, H.; Storage, L.; Fulmer, B.; Shao, L.; Zhu, W.; Glenn, J. US Patent 20100298334.
22. Boebel, T. A.; Lorsbach, B.; Martin, T. P.; Owen, J.; Sullenberger, M. T.; Yao, C. US Patent 201152300.
23. Gabos, B.; Ripa, L.; Stenvall, K. WO Patent 2006004532.
24. Miyamoto, Y.; Yamazaki, C. J. Heterocycl. Chem. 1997, 34, 871.
25. Layeva, A. A.; Nosova, E. V.; Lipunova, G. N.; Trashkakhova, T. V.; Charushin, V. N. J. Fluorine Chem. 2007, 128, 748.
26. Abdalla, M.; Amr, A. E.; Al-Omar, M. A.; Hussain, A. A.; Amer, M. S. Russ. J. Bioorg. Chem. 2014, 40, 568.
27. Sauter, F.; Fröhlich, J.; Ahmed, E. K. Monatsh. Chem. 1996, 127, 319.
28. Chowdhury, A. Z. M. S.; Shibata, Y. Chem. Pharm. Bull. 2001, 49, 391.
29. Weinstock, J.; Gaitanopoulos, D. E.; Sutton, B. M. J. Org. Chem. 1975, 40, 1914.
30. Ott, H. US Patent 3297696.
31. Hardtmann, G. US Patent 3631046.
32. Ott, H. US Patent 3531482.
33. Yip, K.-F.; Tsou, K.-C. J. Org. Chem. 1975, 40, 1066.
34. Yamajj N.; Yuasa Y.; Kato, M. Chem. Pharm. Bull. 1976, 24, 1561.
35. Phillips, S. D.; Castle, R. N. J. Heterocycl. Chem. 1980, 17, 1665.
36. Shishoo, C. J.; Devani, M. B.; Ullas, G. V.; Anathan, S.; Bhadti, V. S. J. Heterocycl. Chem. 1987, 24, 1125.
37. Jefferson, J. R.; Hunt, J. B.; Jamieson, G. A. J. Med. Chem. 1987, 30, 2013.
38. Danswan, G.; Kennewell, P. D.; Tully, W. R. J. Heterocycl. Chem. 1989, 26, 293.
39. Cherkaoui, O.; Essassi, M.; Zniber, R. Tetrahedron Lett. 1990, 31, 5467.
40. Gewald, K.; Jeschke, T.; Gruner, M. J. Prakt. Chem. 1991, 333, 229.
41. Sondhi, S. M.; Rajvanshi, S.; Johar, M.; Barti, N.; Azam, A.; Singh, A. K. Eur. J. Med. Chem. 2002, 37, 835.
42. Gößnitzer, E.; Punkenhofer, A.; Ryder, N. S. Arch. Pharm. 2003, 336, 336.
43. Shafik, R. M.; Shams El-Din, S. A.; Eshba, N. H.; Desheesh, M. A.; Abdel-Aty, A. S.; Ashour, H. M. Pharmazie 2004, 59, 899.
44. Sondhi, S. M.; Goyal, R. N.; Lahoti, A. M.; Singh, N.; Shukla, R.; Raghubir, R. Bioorg. Med. Chem. 2005, 13, 3185.
45. Farghaly, A.-R.; El-Kashef, H. Monatsh. Chem. 2006, 137, 1195.
46. El-Essawy, F. A.; Hawatta, M. A.; Abdel-Megied, A. E.-S.; El-Sherbeny, D. A. J. Heterocycl. Compd. 2010, 46, 325. [Khim. Geterotskli. Soedin. 2010, 415.]
47. Berest, G. G.; Voskoboykin, O. Yu.; Kovalenko, S. I.; Antypenko, O. M.; Nosulenko, I. S.; Katsaev, A. M.; Shandrovskaya, O. S. Eur. J. Med. Chem. 2011, 46, 6066.
48. Berest, G. G.; Voskoboykin, O. Yu.; Kovalenko, S. I.; Nosulenko, I. S.; Antypenko, L. M.; Antypenko, O. M.; Shvets, V. M.; Katsev, A. M. Sci. Pharm. 2012, 80, 37.
49. Kovalenko, S. I.; Nosulenko, I. S.; Voskoboykin, A. Yu.; Berest, G. G.; Antypenko, L. N.; Antypenko, A. N.; Katsev, A. M. Sci. Pharm. 2012, 80, 837.
50. Kovalenko, S. I.; Nosulenko, I. S.; Voskoboykin, A. Yu.; Berest, G. G.; Antypenko, L. N.; Antypenko, A. N.; Katsev, A. M. Med. Chem. Res. 2013, 22, 2610.
51. Soukri, M.; Guillaumet, G.; Besson, T.; Aziane, D.; Aaḍil, M.; Essassi, E.-M.; Akssira, M. Tetrahedron Lett. 2000, 41, 5857.
