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

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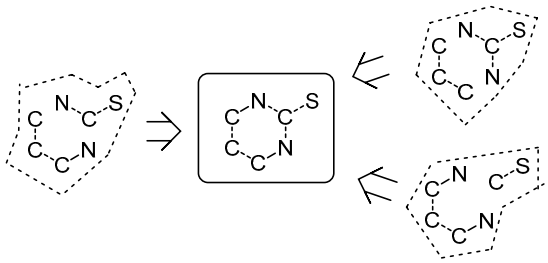


The known methods for synthesis of thioxopyrimidines and their condensed analogs with exocyclic sulfur atom are summarized and discussed. The most popular approaches are based on [3+3], [4+2], [5+1] cyclization processes or domino reactions. The literature data analysis shows that the title compounds 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.

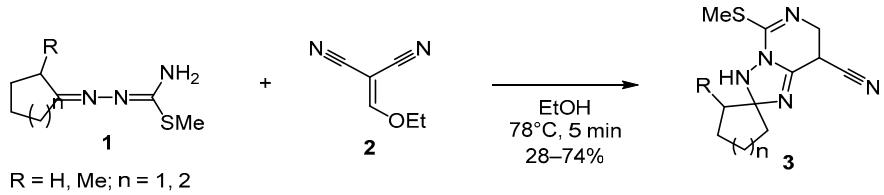
Pyrimidines and their annulated derivatives exhibit significant biological activity and are versatile objects for chemical modification. This class of heterocyclic compounds is represented by a great number of medicines, such as sedative (barbiturates), antiviral (idoxuridine, tenofovir, penciclovir), antimetabolitic (raltitrexed), diuretic (triamterene). However, despite of the decades worth of search for bioactive agents among compounds with pyrimidine moiety their potential is still not exhausted. The progress in high-throughput biological screening technologies and a great variety of heterocyclic derivatives provide almost unlimited potential in creating of physiologically active molecules and thus determines the need to develop new effective method for their synthesis.

First investigations of thiopyrimidines began in XIX century.[1] However, the introduction of thiol group may be considered to be less known direction of chemical modification. It provides additional opportunities for further functionalization and ability to influence the oxidative processes in the organism. Therefore, the present review is devoted to collection and analysis of literature data regarding the methods of synthesis and studies of biological properties of pyrimidine derivatives and their condensed analogs with exocyclic sulfur atom at position 2 of the pyrimidine ring. In many cases methods of synthesis of such heterocyclic systems are limited to direct interaction of various 2-halo derivatives with sulfur-containing reagents.[1–23] There are, however, methods where the formation of 2-thioxopyrimidines and their condensed analogs is based on the [3+3], [4+2], or [5+1] heterocyclization reactions and domino reactions which are the topic of the present review.

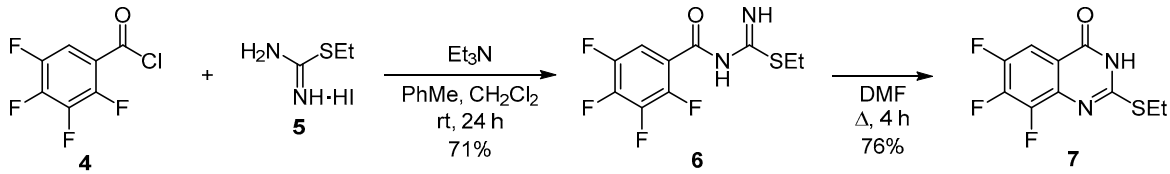
[3+3] Heterocyclizations

Although the formation of 2-thioxo- or 2-mercapto-pyrimidine system using [3+3] heterocyclization process has been less explored there are some published examples in literature. Thus, Miyamoto's[24] group had investigated the interaction of 2-(ethoxymethylidene)malononitrile (**2**) with methyl *N*'-cycloalkylylidenecarbamohydrazonothioates **1**, which led to the formation of spirocondensed heterocyclic systems **3** containing pyrimidine ring (Scheme 1).

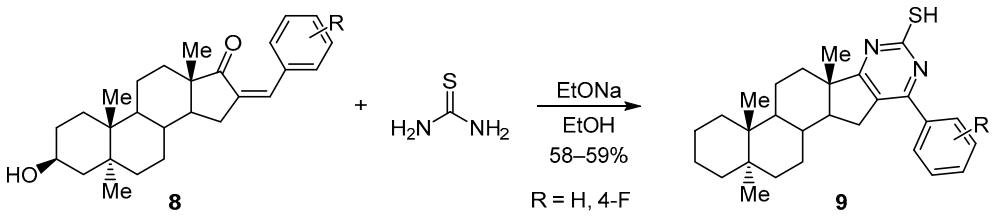
Scheme 1



Scheme 2



Scheme 3



Layeva[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-2-(ethylsulfanyl)quinazolin-4(3*H*)-ones **7**.

Abdalla and coworkers[26] used a previously known method (condensation of α,β-unsaturated ketones **8** with thiourea) to form compounds **9** containing the 2-mercaptopyrimidine fragment condensed with a steroid moiety (Scheme 3).

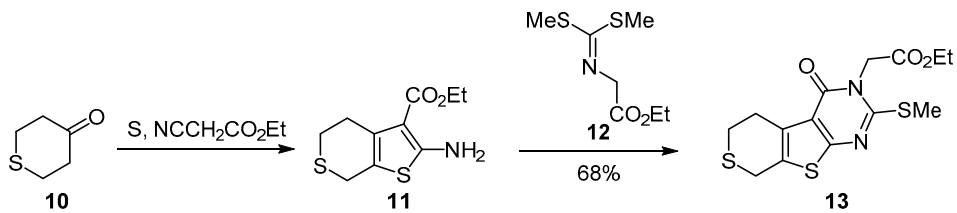
[4+2] Heterocyclization

Methods of synthesis of 2-thioxopyrimidines and their annulated derivatives *via* [4+2] cyclocondensation reactions are more known and original at the same time. In most cases they are based on the interaction between 1,4-binucleophiles and 2-{[bis(methylsulfanyl)methylidene]-amino}acetate, isothiocyanates, and related compounds. Thus, Sauter with his colleagues[27] from ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]thiopyran-3-carboxylate (**11**) (obtained from tetrahydro-4*H*-thiopyran-4-one (**10**)) and ethyl 2-{[bis-(methylsulfanyl)methylidene]amino}acetate (**12**) synthesized an annulated pyrimidine system, namely, ethyl 2-[2-(methylsulfanyl)-4-oxo-5,8-dihydro-4*H*-thiopyrano-[4',3':4,5]thieno[2,3-*d*]pyrimidin-3(6*H*)-yl]acetate (**13**) (Scheme 4).

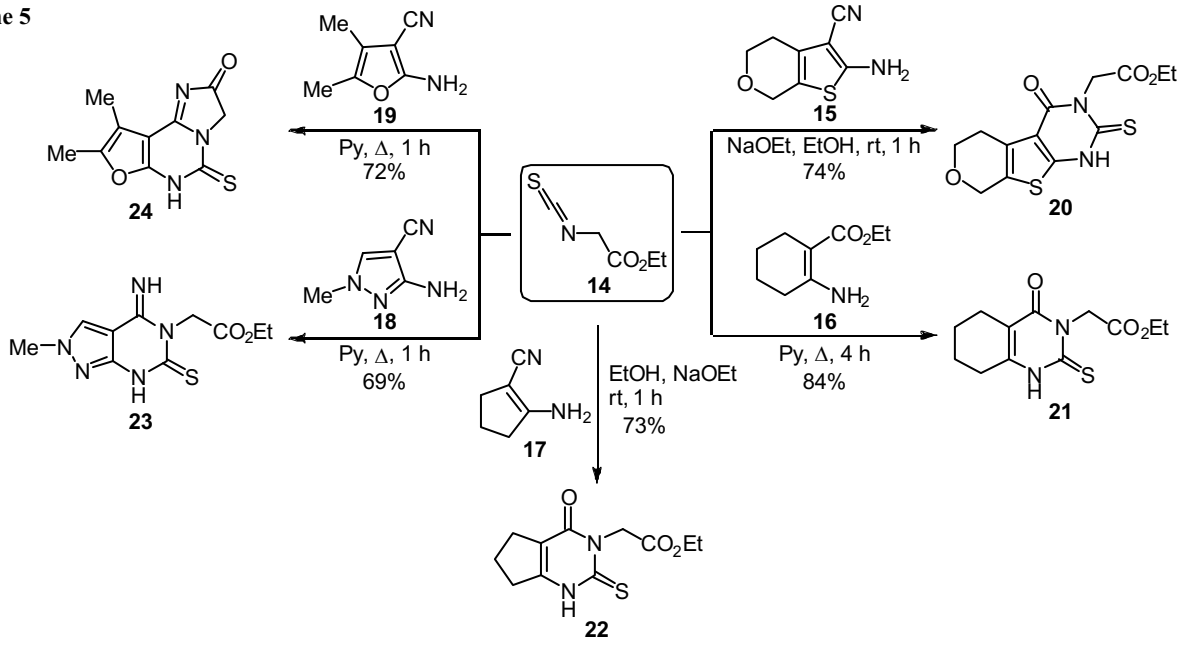
Chowdhury and Shibata[28] published results of the study in which they used a similar approach for pyrimidine derivative formation. Authors used 2-isothiocyanatoacetate (**14**) as electrophilic reagent and various *o*-amino nitriles **15**, **17**–**19** or *o*-amino ester **16** as 1,4-binucleophiles (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-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**24**) as the reaction product.

Weinstock et al.[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-dihydro-1*H*-pyrimido-[5,6,1-*kl*]phenothiazin-3(2*H*)-one (**27**) (Scheme 6).

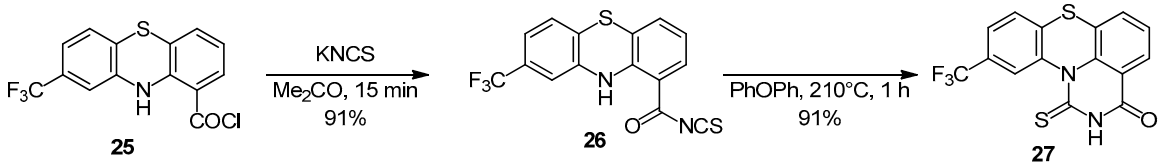
Scheme 4



Scheme 5



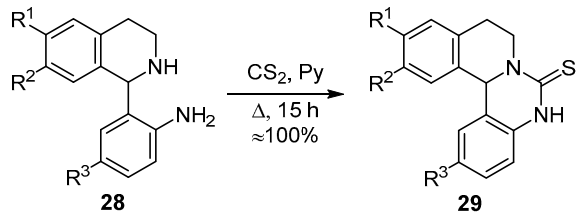
Scheme 6



[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[30] claimed methods for preparation and chemical modification of substituted 5,8,9,13b-tetrahydro-6*H*-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

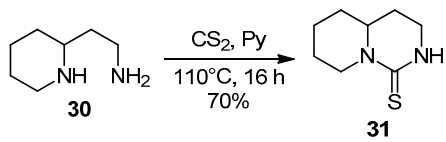


R^1, R^2 = H, OMe; R^3 = H, Cl

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

The same cyclization method was also used for the synthesis of pyrazolo[1,5-*c*]quinazoline-5(6*H*)-thione (**33**) from aniline derivative **32** (Scheme 9). The reaction

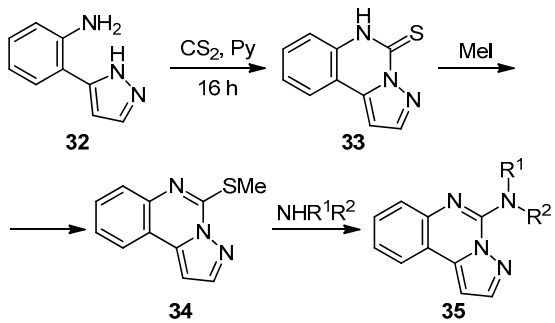
Scheme 8



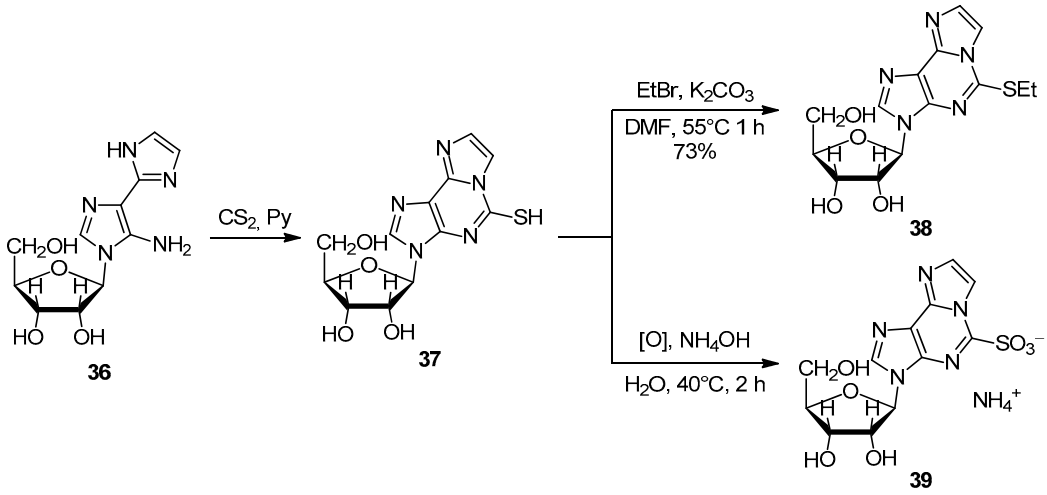
proceeded with quantitative yield.[32] Compound **33** was further alkylated by methyl iodide and the corresponding *S*-methyl derivative **34** was utilized in reactions with amines to synthesize pyrazolo[1,5-*c*]quinazolin-5-amines **35**.

The investigation of Yip and colleagues[33] was devoted to the synthesis of 2-substituted 1-N^6-ethenoadenosides **37**–**39** which are fluorescent analogs of adenosine. (5-Amino-1*H*,1'*H*-[2,4'-biimidazol]-1-yl)-β-D-ribofuranoside (**36**) was used as 1,5-binucleophilic starting material that interacted with carbon disulfide in pyridine medium

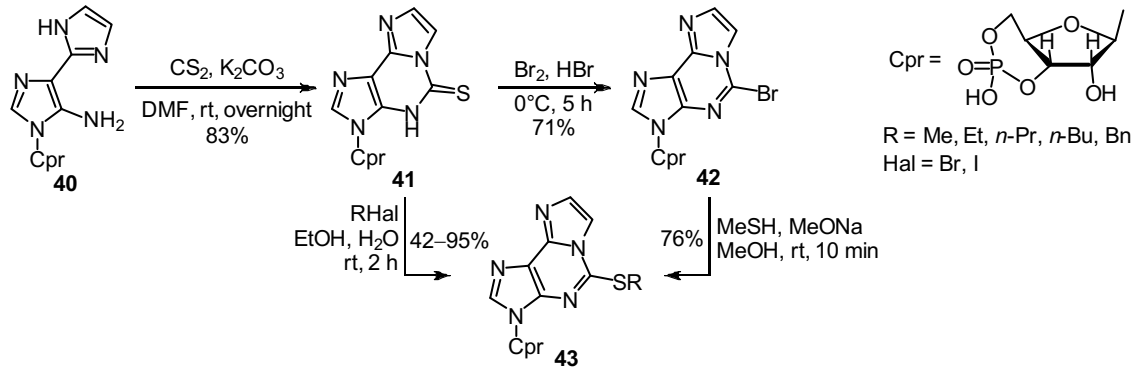
Scheme 9



Scheme 10



Scheme 11

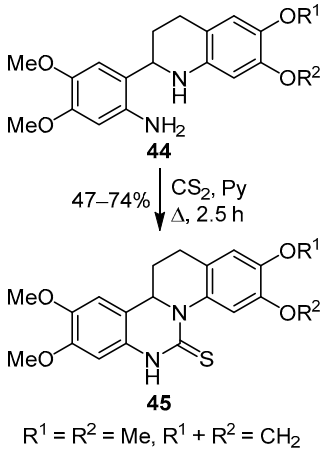


forming compound **37** (Scheme 10). Alkylation and oxidation of compound **37** lead to nucleosides **38** and **39**, respectively. Thiol–thione tautomerism was discussed and proven by comparative analysis of UV spectra of compound **37** and the product of its alkylation **38** in solutions of various pH.

A work published by Yamaji[34] 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-1*H*,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.

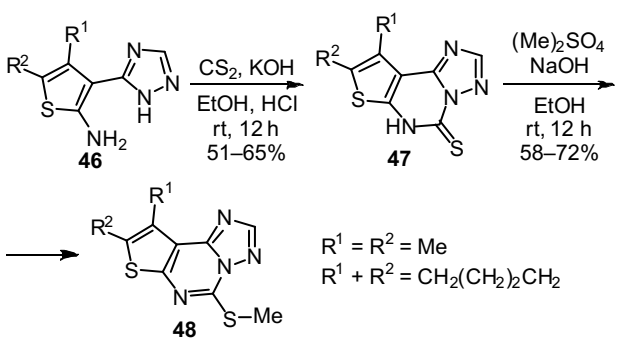
The interaction of substituted 4,5-dimethoxy-2-(1,2,3,4-tetrahydroquinolin-2-yl)anilines **44** with carbon disulfide in pyridine leads to the formation of the corresponding 7,11b,12,13-tetrahydro-6*H*-quinolino[1,2-*c*]quinazoline-6-thiones **45** (Scheme 12).[35]

Scheme 12

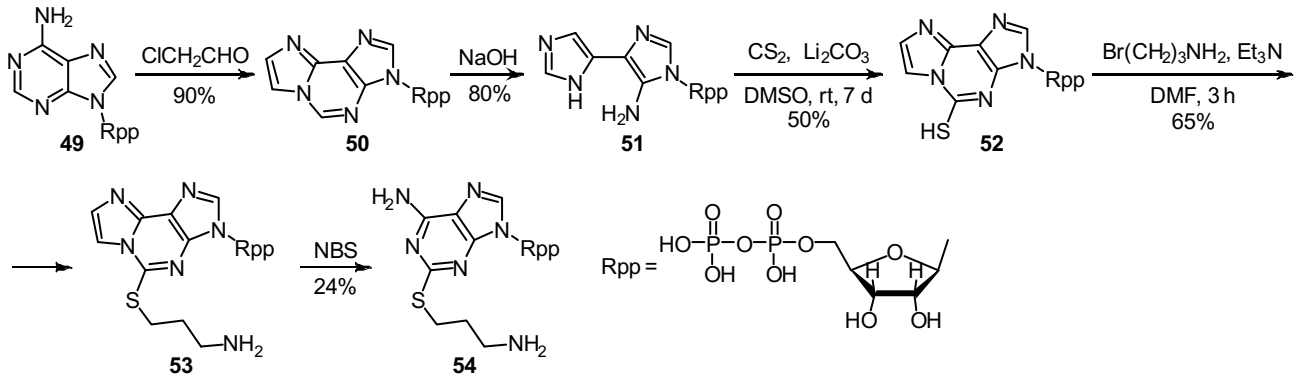


Shishoo et al.[36] investigated the reactivity of 2-amino-3-triazolylthiophenes **46** toward carbon disulfide in the alkaline alcoholic solutions. To the products was assigned the structure of thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thiones **47** (Scheme 13). The IR and mass spectra, 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**.

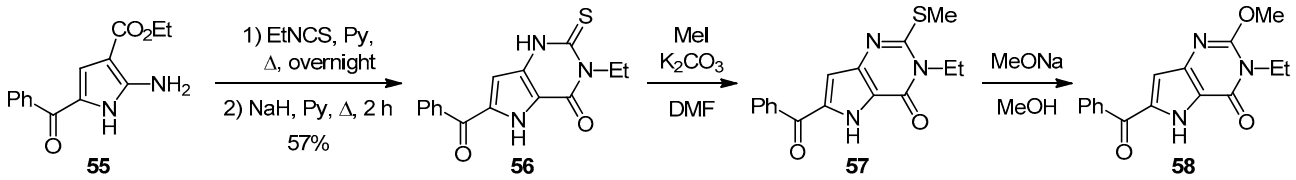
Scheme 13



Scheme 14



Scheme 15



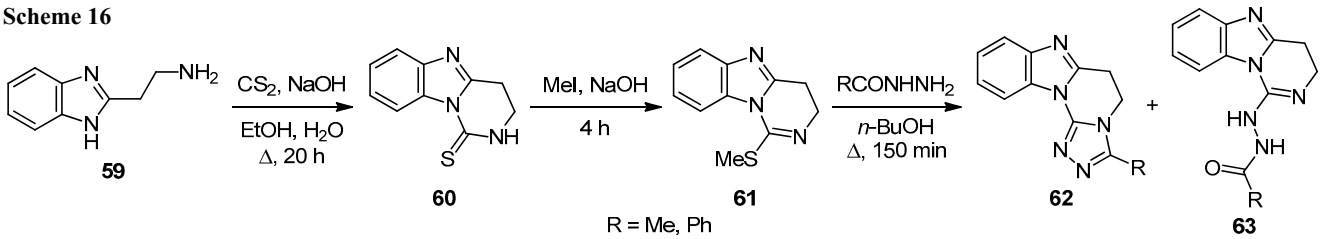
The method of transformation of adenosine diphosphate (ADP, **49**) into thioderivative **52** (Scheme 14) was described by Jefferson.[37] The first stage of the synthesis was interaction of ADP with chloroacetaldehyde that led to the formation of imidazo[2,1-*i*]purine derivative **50**. The subsequent alkaline hydrolysis of compound **50** allowed to obtain 1,5-binucleophile **51** which was then transformed into ribosylpyrophosphate 2-mercapto-1,N^6-ethenoadenosine diphosphate (**52**) *via* [5+1] heterocyclization with carbon disulfide. Alkylation of compound **52** by 3-bromopropanamine yielded the corresponding 2-[(3-aminopropyl)sulfanyl]-1,N^6-ethenoadenosine diphosphate (**53**). Further degradation of the imidazole cycle by *N*-bromosuccinimide allowed to obtain 2-[(3-aminopropyl)sulfanyl]adenosine diphosphate (**54**).

The synthesis of ethyl 2-amino-5-benzoyl-1*H*-pyrrole-3-carboxylate (**55**) and its use for the synthesis of 2-thioxopyrimidine-containing condensed derivatives were described in the work by Danswan et al.[38] Thus, it was shown that interaction of compound **55** with ethyl isothiocyanate yielded 6-benzoyl-3-ethyl-2-thioxo-2,3-dihydro-1*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one (**56**) (Scheme 15). Alkylation of the latter with methyl iodide and subsequent alcoholysis of the obtained methylsulfanyl derivative **57** with sodium methoxide lead to 6-benzoyl-3-ethyl-2-methoxy-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one (**58**).

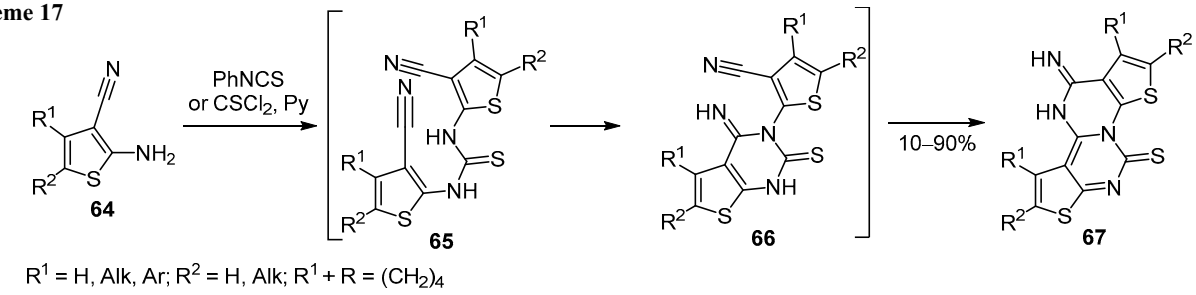
An original method to access the [1,2,4]triazolo[3',4':2,3]pyrimido[1,6-*a*]benzimidazole system **62** that included the stage of formation and modification of partially hydrogenated 2-thioxopyrimidine fragment was presented in the work of Cherkaoui et al. (Scheme 16).[39] The first step of the synthesis was the interaction of 2-(1*H*-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(2*H*)-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-dihydropyrimido[1,6-*a*]benzimidazol-1-yl)aceto(benzo)hydrazides **63**.

An interesting transformation was published by Gewald and his colleagues.[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)[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 iminopyrimidine cycles. It should be noted that the structure of

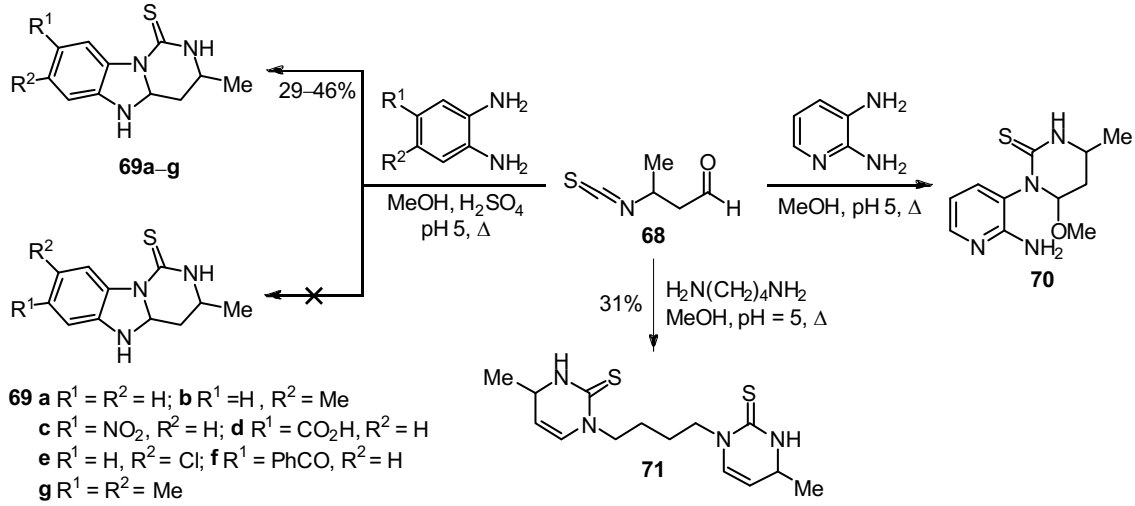
Scheme 16



Scheme 17



Scheme 18

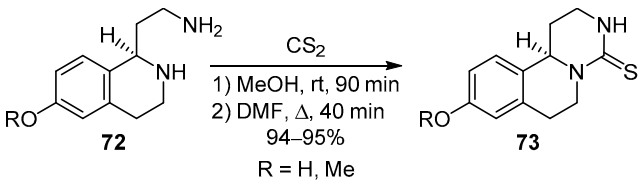


the products **67** was proven both by a complex of physicochemical methods (^{1}H, ^{13}C NMR, IR spectra) and by alternative synthesis with thiophosgene as a reagent.

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(2*H*)-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 nucleophility due to the electron effect of pyridine nitrogen atom. Interaction of 3-isothiocyanatobutanal (**68**) with butane-1,4-diamine yielded bispyrimidine derivative **71**.

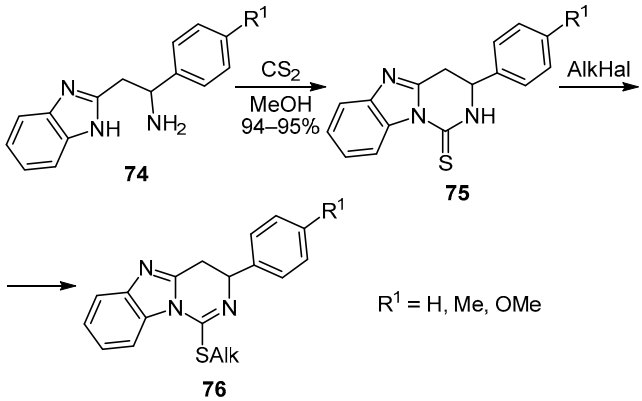
Another good example of the [5+1] heterocyclization process involving carbon disulfide and 1,3-diamines **72** was demonstrated by Gößnitzer et al.[42] in the synthesis of 1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-4-thiones **73** (Scheme 19). Their modification allowed to obtain compounds with significant antimicrobial activity.

Scheme 19



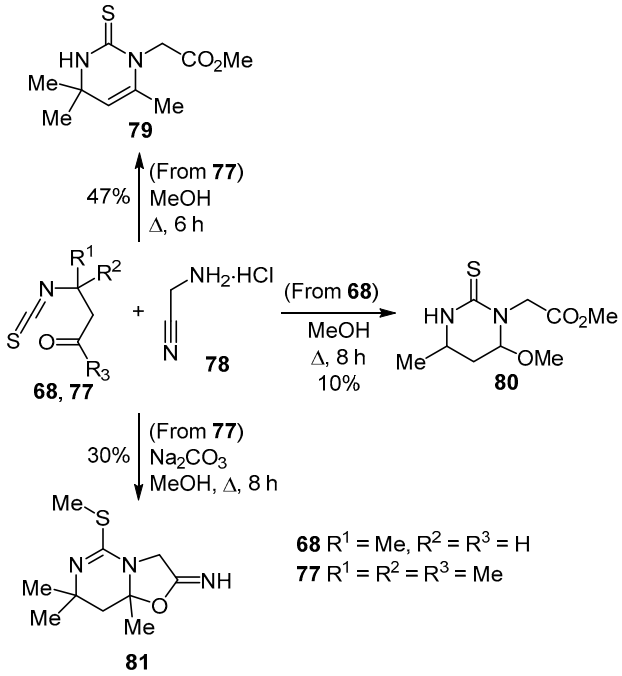
As a part of a study aimed to create new antiulcer drugs, a similar method, starting from benzimidazole derivatives **74** has been developed for the synthesis of 3-aryl-3,4-dihydropyrimido[1,6-*a*]benzimidazole-1(2*H*)-thiones **75** and products of their *S*-alkylation **76** (Scheme 20).[43]

Scheme 20



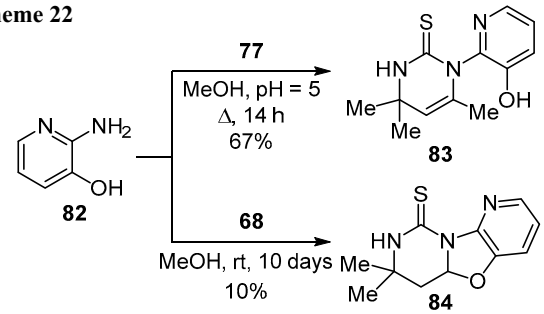
The formation of heterocycles by reactions of multifunctional compounds containing isothiocyanate and carbonyl groups has been systematically studied.[44] It was found that the reaction of isothiocyanates containing aldehyde (compound **68**) or ketone (compound **77**) carbonyl group with 2-aminoacetonitrile 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



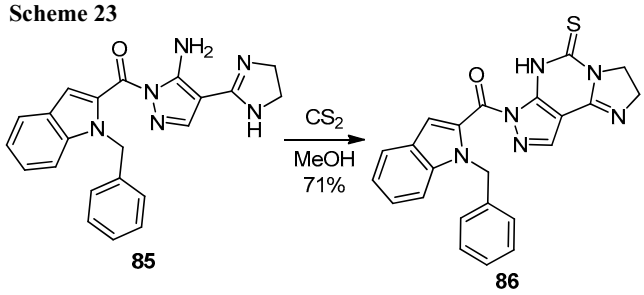
The reaction of compounds **68** and 77 with 2-amino-3-hydroxypyridine (**82**) was also described in the same paper (Scheme 22).[44] Thus, 1-(3-hydroxypyridin-2-yl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione (**83**) was formed using isothiocyanate **77** and refluxing the starting compounds 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-9*H*-pyrido[2',3':4,5]oxazolo[3,2-*c*]pyrimidine-9-thione (**84**).

Scheme 22



Farghaly and El-Kashef[45] published a work that described a [5+1] heterocyclization in which 1,5-binucleophile **85** interacted with carbon disulfide and formed

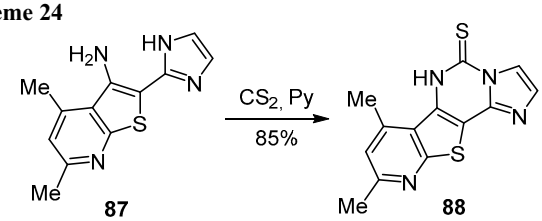
Scheme 23



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

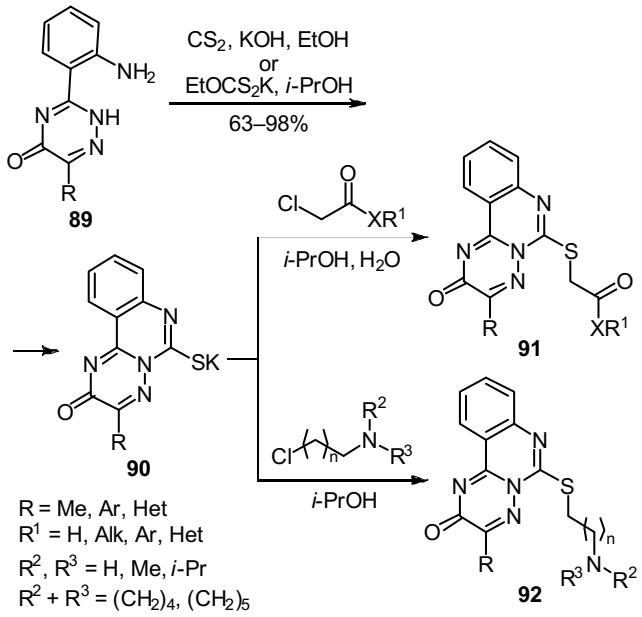
Another good example of the use of a heterocycle assembly as 1,5-dinucleophile was reported by El-Essawy.[46] It was shown that interaction of 2-(1*H*-imidazol-2-yl)-4,6-dimethylthieno[2,3-*b*]pyridin-3-amine (**87**) with carbon disulfide in pyridine led to 7,9-dimethylimidazo[1,2-*c*]pyrido[3',2':4,5]-thieno[2,3-*e*]pyrimidine-5(6*H*)-thione **88** (Scheme 24).

Scheme 24



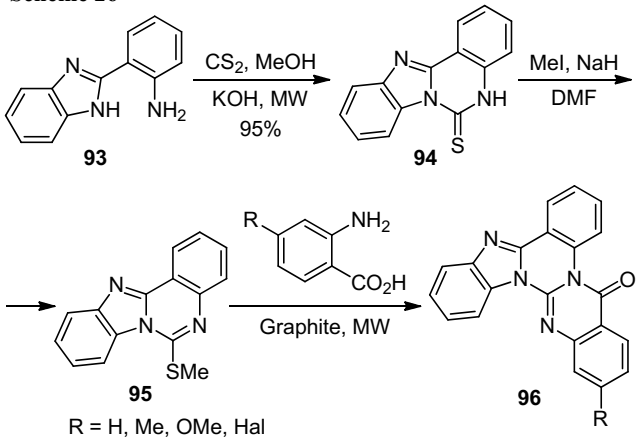
Kovalenko et al.[47–50] published a series of papers devoted to the development of preparative methods and study of antibacterial and anticancer activity of 3-substituted potassium 2-oxo-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-6-thiolates **90** and their *S*-alkylated derivatives **91**, **92** (Scheme 25). The [5+1] heterocyclization of appropriate 3-(2-aminophenyl)-1,2,4-triazin-5(2*H*)-ones **89** with carbon disulfide or ethyl xanthogenate was used to form the target tricyclic system.

Scheme 25



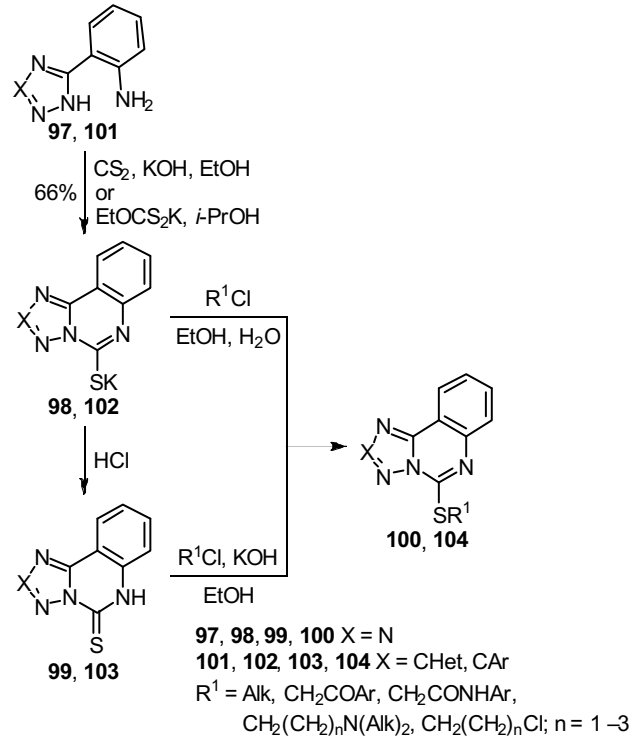
The introduction of microwave-assisted organic synthesis technology has affected also the area under review. From 2-(benzimidazol-2-yl)aniline (**93**) Soukri et al.[51] have synthesized benzimidazo[1,2-*c*]quinazoline-6-thione (**94**) (Scheme 26). The irradiation of a mixture, absorbed on graphite, consisting of alkylation product **95** and an excess of an anthranilic acid derivative led to a new heterocyclic system – 14-substituted 11*H*-benzimidazo[1,2-*c*]quinazolino-[3,2-*a*]quinazolin-11-ones **96**.

Scheme 26



Antypenko et al.[52,53] showed a high potential of 2-(1*H*-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**.

Scheme 27



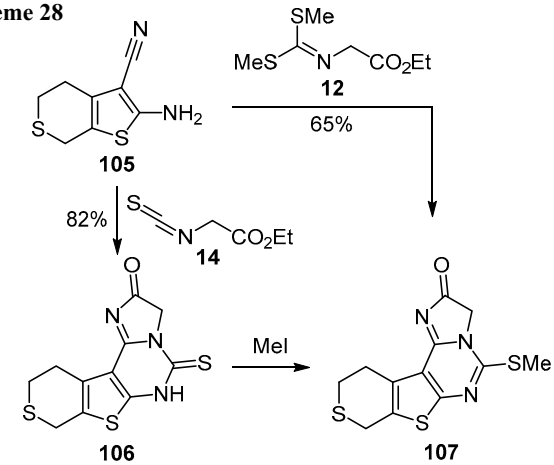
2-(1,2,4-Triazol-3-yl)phenylamines **101** also acted as 1,5-binucleophiles in [5+1] heterocyclization with carbon disulfide in the presence of potassium hydroxide in ethanol or potassium ethyl xanthogenate in isopropanol.[54,55] The possible pathways of the reaction were discussed, and potassium 2-hetaryl[1,2,4]triazolo[1,5-*c*]quinazoline-5-thiolates **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.

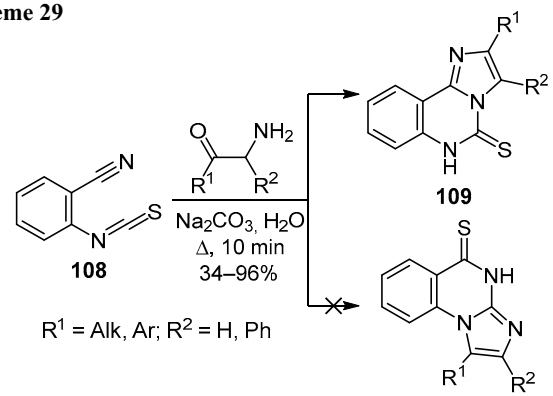
One such domino reaction was developed by Sauter et al.[27] The interaction of ethyl 2-isothiocyanatoacetate (**14**) with 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]thiopyran-3-carbonitrile (**105**) led to the formation of condensed pyrimidine and imidazole fragments forming part of the 5-thioxo-6,8,10,11-tetrahydro-5*H*-imidazo[1,2-*c*]thiopyrano[4',3':4,5]-thie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

Scheme 28

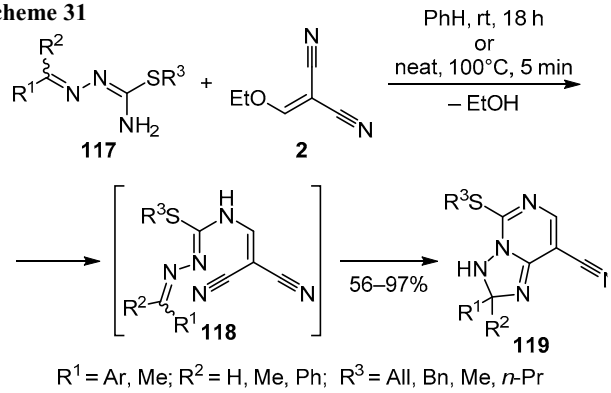


An interaction of 2-isothiocyanatobenzonitrile (**108**) with α-aminoacetophenones was described by Bodtke and coworkers.[56] The results of their research showed that the studied reaction yielded 2,3-disubstituted imidazo[1,2-*c*]-quinazoline-5(6*H*)-thiones **109** (Scheme 29). Formation of alternative products through the Dimroth rearrangement, such as 1,2-disubstituted imidazo[1,2-*a*]quinazoline-5(4*H*)-

Scheme 29



Scheme 31



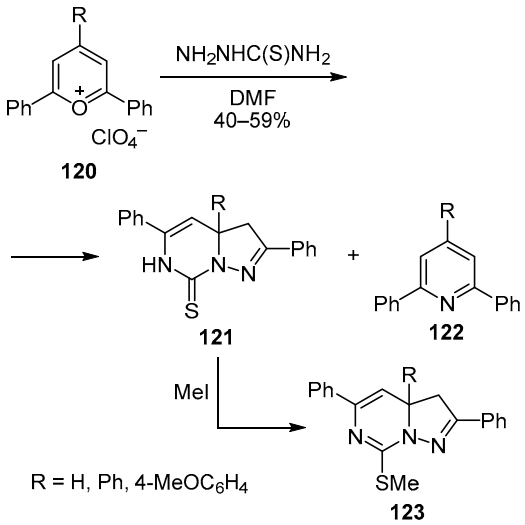
thiones was disproven by NOESY experiment and X-ray diffraction analysis.

Synthesis and transformations of 6,10b-dihydropyrazolo-[1,5-*c*]quinazoline-5(1*H*)-thiones **112** was described by Hull and Swain[57] 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-2*H*-5-thia-2a,2a[1],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.

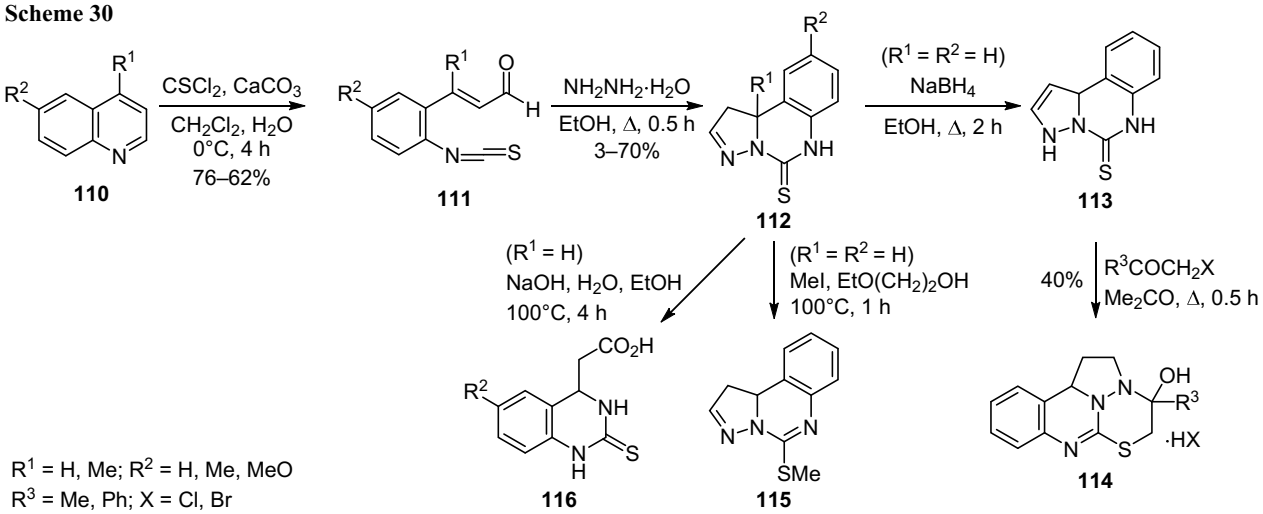
An original method of the construction of mercaptopyrimidine fragment was offered by Yamazaki.[58] It was shown that substituted alkyl *N*'-methylidenecarbamohydrazonothioates **117** readily interact with 2-(ethoxymethylene)malononitrile (**2**) and form 2,2-disubstituted 5-alkylsulfanyl-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitriles **119** (Scheme 31). The product of nucleophilic substitution **118** was proposed as an intermediate of this reaction.

The use of 2,4,6-triarylpyrilium perchlorate (**120**) in the synthesis of heterocyclic systems was described in works by Zvezdina et al.[59,60] A thiosemicarbazide-mediated pyran ring opening in compounds **120** led to 3a-substituted 2,5-diphenyl-3a,6-dihydropyrazolo[1,5-*c*]pyrimidine-7(3*H*)-thiones **121** obtained together with pyridine derivatives **122** (Scheme 32). The alkylation of thiones **121** with methyl iodide provided new *S*-methyl derivatives **123**. The

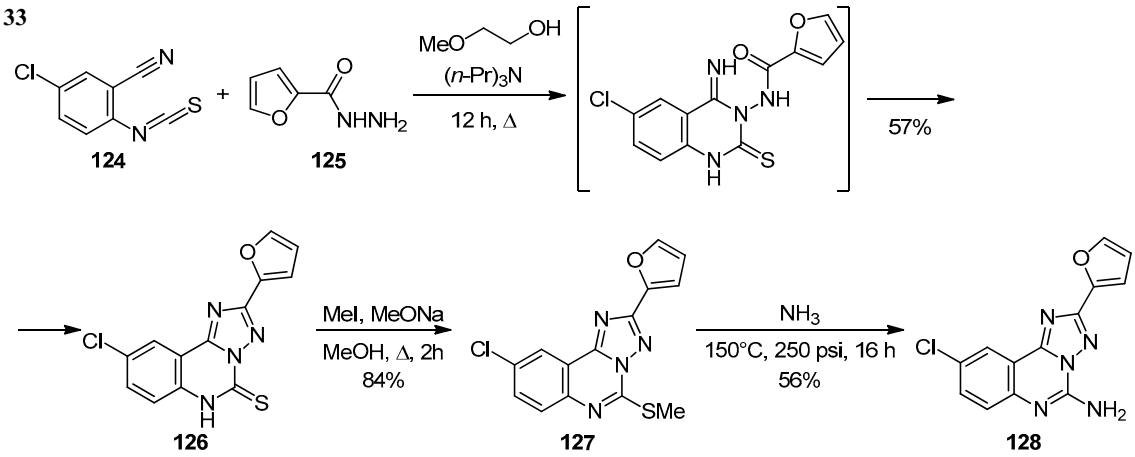
Scheme 32



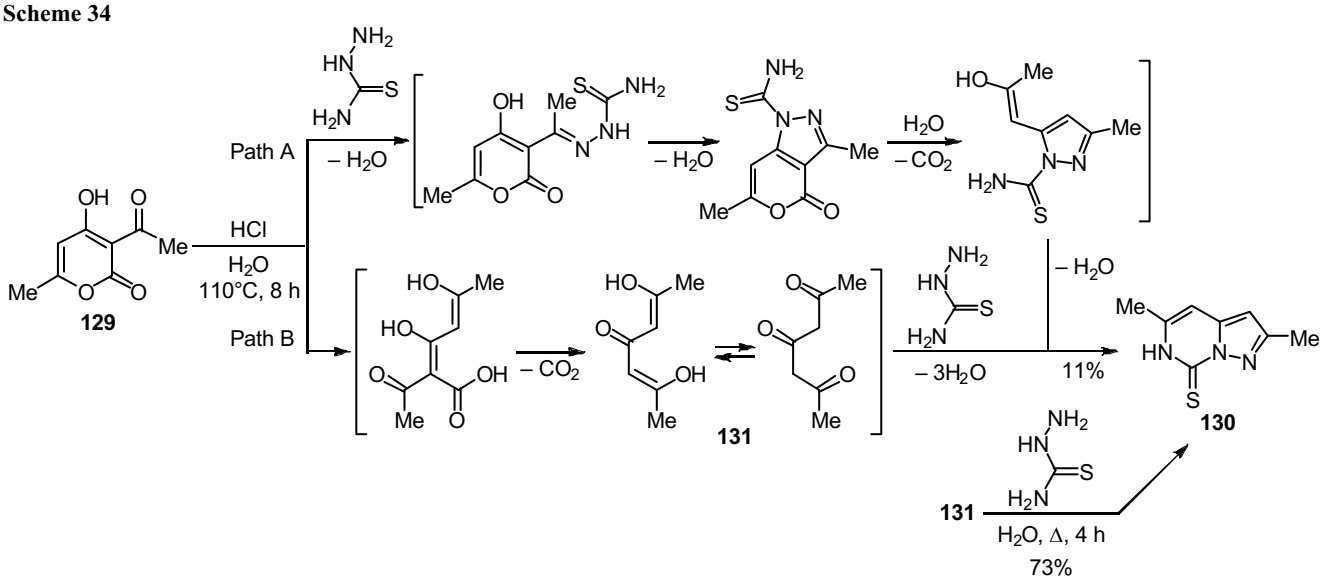
Scheme 30



Scheme 33



Scheme 34



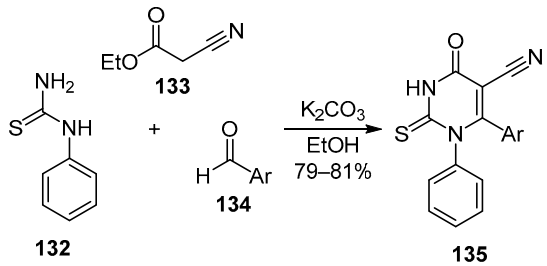
possibility of tautomeric transformations of compounds **121** was studied by UV spectrometry method.

Francis et al.[61] 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 -carbohydrazide (**125**) led to the formation of 2-(furan-2-yl) [1,2,4]triazolo[1,5-*c*]quinazoline-5(6*H*)-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.[62] published a work describing the synthesis of 2,5-dimethylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thione (**130**) *via* condensation of dehydroacetic acid (3-acetyl-2-hydroxy-6-methyl-4*H*-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.

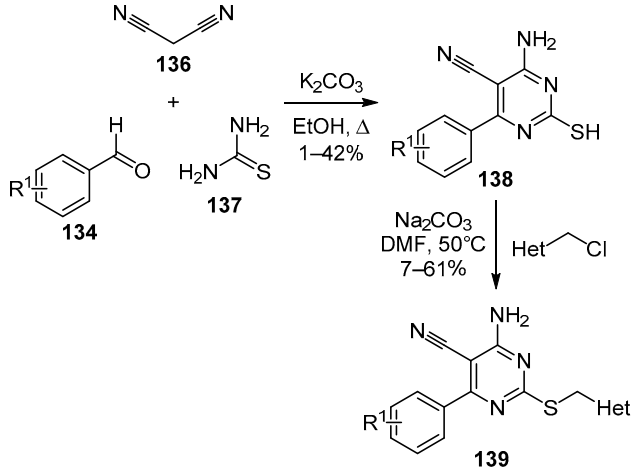
El-Ansary[63] at al. described the synthesis and modification of 2-thioxopyrimidine-5-carbonitriles **135**. The latter were obtained *via* three-component condensation of *N*-phenylurea (**132**), ethyl 2-cyanoacetate (**133**), and aromatic aldehyde **134** in ethanol (Scheme 35). Compounds **134** were used as starting materials for the synthesis of condensed heterocyclic systems containing 2-thioxopyrimidine moiety.

Scheme 35

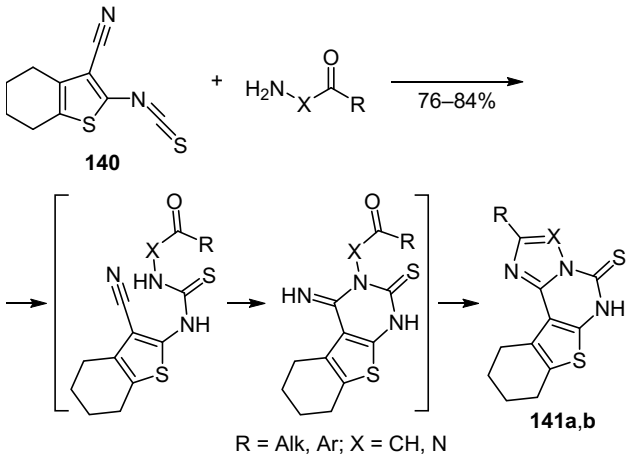


Louvel and coworkers[64] published the results of their work aimed at the search for novel non-glycoside agonists of A_1 adenosine receptors. 4-Amino-6-aryl-2-[(hetaryl-methyl)sulfanyl]pyrimidine-5-carbonitriles **139** were selected as the target compounds and synthesized in two-step procedure that included a one-pot three-component

Scheme 36



Scheme 37



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.[65] 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(6*H*)-thiones **141a**, as well as 2-substituted 8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*]imidazo-[1,5-*c*]pyrimidine-5(6*H*)-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[66] which discussed, along the methods of synthesis, the antiarthritic activity of 1-thioxo-10-(trifluoromethyl)-1,2-dihydro-1*H*-pyrimido-[5,6,1-*kl*]phenothiazin-3(2*H*)-one (**27**).

The work by Jefferson[37] 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,N^6-ethenoadenosine diphosphate (**53**) that showed a strong ability to initiate platelet aggregation. Thus, ribosylpyrophosphate 3*H*-imidazo[2,1-*i*]purine-5-thiol (**52**) could be successfully used as a starting product for the synthesis of other 2-thio derivatives of adenosine with an ability to initiate platelet aggregation.

El-Essawy[46] 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(6*H*)-thiones were described by Antypenko et al.[52,53] 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*,

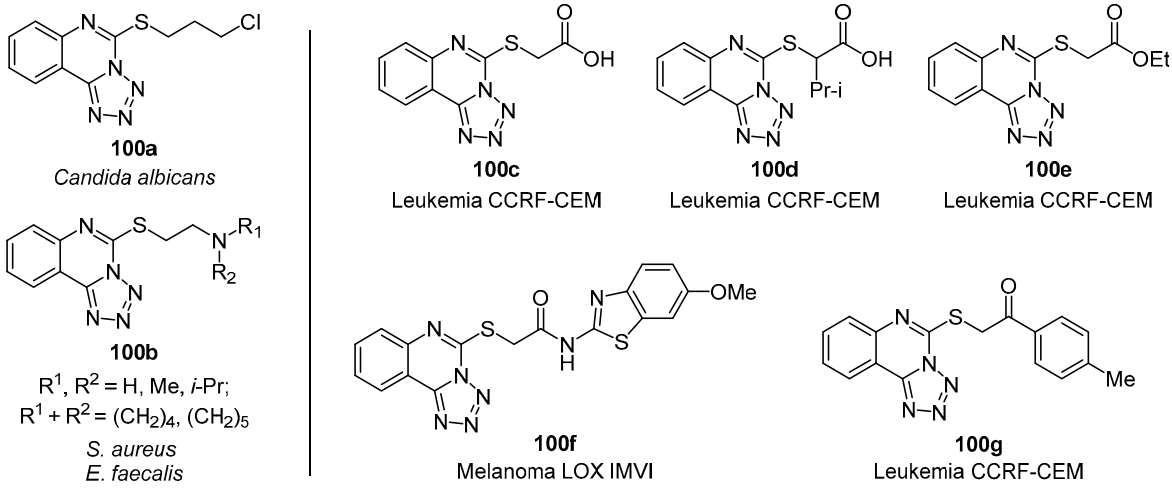


Figure 1. Biological activities of *S*-substituted tetrazolo[1,5-*c*]quinazoline-5(6*H*)-thiones.

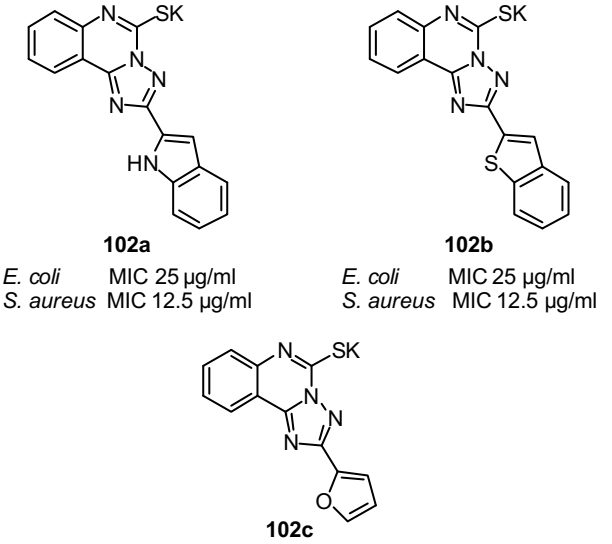


Figure 2. Potassium 2-hetaryl[1,2,4]triazolo[1,5-*c*]quinazoline-5-thiolates with antibacterial activity.

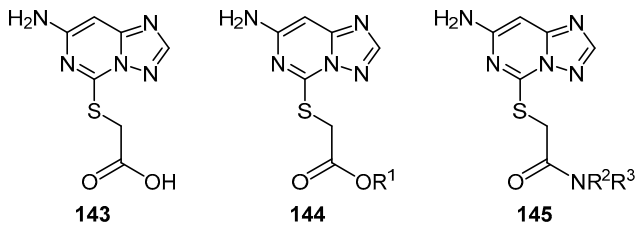
compound **100b** inhibited growth of *S. aureu*s and *E. faecalis*. Compounds **100c**–**g** revealed moderate antitumor activity against standard NCI lines panel (Fig. 1).

Antitumor and antifungal activities of 2-hetaryl[1,2,4]-triazolo[1,5-*c*]quinazoline-5(6*H*)-thiones were also observed by Biliy et al.[55] Thus, potassium 2-hetaryl[1,2,4]triazolo-[1,5-*c*]quinazoline-5-thiolates **102a**,**b** exhibited high antibacterial activity against *S. aureus* (MIC 12.5 μg/ml and MBC 25 μg/ml) (Fig. 2). It is important to note that potassium 2-(furan-2-yl)[1,2,4]triazolo[1,5-*c*]quinazoline-5-thiolate (**102c**) was also effective against methicillin-resistant strains of *S. aureus*.

Ram's work[67] 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-mercaptopyrimidine-5-carbonitriles **142a–c** (Fig. 3) showed the highest activity.

Herbicidal 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.



144 a R^1 = Me, **b** R^1 = Et
145 a R^2 = R^3 = H; **b** R^2 =Me, R^3 = H; **c** R^2 = Me, R^3 = Me;
d R^2 = NH_2, R^3 = H; **e** R^2 = N=$CHC_6H_4NO_2$-*p*, R^3 = H;
f R^2 = N=CHC_6H_4OH-*o*, R^3 = H; **g** R^2 = N=CHCBrPh, R^3 = H

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

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 work[69] 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).

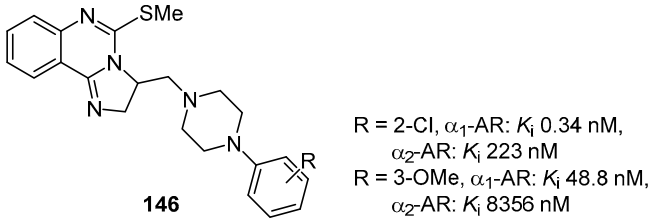


Figure 5. Adrenoreceptor antagonists with imidazo[1,2-*c*]-quinazoline moiety.

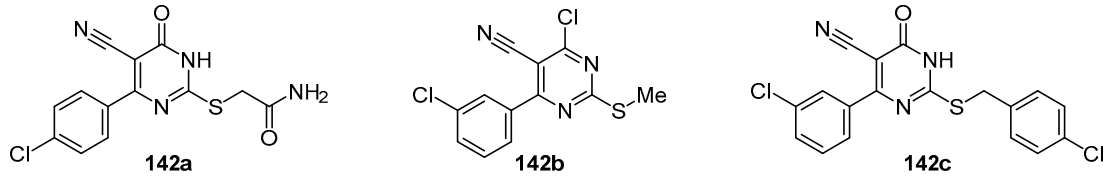


Figure 3. 2-Thiosubstituted pyrimidines with leishmanicide activity.

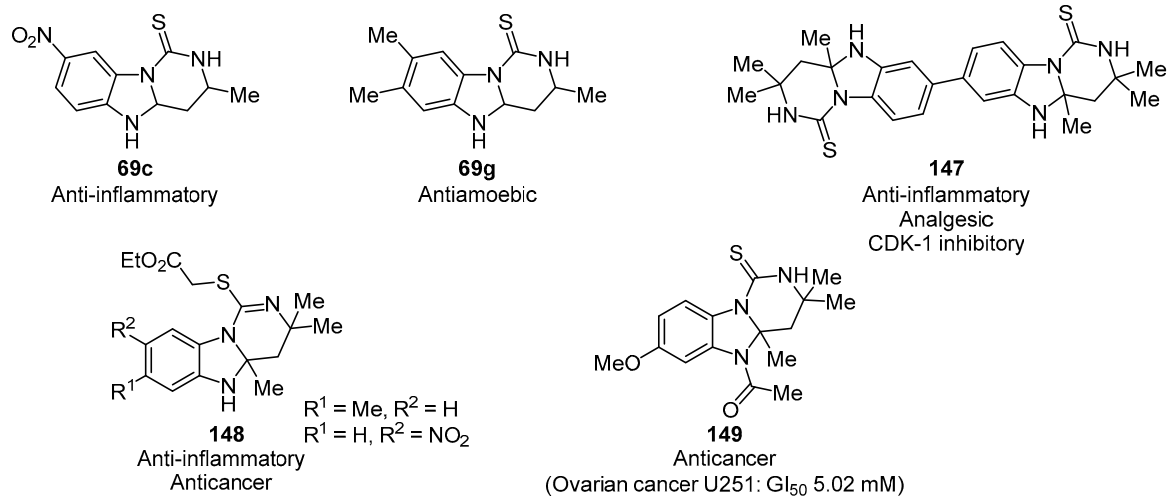


Figure 6. Pyrimido[1,6-*a*]benzimidazole-1(2*H*)-thione derivatives with diverse biological activities.

In the work by Sondhi and his colleagues,[70] 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[41] 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 **69c** showed a moderate anti-inflammatory activity, while compound **69g** showed high antiamoebic activity (IC_{50} 1.82 μM).

The same authors[70] identified a related biheterocyclic compound **147** 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,[71] the same group reported anti-inflammatory and anticancer activities in the same fused pyrimidine series. The results showed that compounds **148** that are *S*-substituted analogs of compounds **69** (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 **149**, an *N*-acylated analog of compounds **69**, 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[72] 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 **150a**,**b** of this series exhibited anxiolytic, antiamnestic, ataxic, and anticorazol activities.

Li and colleagues[73] reported 2-[(aroyl(phenylacetyl)-methyl)sulfanyl]-1,N^6-ethenoadenosine triphosphates **151** as promising nucleoside-based reverse transcriptase inhibitors (Fig. 8).

Bhuiyan and his colleagues[74] reported on significant antimicrobial and antifungal activities of 5-methysulfanyl-8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**152**) (Fig. 9).

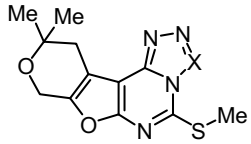


Figure 7. Tetracyclic 2-thiopyrimidine derivates with versatile psychotropic activity.

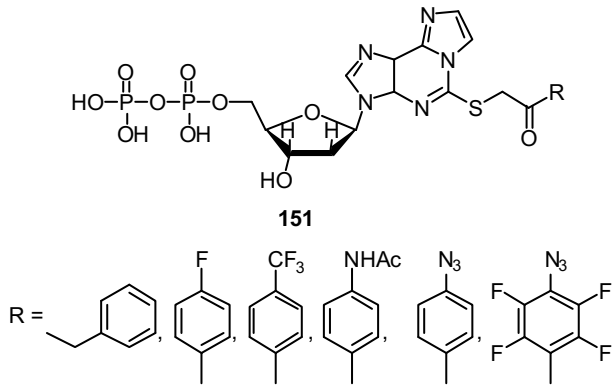


Figure 8. Nucleoside-based reverse transcriptase inhibitors with thiopyrimidine moiety.

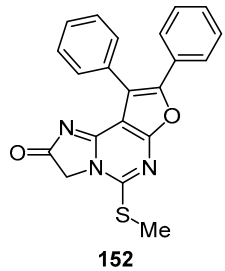


Figure 9. A furo[3,2-e]imidazo[1,2-c]pyrimidine with antibacterial and antifungal activity.

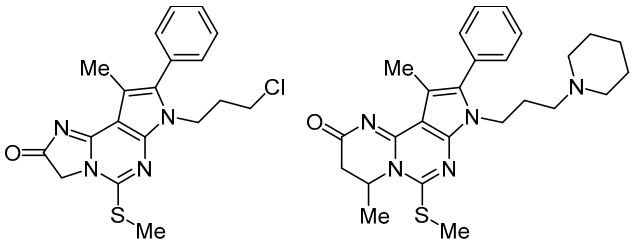


Figure 10. Anticancer agents with pyrrolopyrimidine moiety

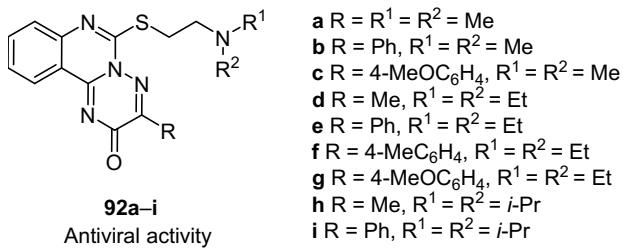


Figure 12. *S*-substituted 6-thioxo[1,2,4]triazino[2,3-*c*]quinazolin-2-ones with antiviral activity.

Lauria et al.[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[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[77] continued the search for antioxidant, anti-inflammatory, and analgesic agents among azopyrimidoquinolines and pyrimidoquinazolines. 5-Aryl-9-arylidene-2-thioxo-2,3,5,6,7,8,9,10-octahydropyrimido[4,5-*b*]quinolin-4(1*H*)-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.[47–50,78–82] presented the results of biological activity study of 3-R-6-thioxo-6,7-dihydro-2*H*-[1,2,4]-triazino[2,3-*c*]quinazolin-2-ones and products of their modification. According to the obtained data, these compounds have a wide range of biological effects, including anticancer, antivirial, antibacterial, and antifungal. It was shown[78–82] that antiviral properties were more characteristic for 6-thio-substituted 2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones **92a**–**i** (Fig. 12) with dialkylaminoethyl moiety. These compounds inhibited Tacaribe virus (EC_{50} 4.8–7.2 μg/ml, SI 9.5), SARS coronavirus (EC_{50} 1.8–11.0 μg/ml, SI 4.77–33), Venezuelan equine encephalitis virus (EC_{50} 10 μg/ml, SI 4.3), influenza virus type A H5N1 (EC_{50} 3.6–7.9 μg/ml, SI 3.5–49), influenza virus type A H3N2 (EC_{50} 3.1–4.1 μg/ml, SI 14–31), influenza virus type B (EC_{50} 1.1–1.4 μg/ml, SI 22–24), influenza virus type A H1N1 (EC_{50} 3.2–8.5 μg/ml, SI 16–35).

It was also shown that the 3-substituted 6-thioxo-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones **91**, **92** are most active against the following tumor cell lines: K-562 (pGI_{50} 6.47), SR (pGI_{50} 6.42) of leukemia; SNB-75 (pGI_{50} 6.07) of CNS cancer; CAKI-1 (pGI_{50} 5.94), A498 (pGI_{50} 5.93–7.57) of renal cancer; NCI-H522 (pGI_{50} 6.65) and HOP-92 (pGI_{50} 6.01–6.20) of non-small lung cancer; HCT-116 (pGI_{50} 5.93–6.35), HT29 (pGI_{50} 5.96–6.39), COLO 205 (pGI_{50} 6.30) and KM12 (pGI_{50} 6.31) of colon cancer; MALME-3M (pGI_{50} 6.28), SK-MEL-5 (pGI_{50} 6.32) of melanoma; OVCAR-3 (pGI_{50} 6.59) of ovarian cancer; MCF7 (pGI_{50} 6.32, SI 4.52) of CNS cancer (SI 3.25–6.75), of melanoma (SI 3.43), of renal cancer (SI 8.56), of prostate cancer (SI 4.98) and breast cancer (SI 4.72)[47–50,79] The *N*-(3-ethylbicyclo[2.2.1]heptan-2-yl)-2-{[3-(4-methoxyphenyl)-2-oxo-2*H*-[1,2,4]triazino[2,3-c]quinazolin-6-yl]-sulfanyl}acetamide (**91a**) (Fig. 13) was identified as lead compound with remarkable anticancer activity.[47] The significant number of compounds tested for anticancer activity allowed to evaluate quantitative structure–activity relationships.[82]

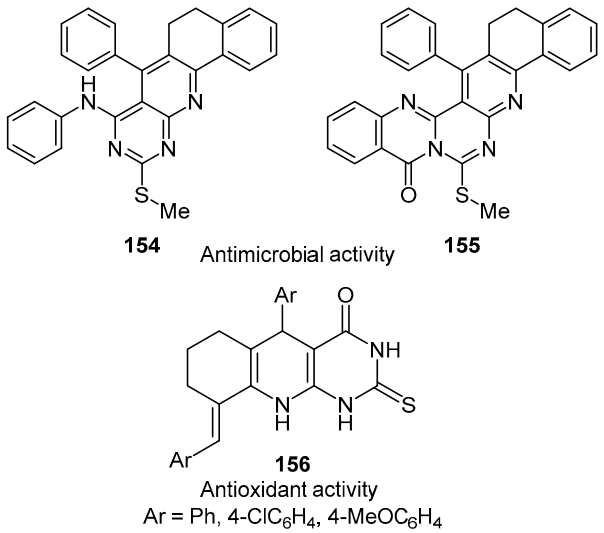
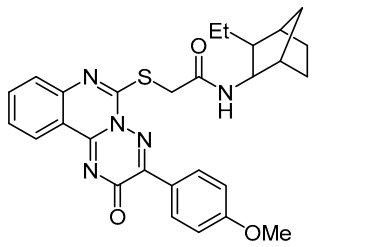


Figure 11.Biologically active pyrimido[4,5-*b*]quinolines **154**–**156**.



Cancer type	Cell line	pGI_{50}
Leukemia	SR	5.87
Non-small cell lung	HOP-92	6.01
CNS	U251	6.00
Renal	RXF 393	5.83
Ovarian	OVCAR-3	5.83
Breast	MDA-MB-468	5.87

Figure 13. A promising anticancer agent – derivative of 6-thioxo-[1,2,4]triazino[2,3-*c*]quinazolin-2-one.

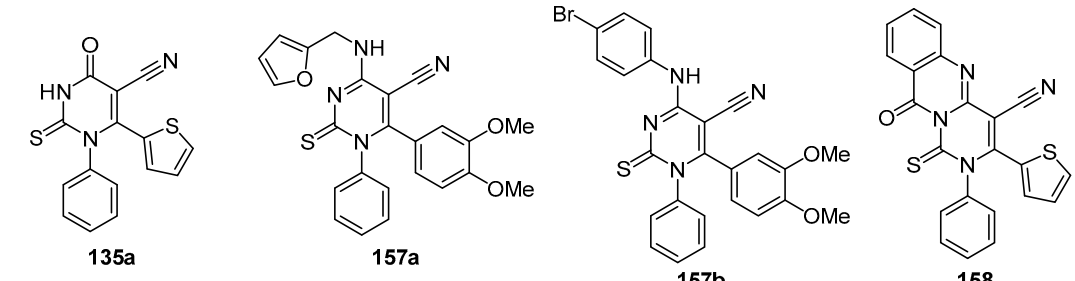


Figure 14. 2-Thioxopyrimidine-5-carbonitriles with anticancer activity.

El-Ansary[63] and coworkers studied the anticancer activity of 2-thioxopyrimidine-5-carbonitriles **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(1*H*)-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).

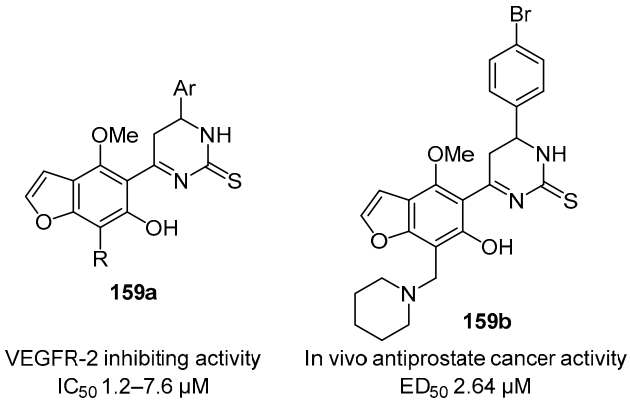


Figure 15. Anticancer agents with 2-thiopyrimidine and benzofuran moieties.

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)diazenyl]-*N*-(4-methylpyrimidin-2-yl)benzenesulfonamide (**160**) and 6-amino-5-[(4-chlorophenyl)diazenyl]-1,3-dimethyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one complex with $Pt(II)Cl_2$ (**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 A_1 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 A_1 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).

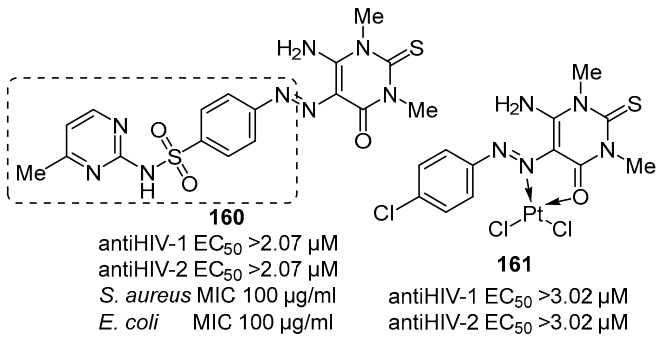
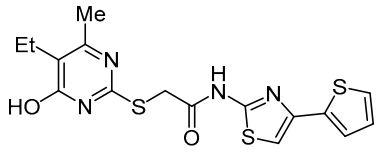


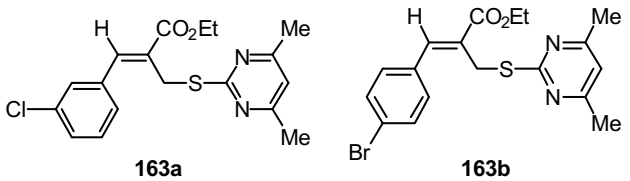
Figure 16. 2-Thioxopyrimidines and their complexes as antiviral and antibacterial agents.



162

TMEM16A/Ano1 IC_{50} 1 μM

Figure 17. A TMEM16A/Ano1 inhibitor with thiopyrimidine moiety.



163a **163b**

IC_{50} 5.88 μM IC_{50} 3.17 μM

Figure 18. 2-Thiopyrimidines as COX-2 inhibitors.

Santhoshi and coauthors[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.

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