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SUBSTITUTED ACYL THIOUREAS AND ACYL THIOSEMICARBAZIDES: SYNTHESIS AND BIOLOGICAL ACTIVITY (MINIREVIEW)

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Acyl isothiocyanates and their functional derivatives (acyl thioureas and acyl thiosemicarbazides) are an important group of organic compounds that are widely used in the synthesis of heterocycles and in chemistry as catalysts, ligands, colorimetric hemosensors, etc. In recent years, there has been an increased interest towards this class of compounds as promising biologically active compounds, especially since the latest advances in medicinal chemistry for them are not sufficiently studied.

The aim. *To summarize and systematize information for the last 10 years on methods of synthesis and biological activity of substituted acyl thioureas and acyl thiosemicarbazides.*

Materials and methods*. Web-tools for finding scientific information (Reaxys, Scopus, Google Scholar, ScienceResearch, SciFinder, Web of Science, etc.).*

Results and discussion. *Literature sources related to the methods of synthesis of substituted acyl thioureas and acyl thiosemicarbazides were systematized and analyzed. The main approaches for the formation of these compounds are revealed: stepwise formation from carboxylic acids, through acyl chlorides and acyl isothiocyanates followed by nucleophilic addition of amines or hydrazides of carboxylic acids ("one-pot synthesis"), nucleophilic addition of amines or hydrazides of carboxylic acids directly to acyl isothiocyanates and parallel microwave synthesis using acyl isothiocyanates and amines as reagents. The possibility of their use as ligands for the formation of complex compounds with transition metal ions was discussed. In the review biological activity of these structures, namely antimicrobial, fungicidal, antitumor, antiviral, antifungal and other activities was detailazed.*

Conclusions*. The basic approaches to the synthesis of substituted acylthuoureas and acyl thiosemicarbazides which include the application of carboxylic acids, their derivatives (acyl halides and isothiocyanates) and N-nucleophiles as initial compounds were discussed. It was shown that aforementioned class of the compounds reveals the versatile biological activity and are promising for further structural modification aimed to the search of novel drugs*

Keywords*: synthesis, acyl isothiocyanates, substituted anilines and aroyl hydrazides, nucleophilic addition, acyl thioureas, acyl thiosemicarbazides, complexes, biological activity*

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1. Introduction

Unlike alkyl(aryl-, hetaryl-) isothiocyanates and their derivatives, acyl isothiocyanates are a less studied class of organic compounds [1–8]. Methods for the synthesis of acyl isothiocyanates are known and based on the interaction of acyl chlorides with isothiocyanic acid salts [1, 2, 6]. Other methods of synthesis are described as well. Among them is one-stage synthesis of aroyl isothiocyanates from carboxylic acids, trichloroisocyanuric acid and triphenylphosphine at room temperature [7]. It is important that acyl isothiocyanates, are more reactive than isothiocyanates due to the presence of an acyl group in the molecule. Their reactivity is determined by the electrophilic properties of two Carbon atoms and the nucleophilic Nitrogen atom. Due to the presence of these active centers, acyl isothiocyanates are high reactive in the addition or heterocyclization. Moreover, acyl thioureas and acyl thiosemicarbazides are intermediates or starting compounds for the synthesis of azoles and azines from acyl isothiocyanates [1–5, 8]. Despite the published reviews devoted to acyl isothiocyanates and products of their modification, which reflect their role in organic synthesis as precursors and catalysts, ligands in coordination chemistry, chemo sensors in analytical chemistry, liquid crystalline materials in the production of displays, light modules, optical switches, switches detectors, etc. [1, 8], the current state and recent advances of their usage in medical chemistry are insufficiently disclosed. Reports of their biological activity relate only to the use of coordination compounds as antitumor, antibacterial, mycostatic, antimalarial and anti-inflammatory agents, etc. [8, 9].

Therefore, this review is an attempt to summarize the literature on the use of acyl isothiocyanates in the synthesis of substituted acyl thioureas and acyl thiosemicarbazides as biologically active compounds that can be used as promising drugs.

2. Materials and methods

Web-tools for finding scientific information (Reaxys, Scopus, Google Scholar, ScienceResearch, SciFinder, Web of Science, etc.).

3. Results and discussion

Synthetic approaches to preparation of biologically active acyl thioureas and acyl thiosemicarbazides are based on the addition of *N*-nucleophiles directly to alkanoyl-(aroyl-, hetaroyl-) isothiocyanates, their stepwise formation from the corresponding carboxylic acids, through acyl chlorides, acyl isothiocyanates and *N*-nucleophiles or parallel microwave synthesis using acyl isothiocyanates and *N*-nucleophiles as reagents. Aromatic and heterocyclic amines and hydrazides of aromatic and heterocyclic acids were the most used nucleophiles studied in these reactions.

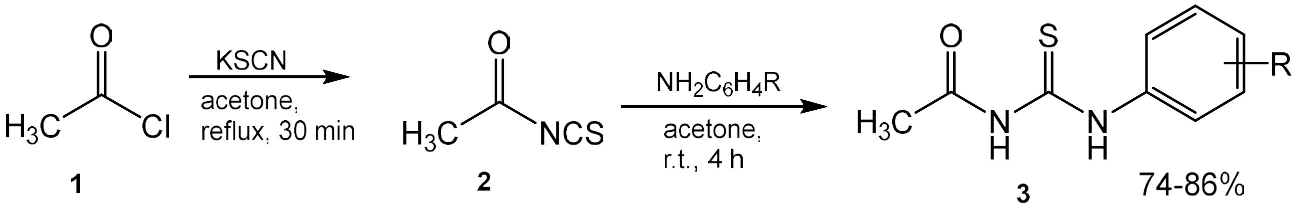
Thus, a targeted search for cholinesterase inhibitors as potential drugs was performed among substituted acetyl thioureas (**3**) [10]. Thus, the authors synthesized several new *N*-(arylcarbamothioyl) acetamides (**3**) by the interaction of acetyl isothiocyanate (**2**), obtained *in situ* from acetyl chloride (**1**) and potassium thiocyanate, with substituted anilines (Fig. 1). Screening of the synthesized compounds for acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity revealed several effective inhibitors. Thus, *N*-(2,4-dimethylphenylcarbamothioyl) acetamide is an effective inhibitor of AChE (IC_{50}=1.99 μM) and *N*-(4-methoxyphenylcarbamothioyl)acetamide is an effective inhibitor of BChE (IC_{50}=1.99 μM), which according to the data of inhibition exceeds the drug “Neostigmine” (IC_{50}=49.6 μM). In addition, the authors confirmed the probable mechanism of their action by molecular docking and the reaction kinetics for active compounds.

New nitro-substituted acyl thioureas (**4**) have been synthesized and their antioxidant, cytotoxic, antibacterial, and antifungal effects have been studied [11]. The synthesis of the latter was carried out by reacting acetyl chloride (**1**) with potassium thiocyanate, the formed acetyl isocyanates (**2**) were easily attached to various nitro-substituted anilines. The result of the addition is nitro-substituted acetyl thioureas (**4**) with a yield of 90–92 % (Fig. 2). Acetyl thioureas moderate inhibite bacteria *M. luteus, S. aureus, B. bronchiseptica, S. typhimurium, E. aerogens* and cultures of fungi *F. fumigatus, F. Mucor, F. niger, F. flavus* and possess high antioxidant activity. The synthesized compounds showed a significant inhibition of amylase (93.2 %) and glucosidase (73.7 %) in a concentration-dependent manner. In addition, the authors investigated the ability of compounds 4 to form complexes with of increasing concentrations of DNA (0.5×10^{-6}–1.0×10^{-5} M) and according to molecular docking showed promising aspects of their use as antitumor agents.

A team of scientists [12] developed the synthesis of acyl- (aroyl-) thiourea (**8**) as promising fungicidal agents. In this work, a standard approach was used for their synthesis, and the conversion of carboxylic acids (**5**) into acylchlorides (**6**) by interaction with thionyl chloride in DMF, the latter in interaction with potassium thiocyanate form acyl isothiocyanates (**7**), which were treated with the corresponding anilines (Fig. 3). The study found that compounds 8 showed moderate antifungal activity inferior to the reference drug Terbinafine. However, they are highly effective and selective inhibitors of α-amylase (IC_{50} 8.1–16.8 μg/ml) and radical “traps” (IC_{50} 7.5–10.2 μg/ml), exceeding acarbose (IC_{50} 17.1 μg/ml) and ascorbic acid (IC_{50}) 11.9 μg/ml). The structure-activity analysis performed by the authors showed that the more active compounds are those that contained an alkyl function in the molecule.

A study [13] developed an approach to the synthesis of N^1-carbamothioyl-N^6-phenyladip-(pimelin-)amides (**15 a, b**, Fig. 4) and the latter have been shown to be cytotoxic to cancer cell lines HRT-18 (adenocarcinoma of the colon), HC-04 (mouse hepatoblastoma) and HBL-100 (epithelial cells derived from healthy breast). It was shown that the mean inhibitory concentration (IC_{50}) against the HC-04 cell line and the HRT-18 cell line for compound **15b** was 21.44 μM and 24.12 μM, respectively, and for compound **15a** – 27.37 μM and 30.42 μM, respectively. Molecular docking, combined with cytotoxicity results, allowed the authors to claim that the compounds are histondiacylase inhibitors (HDACs).

Chiral urea, thiourea and acylthiourea with a fragment of (R)-2-amino-1-butanol (**16a**, Fig. 5) were synthesized for the directed search of anti-tuberculosis drugs [14]. The synthesis of compounds **18** was performed by mixing **16a** and the corresponding isocyanates in dichloromethane (DCM). Urea **16** was synthesized from the parent compound and urea, and alkyl thiourea (**17**) and acyl thiourea (**19**) under standard addition conditions of alkyl- (acyl-) isothiocyanates. After purification and structure characterization, the antimycobacterial activity of the compounds was evaluated *in vitro* against strains of *M. tuberculosis* (H37Rv and MDR strain 43). Compounds **19** showed high activity against *M. tuberculosis* H37Rv (MIC 0.36–7.46 μM), approaching the indicators of the reference drug ethambutol (MIC 7.22 μM).



R = Bn, 2,4,6-*tri*-Me, 2,4-*di*-Me, 2-MeO, 2-Cl, 4-Br, 2,3-*di*-Cl, 4-MeO, 3-NO_2, 4-Me, 3-MeO, 3-Cl, 2,6-*di*-Br-4-F, 4-Br, 2-F, thiazolyl-2

Fig. 1. Approaches to the synthesis of *N*-(arylcarbamothioyl)acetamides

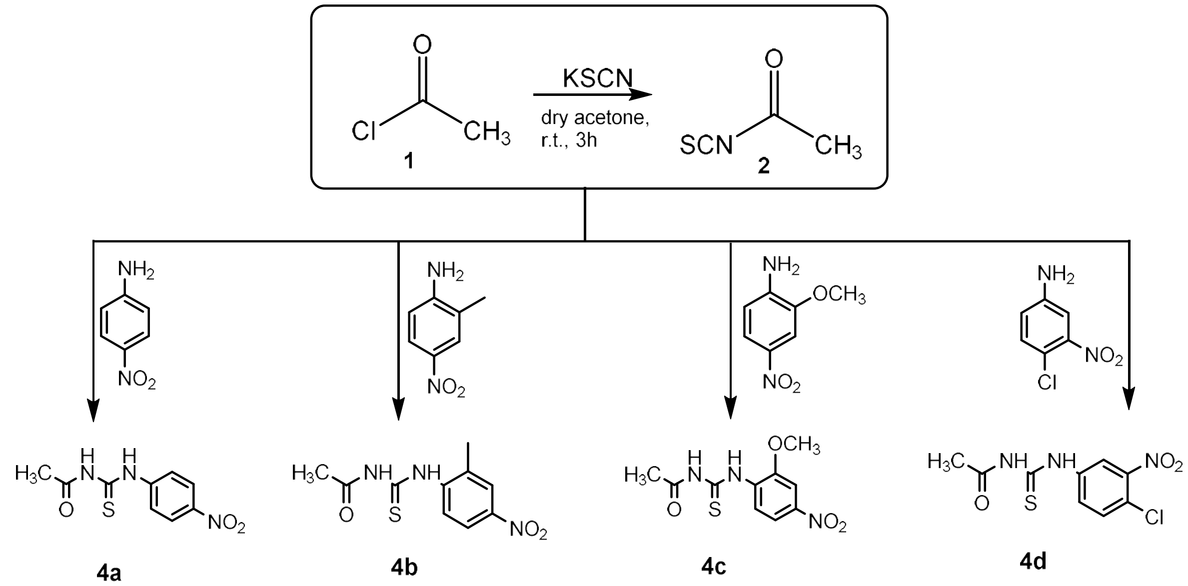


Fig. 2. Synthesis of nitro-containing *N*-(arylcarbamothioyl)acetamides

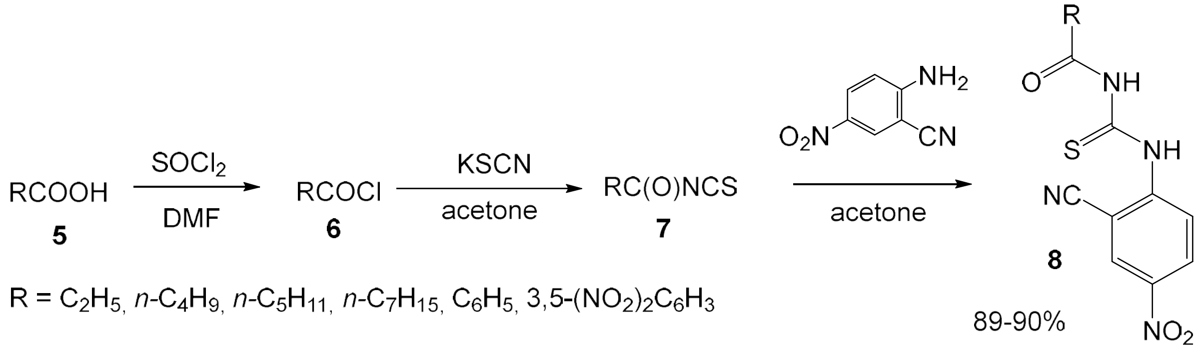


Fig. 3. Approaches to the synthesis of *N*-[(2-cyano-4-nitrophenyl)carbamothioyl]acylamides

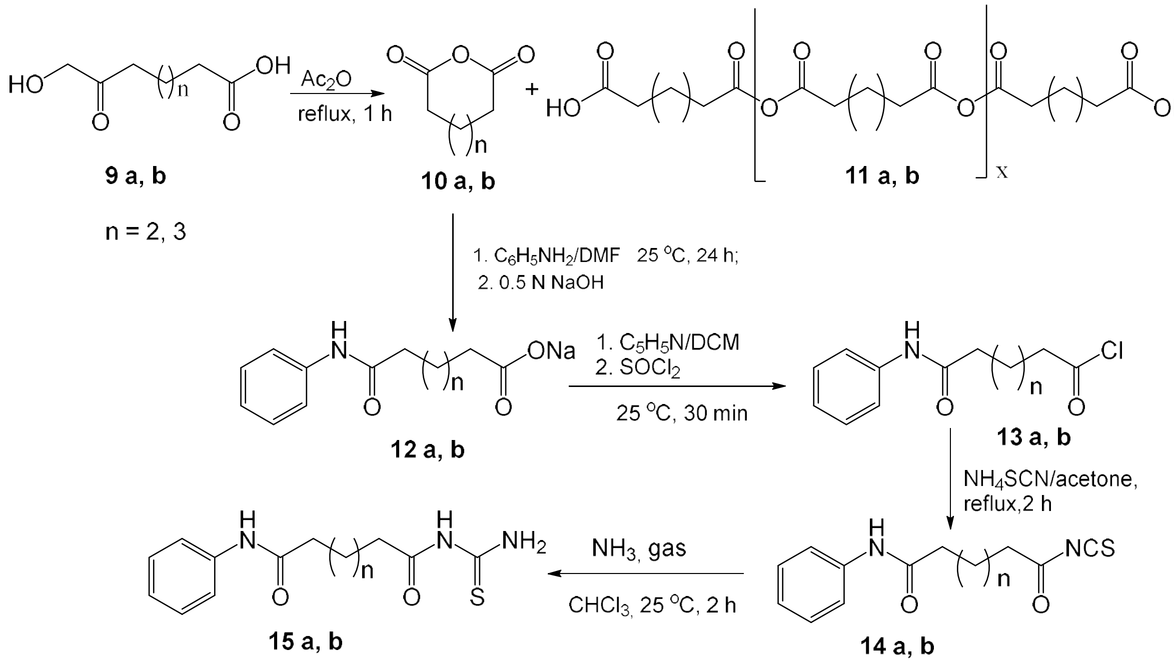
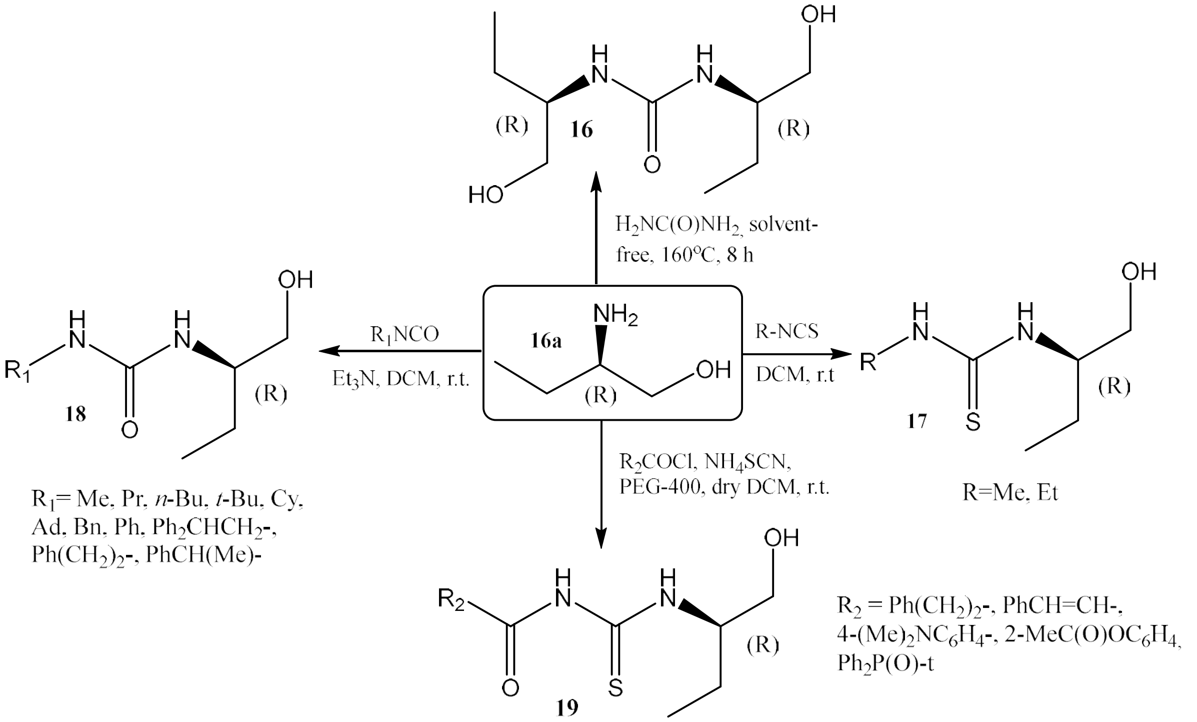


Fig. 4. Approaches to the synthesis of N^1-carbamothioyl-$N^{6(7)}$-phenyladipin-(pimelin-)amides

A targeted search for antifungal agents was performed among the new diacyl semicarbazides (**22**) and hydrazine-1,2-bis(carbothioamide) (**23**) with a cyclopropanecarboxamide moiety in the molecule (Fig. 6) [15]. “One-pot” synthesis of the latter was carried out in acetonitrile by sequential addition to cyclopropanecarbonyl chloride (**20**) equimolecular amounts of ammonium isothiocyanate and hydrazides of carboxylic acids or thiosemicarbazide. The authors note that the method is selective, characterized by good yields and has high purity of the final products. *In vitro* studies of their antifungal activity on 11 fungi and three *Phytophthora* strains of phytopathogenic significance revealed several promising compounds (16.6–50.0 µg/ml). The *Salmonella* reverse mutagenicity assay ("Ames Test"), lipophilicity assessment, and quantum chemical calculations attribute a low toxicity profile to compounds **22** and **23** to diacyl semicarbazides. Molecular docking studies indicate that they are possible inhibitors of 14α-demethylase (CYP51) and *N*-myristoyltransferase (NMT). The paper also discusses SAR analysis.

A similar work is devoted to the search for antifungal agents among the new *N*-cycloalkylcarbonyl-*N'*-arylthiourea [16]. The authors developed a method for the synthesis of thioureas (**25**), which consisted in the sequential addition to cycloalkylcarbonyl chlorides (**24**) of equimolecular amounts of ammonium isothiocyanate and substituted anilines (Fig. 7). The results of antimicrobial screening for standard microorganisms and molecular docking methods selected a few structures for testing for antifungal and genetic toxicity. *In vitro* screening of 9 compounds for antifungal potential for 11 fungi and three *Phytophthora* strains of phytopathogenic significance revealed several compounds that at a concentration of 50 µg/ml show activity at the level of the standard antifungal agent "Ciproconazole". Analysis of the mutagenicity/gene-toxicity of disubstituted thioureas using the *Salmonella* reverse mutagenicity assay ("Ames Test") showed a low profile of their toxicity.

A method for the formation of substituted (cycloalkylcarbonylthioureido)aryl-(benzyl-)carboxylic(sulfonic) acids (**26**, **27**) as promising plant growth regulators with fungicidal activity has been proposed [17]. The authors showed that the latter are easily formed by the sequential interaction of cyclopropanecarbonyl chloride (**20**), ammonium isothiocyanate and aminoaryl (benzyl-) carboxylic, sulfanilic acids or sulfamide (Fig. 8). It was found that the synthesized compounds show moderate antimicrobial activity against *S. aureus* and *P. aeruginosa* (MIC 50 µg/ml, MBC 100 µg/ml) and significant antifungal activity against *C. albicans* (MIC 25–50 µg/ml, MFC 25–50 µg/ml). A few compounds that are effective regulators of wheat growth and auxin-like action exceed the natural analogue – "Heteroauxin" (3-indoleacetic acid).

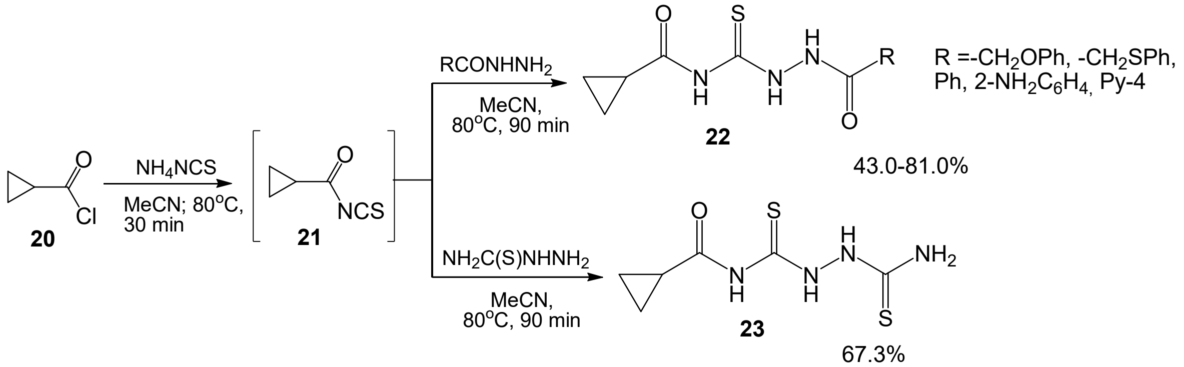


R_1= Me, Pr, *n*-Bu, *t*-Bu, Cy, Ad, Bn, Ph, Ph_2CHCH_2-, $Ph(CH_2)_2$-, PhCH(Me)-

R=Me, Et

R_2 = $Ph(CH_2)_2$-, PhCH=CH-, 4-$(Me)_2NC_6H_4$-, 2-$MeC(O)OC_6H_4$, $Ph_2P(O)$-t

Fig. 5. Synthesis of chiral urea, thiourea and acylthiourea with a fragment of (R)-2-amino-1-butanol

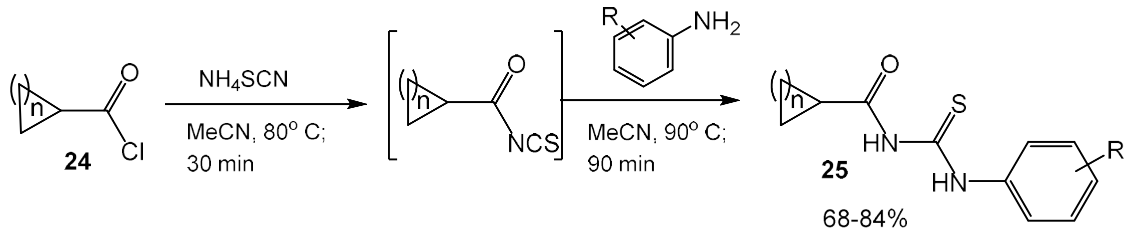


R =-CH_2OPh, -CH_2SPh, Ph, 2-$NH_2C_6H_4$, Py-4

43.0-81.0%

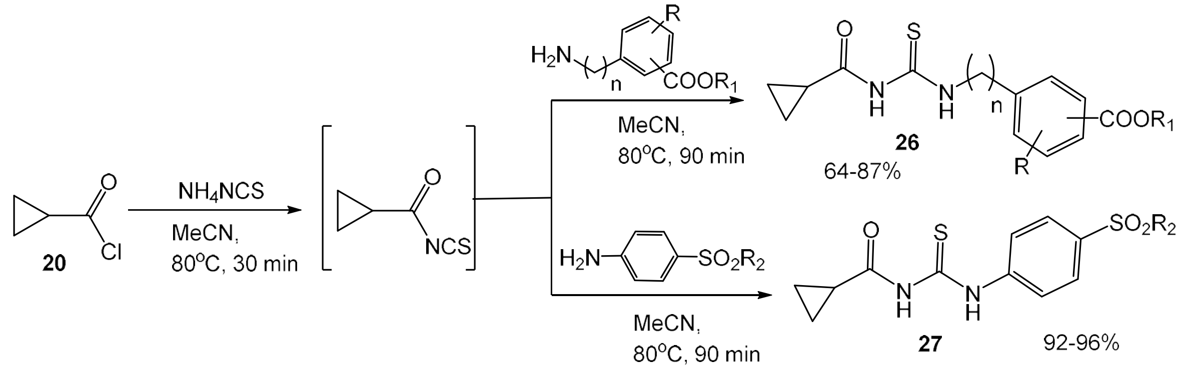
67.3%

Fig. 6. "One-pot" synthesis of diacylsemicarbazides and hydrazine-1,2-bis(carbothioamide) with cyclopropane moiety



n = 1,2,3; R = H, 2-Me, 3-Me, 4-Me, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 3-CF$_3$, 2-MeO.

Fig. 7. "One-pot" synthesis of *N*-cycloalkylcarbonyl-*N*′-arylthioureas



n = 1, 3; m= 0,1; R = H, F, Cl, Br, COOEt; R$_1$ = H, Et; R$_2$ = OH, NH$_2$

Fig. 8. Approaches to the synthesis of substituted *N*-(cycloalkylcarbonylthioureido)aryl-(benzyl-)carboxylic(sulfonic)acids

A strategy for the search for diuretics among cycloalkylcarbonyl thiourea derivatives and thiosemicarbazides has been developed and implemented and published by a team of scientists from Ukraine [18]. Compounds **29** and **30** were synthesized from cycloalkylcarbonyl chlorides (**24**), equimolecular amounts of ammonium isothiocyanate and substituted anilines or hydrazides (Fig. 9). The study of diuretic activity revealed effective compounds that compete with the reference drug "Hydrochlorothiazide" in terms of diuretic effect. According to the results of molecular docking, the synthesized compounds, like the reference drug, have a similar mechanism of action (carbonic anhydrase II inhibitors), and expressed diuretic effect is associated with the ability of substituted thioureas to form coordination with the zinc cation in the active site of CA II.

The original strategy for finding new anticonvulsants was developed based on structural modification of diacyl thiosemicarbazides [19]. This strategy included virtual target-oriented screening of synthesized compounds to active sites of GABA$_A$, GABA$_T$-receptors and NVSCs, direct synthesis and study of their activity in the pentylenetetrazole seizure model. New diacyl thiosemicarbazides (**32**–**34**) were synthesized by the *in situ* method, namely the interaction of cycloalkanecarbonyl chlorides (**24**) with ammonium isothiocyanate followed by nucleophilic addition of cycloalkyl-(aralkyl, aryl-, hetaryl)carbonyl hydrazides (Fig. 10). The biological screening showed that diacyl thiosemicarbazides, which contain cyclopropane and cyclopentane carbamide groups in their structure, show anticonvulsant activity that exceeds or competes with the reference drug "Depakine". The structure-activity relationship is discussed.

A series of biologically active substituted cyclohexylcarbonyl thioureas (**36**), which were obtained by "one-pot synthesis" from cyclohexanecarbonyl chloride (**24**), potassium thiocyanate and various primary amines (Fig. 11), is presented [20]. Studies on the ability of compounds to inhibit DPPH and hemolytic activity have shown that most of them show moderate antiradical activity and do not cause hemolysis of erythrocytes. In addition, the authors evaluated their prospects for screening for anti-tuberculosis and antitumor activity using the molecular docking methodology for decaprenylphosphoryl-D-ribose oxidase (DprE1) and heat shock protein (HSP90).

Synthesis and evaluation of antibacterial activity against *S. enterica* (SE), *M. luteus* (ML), *B. subtilis* (BS) and *P. aeruginosa* (PS) acylthioureas (**38**) and diacyl-bis-thioureas (**39**) have been discussed by Iranian scientists [21]. The authors developed a "one-pot two-step" synthesis of compounds **38** and **39** and their final structure was established by X-ray crystallography (Fig. 12). According to the results of antibacterial tests, it was found that the synthesized compounds show significant antibacterial activity (growth inhibition zone 6–16 mm) exceeding to the standard "Tetracycline" (6–10 mm). The authors note that the activities of the synthesized compounds against *S. enterica* and *M. luteus* was higher than for *B. subtilis* and *P. aeruginosa.* It is also noted that compounds **39** with 3-hydroxyphenyl substituent are the most active (inhibition zone 10–16 mm).

A series of new *N*-(quinolin-3-yl)carbamothioyl) acyl-(aroyl-)amides (**41**) was synthesized by the classical method and their inhibitory effect on fungal tyrosinase was investigated (Fig. 13) [22]. It was shown that the compound with hexanoyl substituent showed the maximum inhibitory effect on tyrosinase (IC$_{50}$=0.0070±0.0098 μM) and thus exceeds the reference standard – kojic acid

(IC_{50}=16.8320±0.0621 μM). The authors analyzed SAR and estimated the binding energy of compounds in the active site of fungal tyrosinase by molecular docking. Tyrosinase is noted to play a vital role in melanin biosynthesis and enzymatic browning of vegetables and fruits.

The search for antitumor agents was performed among asymmetrically disubstituted acylthiourea (**45**) with a dihydrophenatrene fragment in the molecule [23]. For the synthesis of the latter, as starting compounds Δ^8-dehydroabietin ((1*S*, 4a*R*, 10a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydro-phenanthrene-1-carboxylic acid, **42a**) and dehydroabietic ((1*S*, 4a*R*, 10a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid, **42b**), which were converted under classical conditions into the corresponding acyl chlorides (**43**), acyl isothiocyanates (**44**) and acyl thioureas (**45**, Fig. 14). According to the authors, the steric obstacles of the tricyclic structure do not affect the conditions and timing of the reaction and the yields of the final products (28–90 %). Cytotoxicity studies on lung cancer cell lines (A549) and hepatocarcinoma (SMMC7721) revealed several highly effective compounds with an IC_{50} between 1.87–12.67 μM for SMMC7721 cells and 2.20–6.79 μM for A549 cells, in accordance. SAR analysis showed that the most active cytostatics were compounds with furyl-2-methyl substituent.

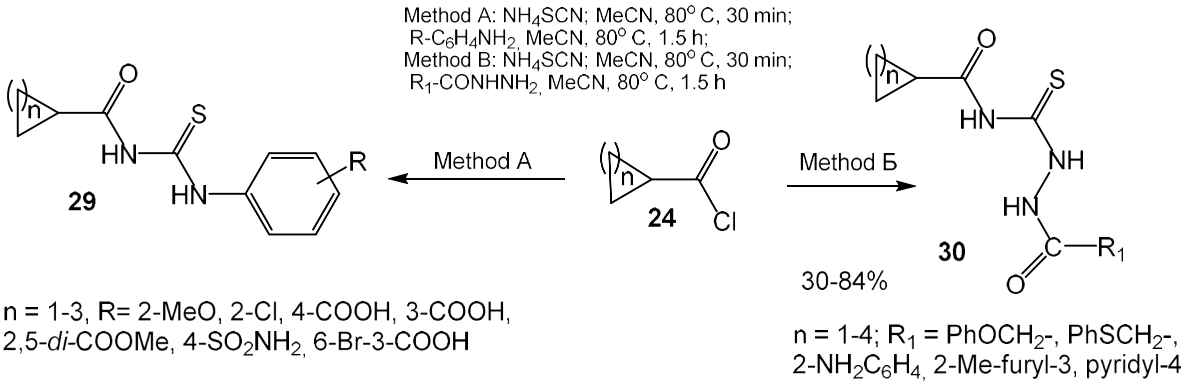


Fig. 9. "One-pot" synthesis of *N*-cycloalkylcarbonyl-*N'*-arylthioureas and *N*-cycloalkylcarbonyl-*N'*-acyl-(aroyl-, hetaroyl-)thiosemicarbazides

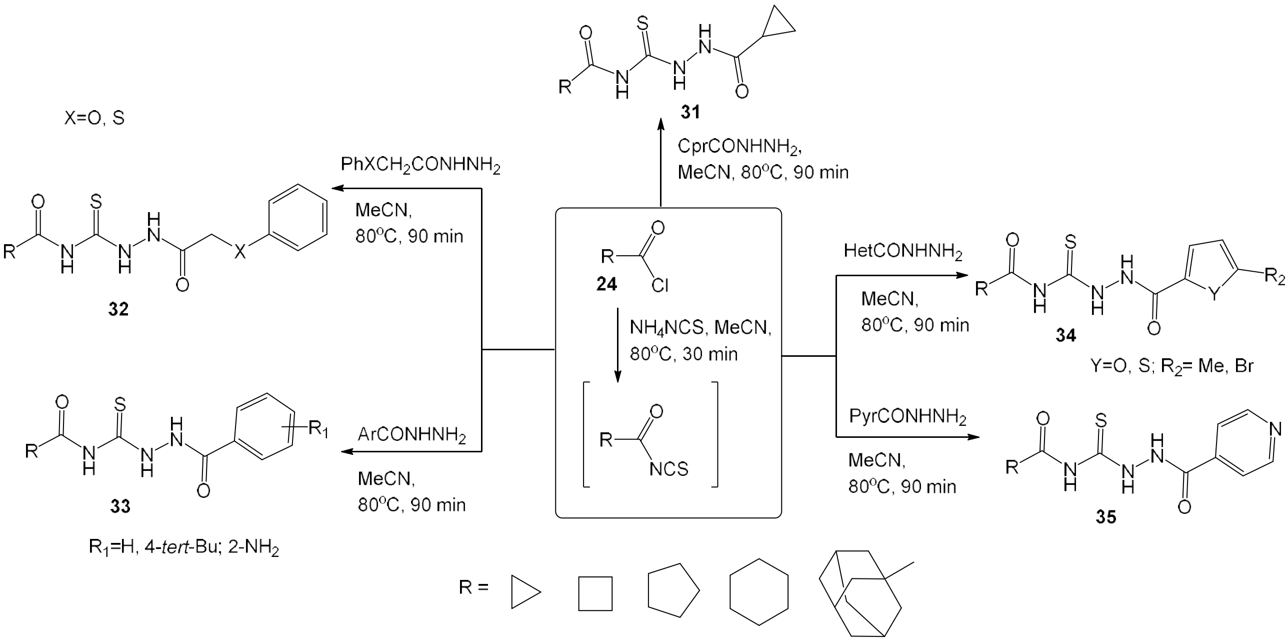


Fig. 10. Structural modification of diacyl thiosemicarbazides to target anticonvulsants

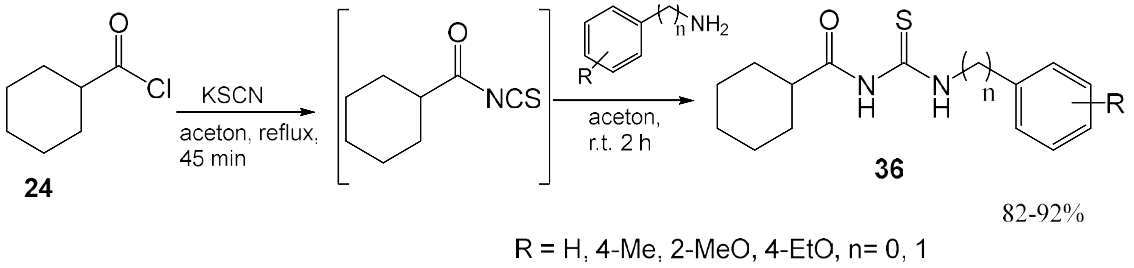
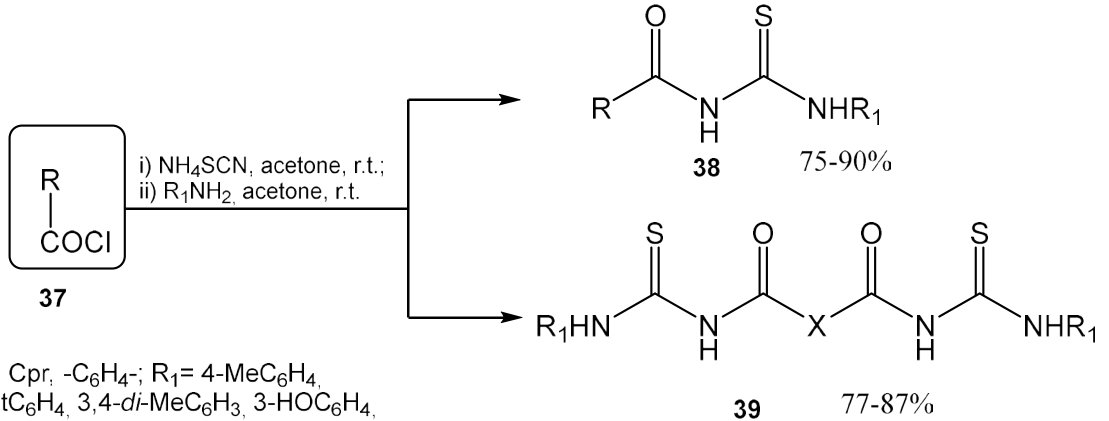
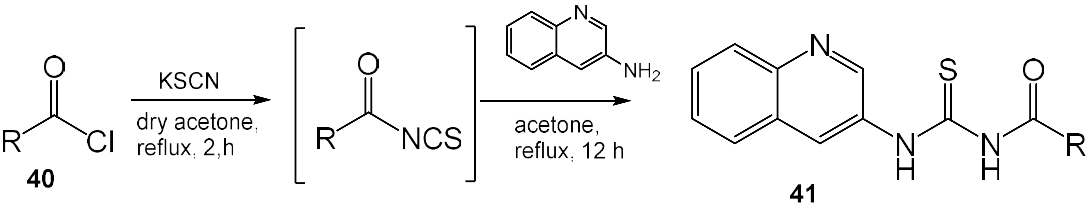


Fig. 11. "One-pot" synthesis of *N*-(aryl-(benzyl-)carbamothioyl)cyclohexanecarboxamides



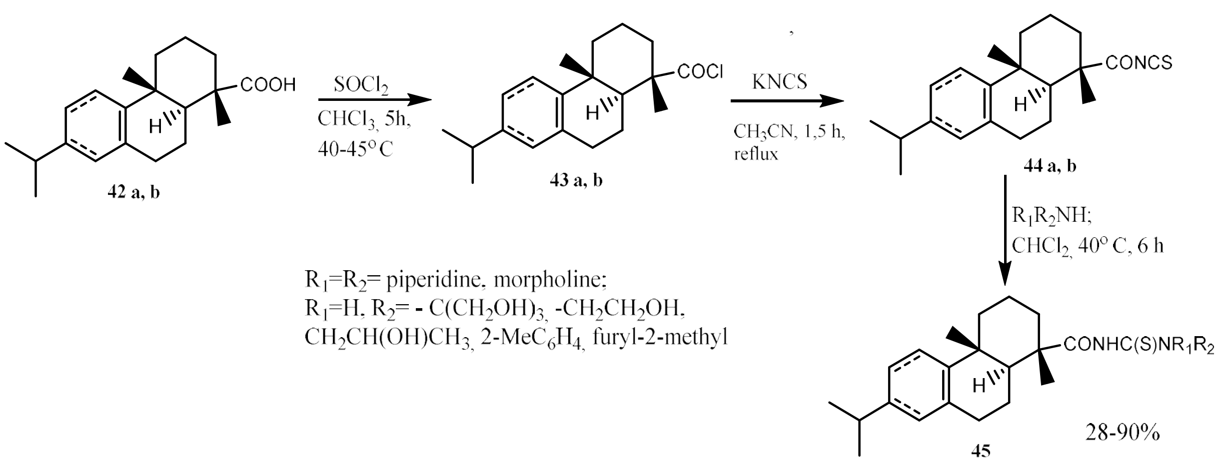
R = Cpr, $-C_6H_4-$; R_1= $4-MeC_6H_4$, $4-EtC_6H_4$, $3,4-di-MeC_6H_3$, $3-HOC_6H_4$, $3-MeOC_6H_4$, $4-MeOC_6H_4$, $4-EtOC_6H_4$, $3,4,5-tri-MeOC_6H_2$, naphthyl-1

Fig. 12. "One-pot two-step" synthesis of acylthioureas and diacyl-bis-thioureas



R = C_3H_7, $n-C_4H_9$, $n-C_5H_{11}$, $n-C_6H_{13}$, $n-C_7H_{15}$, $n-C_9H_{19}$, Ph, $4-MeC_6H_4$, $2,4-di-ClC_6H_3$, $3,5-(NO_2)_2C_6H_3$

Fig. 13. Synthesis of *N*-(quinolin-3-yl)carbamothioyl)acyl-(aroyl-)amides effective inhibitors of fungal tyrosinase



R_1=R_2= piperidine, morpholine;
R_1=H, R_2= - $C(CH_2OH)_3$, $-CH_2CH_2OH$, $CH_2CH(OH)CH_3$, $2-MeC_6H_4$, furyl-2-methyl

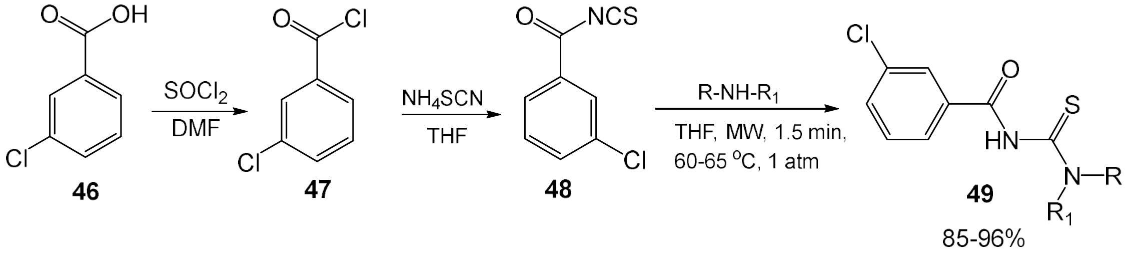
Fig. 14. Approaches to the synthesis of asymmetrically disubstituted acyl thioureas with dihydrophenatrene fragment

Parallel microwave synthesis in the liquid phase was used to obtain of 3-chloro-*N*-(R, R_1-carbamothioyl) benzamides (**49**) [24]. *In situ* prepared 3-chlorobenzoyl isothiocyanate (**48**) was mixed in equimolar ratios with primary amines in dry THF and subjected to microwave irradiation (Fig. 15). In this case, after infusion of the reaction mass into a solution of hydrochloric acid (pH 4–5), 3-chloro-*N*-(cycloalkyl-(benzyl, aryl-, het-aryl-)carbamothioyl)benzamides (**49**) are formed with a yield of 85–96 %. The synthesized compounds were evaluated for urease inhibitory activity *in vitro*. Most of them inhibit urease at IC_{50} 1.92–28.1 μM, and the compound with 2,4,6-trimethylphenyl substituent – with IC_{50} value of 1.23±0.1 μM. An antitumor activity study showed that all compounds showed moderate antitumor activity against lung carcinoma cell lines (H-157, ATCC CRL-5802), inhibiting their growth by 32.4–60.9 %.

Structural modification of carvacrol (**50**) was performed to develop effective plant protection products with polyvector action (insecticidal and antifungal) [25]. The latter provided the stepwise synthesis of 4-nitrosocarvacrol (**51**), 4-amino-carvacrol (**52**) and the corresponding *N*-((4-hydroxy-2-isopropyl-5-methylphenyl)-carbamothioyl)arylamides (53, Fig. 16). In addition, the paper shows the possibility of modifying the corresponding thioureas (**53**) to *N*-((4-hydroxy-2-isopropyl-5-methylphenyl)carbamoyl)arylamides (**54**). Studies have confirmed the authors' expectations, namely compounds **53** and **54** showed high insecticidal activity against the red cotton bug (*Dysdercus koenigii*). Thus, the LD_{50} for compounds **53** is in the range of 11.3–23.6 μg/ml, and **54** – 9.5–21.5 μg/ml). Compounds **53** and **54** show fungicidal activity (MIC 128–512 μg/ml) against phytopathogenic fungal strains (*Magnporthe grisea, Fusarium oxysporum, Dreschlera oryzae*) and yeast *(Debaromyces hansenii, Pichia membranifacie*). However, most thioureas (**53**) and ureas (**54**) have been shown to be effective fungicides against various strains of human pathogenic fungi (*C. albicans, C. glabrata, C. neoformans* and their resistant clinical strains) and do not cause hemolysis of erythrocytes at concentrations>1000 μg/ml. According to the authors, these derivatives can be used in agriculture and medicine.

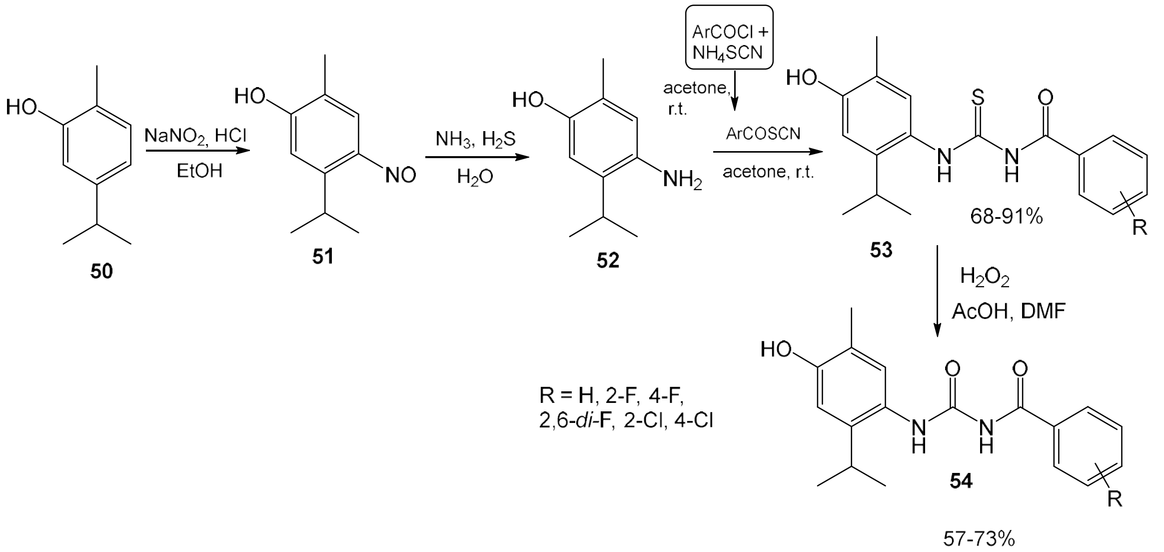
Screening results of two aroylthioureas [4-(*tert*-butyl)-*N*-((2-chlorophenyl)carbamothioyl]benzamide and *N*-[4-(3-(4-(4-(*tert*-butyl)benzoyl)thioureido]-2-methoxyphenyl)-2-chlorobenzamide against *Rift Valley fever virus* (RVFV, EC_{50}=0.25 and 0.5 μM) and *La Crosse virus* (LACV, EC_{50}=0.27 and 0.28 μM) allowed to create and synthesize a combinatorial library of more than 206000 small molecules [26]. The synthesis of modified aroyl thioureas is quite simple and involved the interaction of 4-(*tert*-butyl)benzoyl isothiocyanate (**55**), which was obtained *in situ* from the corresponding acid, with various substituted anilines (Fig. 17). *S*-alkylation products (**57**) were obtained by alkylation of aroyl thioureas (**56**) with haloalkanes, haloalkylamines or halocarboxylic acid esters, and the corresponding methyl *N*-(3-R_2-4-(2-chlorobenzamido)phenyl)-*N'*-(4-(*tert*-butyl)benzoyl)carbamidothiolate is converted to the corresponding cyanoguanidine (**58**). Conducted total high-performance screening (High Throughput Screening) of synthesized compounds for these strains of the virus, allowed the authors to identify 26 'leader structures" (EC_{50} 0.06–1.91 μM, 0.05–1.38 μM to viruses RVFV and LACV, respectively), which subsequently were tested for influenza virus (*Orthomyxoviridae*), *Tacaribe virus* (*Arenaviridae*) and dengue virus (*Flaviviridae*). Research in this direction continues.

Methods for the synthesis of *bis*-(arylcarbamothioyl) *tere*phthalamides (63) with different "pharmacophore" groups have been developed according to the standard procedure, namely the nucleophilic addition reaction of halogen-substituted anilines to *tere*-phthaloyl diisothiocyanate (62) (Fig. 18) [27]. Studies on antibacterial activity by Kirby-Bauer disk diffusion against *E. coli* and *S. aureus* showed that *N*^{1},*N*^{4}-*bis*-[(2-chlorophenyl)- and *N*^{1}, *N*^{4}-*bis*-[(2-bromophenyl)-carbamothioyl]*tere*-phthalamide have a higher activity (growth inhibition zone 18 mm) compared to Ampicillin. Based on these data, the authors conclude that the substituent in the *ortho* position has a positive effect on the activity, compared with the substituents in the meta and para positions of the phenyl substituent of the molecule.



R = H, R_1 = Cy, Bn, 2-ClBn, Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2,3-*di*-MeC_6H_3, 2,4,6-*tri*-MeC_6H_2, 2,6-*di*-EtC_6H_3, 4-(*n*-Bu)C_6H_4, haphthyl-1, 2-$CF_3C_6H_4$, 3-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 2-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,3-*di*-ClC_6H_3, 2,4-*di*-ClC_6H_3, 2,5-*di*-ClC_6H_3, 2,6-*di*-ClC_6H_3, 3,4-*di*-ClC_6H_3, 3,5-*di*-ClC_6H_3, 2,4,5-*tri*-ClC_6H_2, 2,4,6-*tri*-ClC_6H_2, 2,3,5,6-*tetra*-ClC_6H, 3-BrC_6H_4, 2,4-*di*-BrC_6H_3, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-*di*-$NO_2C_6H_3$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, benzothiazol-2-yl, pyrimidin-2-yl; R_1=R_2=-CH_2-$(CH_2)_3CH_2$-

Fig. 15. Parallel microwave synthesis of 3-chloro-*N*-(R, R_1-carbamothioyl)benzamides



R = H, 2-F, 4-F,
2,6-*di*-F, 2-Cl, 4-Cl

Fig. 16. Structural modification of carvacrol for the development of effective plant protection products of polyvector action

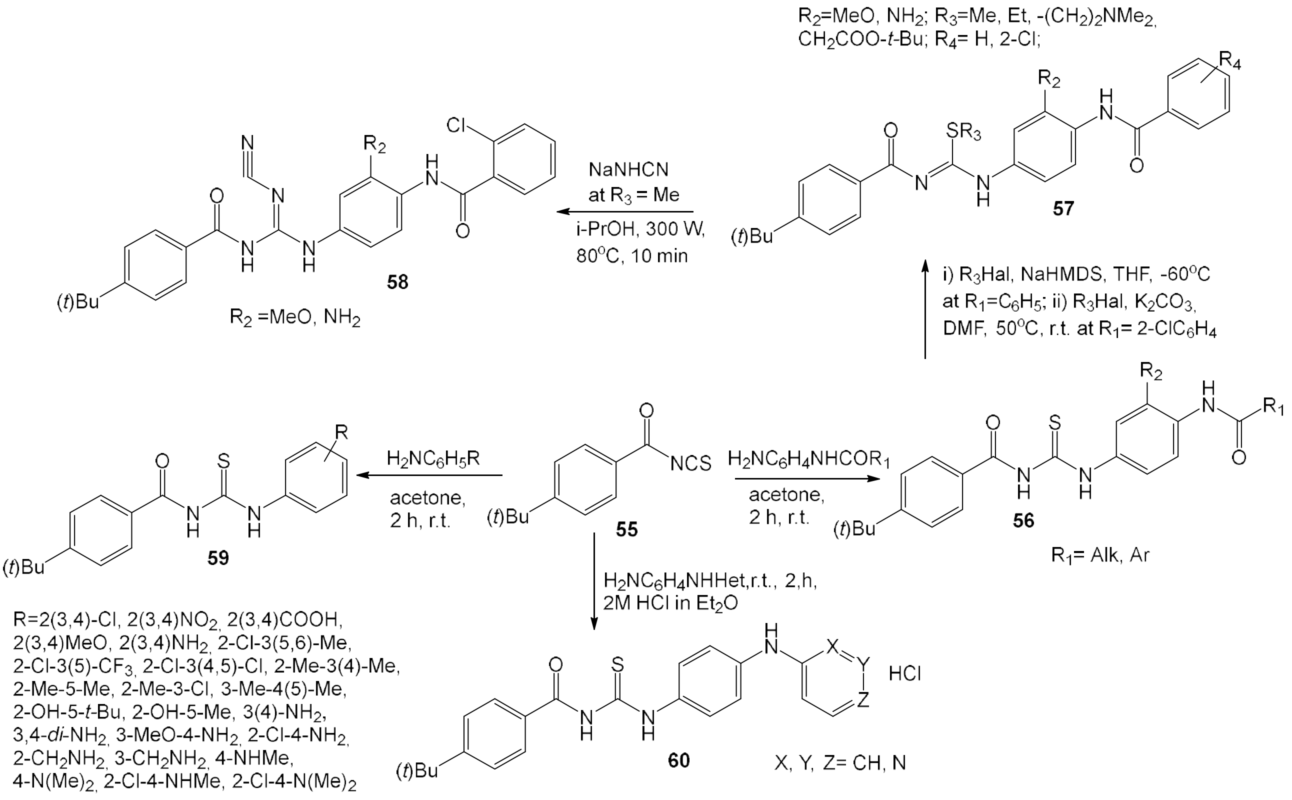


Fig. 17. Approaches to the synthesis of a combinatorial library of antiviral agents based on 4-(tert-butyl)benzoyl isothiocyanates

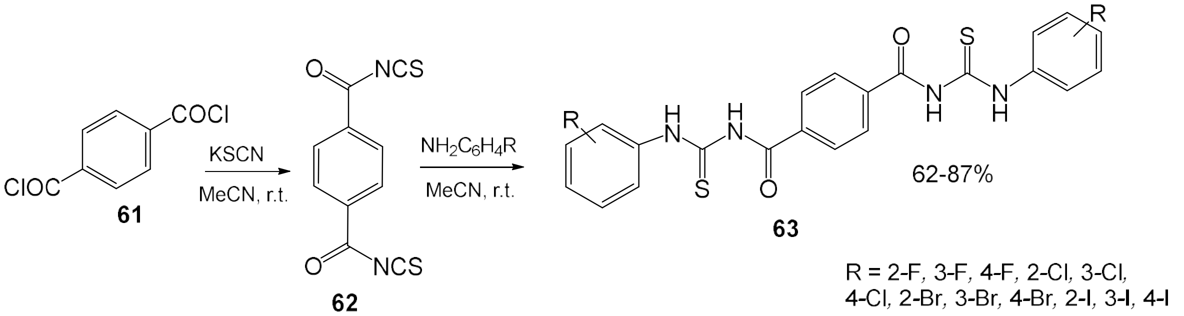
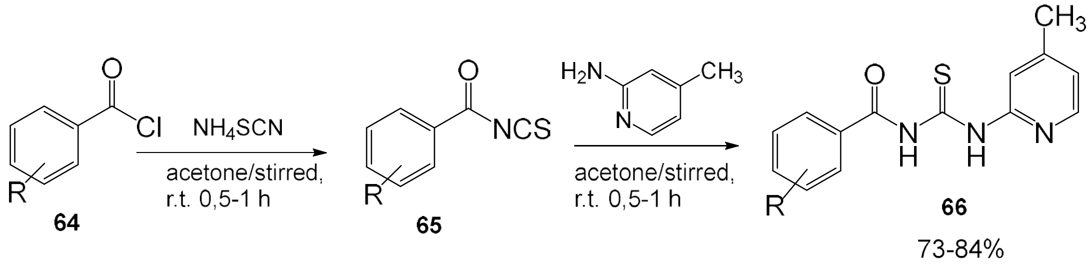


Fig. 18. Approaches to the synthesis of *bis*-(arylcarbamothioyl)*tere*-phthalamides

Another work is devoted to the synthesis and study of antibacterial activity of substituted thioureas (**66**) which combine aroyl and heteroaryl fragments in the molecule [28]. The synthesis of the target products was carried out according to the standard procedure, namely the reaction of nucleophilic addition of 4-methylpyridin-2-amine to aroyl isocyanates (**65**, Fig. 19). The authors note that substituted *N*-((4-methylpyridin-2-yl)carbamothioyl)benzamides (**66**) showed a wide range of antibacterial activity of both gram-positive and gram-negative bacterial strains. It is noted that the zones of growth inhibition against the strain *S. typhi* are in the range of 7-9 mm, and the strain *B. cereus* – in the range of 6–8 mm. Therefore, the synthesized compounds show moderate antibacterial activity.

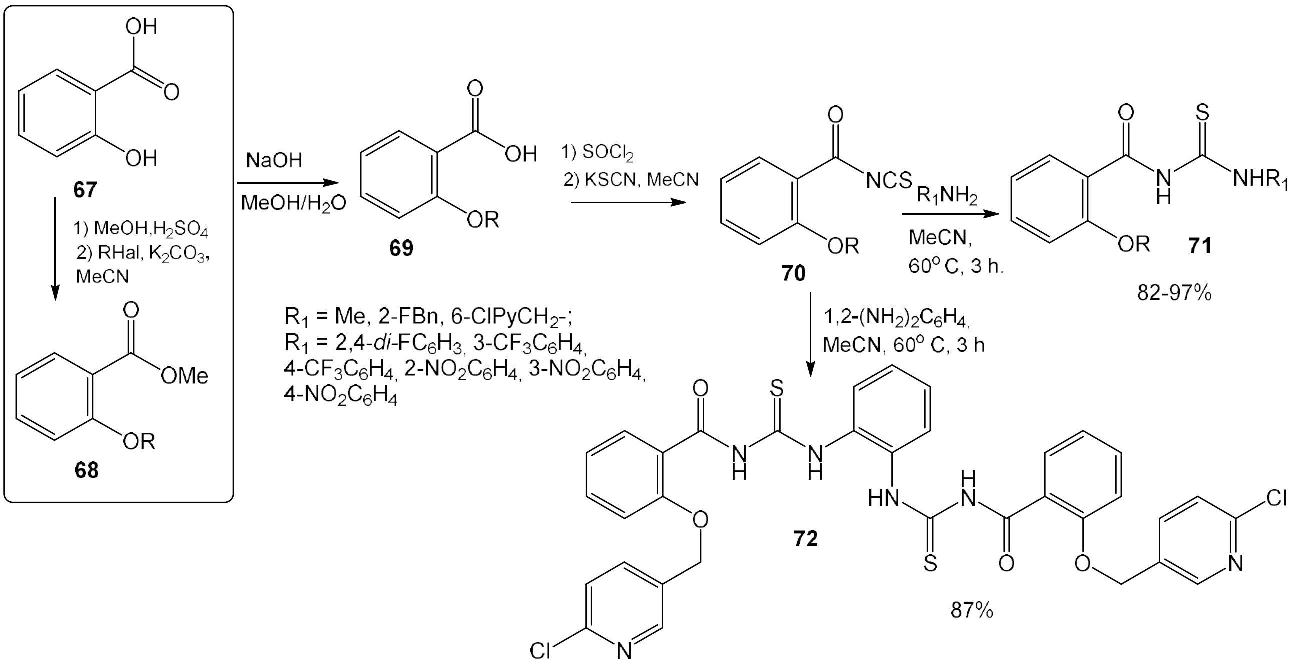
New salicylic acid-oriented derivatives of thiourea (**71**) and bis-thiourea (**72**) were synthesized by the nucleophilic addition reaction (Fig. 20) [29]. Herbicidal activity and growth-regulating activity were tested on *Amaranthus albus L., Brassica campestris L.* and *Oryza sativa L.* The study found that compounds **71** has moderate inhibitory activity against plant root and hypocotyl. While compound **72** showed a high inhibitory effect on the root and hypocotyl of *Amaranthus albus L.* (growth rate inhibition was 89.16 and 55.34 %, respectively), and 1-(4-fluorophenyl)-3-(2-methoxy-benzoyl)thiourea had a stimulating effect on root and hypocotyl growth *Oryza sativa L.*

A very interesting strategy for the search for antibacterial agents based on known antibacterial agents, namely sulfamide drugs (**74**) [30]. This strategy was implemented in several stages, first, the formation of the corresponding *N*-((4-(*N′*-R-sulfamoyl)phenyl)carbamothioyl)-2-phenylacetamides (75) by reacting the starting compounds **74** with 2-phenylacetyl isothiocyanate (**73**, Fig. 21). Second, the synthesis of *N*-substituted ethyl 4-(3-carboxythioureido)benzenesulfamides (**77**) by sequential formation with **74** 4-isothiocyanato-*N*-R-benzenesulfamides (**76**), followed by nucleophilic addition of ethyl carbamate. The antimicrobial activity of the *in vitro* synthesized compounds was evaluated against gram-positive (*S. aureus, Methicillin-Resistant S. aureus* (*MRSA*), *B. subtillis, St. pyogenes*), gram-negative bacteria (*E. coli, Pr. Vulgaris, Erwiniacarotovora*) and fungus (*C. albicans*). The study revealed 2-phenyl-*N*-{[(4-(*N*-thiazol-2-yl)sulfamoyl)phenyl]-carbamothioyl}acetamide and ethyl {4-[(5-methyl-1,2-oxazole-3)-yl)sulfamoyl)-phenyl]carbamothioyl}carbamate are highly active antimicrobial agents against *B. subtilis* (MIC 70 and 80 µm/ml, respectively). However, conducted by authors molecular docking for bacterial dihydropteroate synthase (DHPS) did not make it possible to assess their probable mechanism of action.



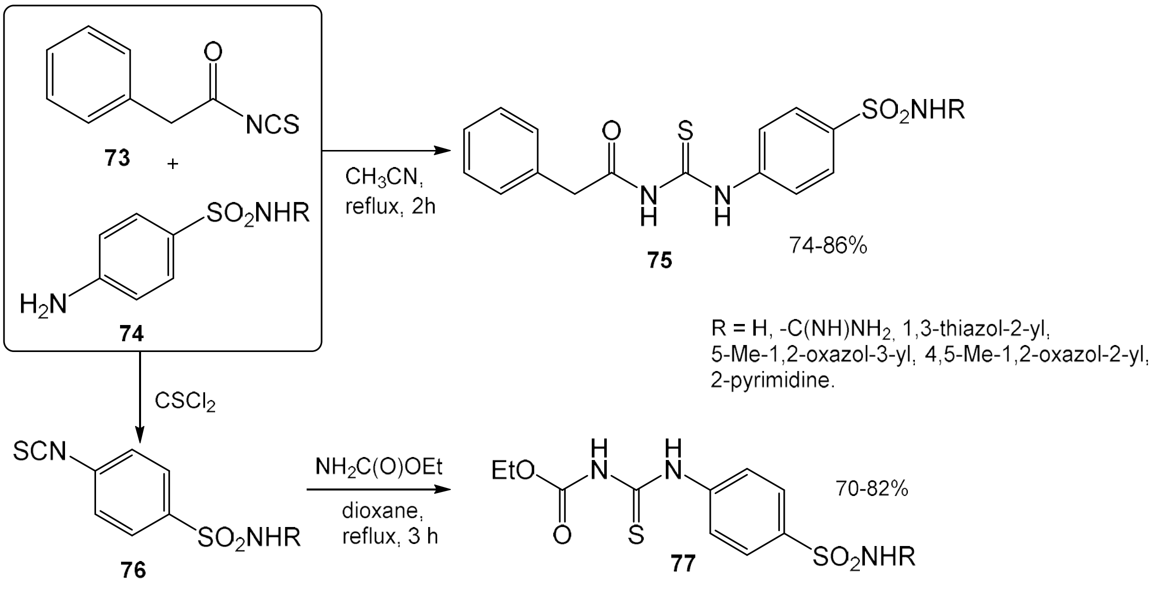
R = 2-Me, 4-Me, 2-NO$_2$, 3-NO$_2$, 4-NO$_2$, 3-Cl

Fig. 19. Approaches to the synthesis of substituted thioureas with aroyl and heteroaryl fragments



R$_1$ = Me, 2-FBn, 6-ClPyCH$_2$-;
R$_1$ = 2,4-*di*-FC$_6$H$_3$, 3-CF$_3$C$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

Fig. 20. Synthesis of salicylic acid-oriented thioureas and bis-thioureas



R = H, -C(NH)NH$_2$, 1,3-thiazol-2-yl, 5-Me-1,2-oxazol-3-yl, 4,5-Me-1,2-oxazol-2-yl, 2-pyrimidine.

Fig. 21. Strategy of searching for antibacterial agents based on known sulfamide drugs

To improve the pharmacokinetic characteristics of sulfadiazine (**78**) its structural modification with various acyl isothiocyanates was performed (**79**, Fig. 22) [31]. Compounds **60** were subjected to alkaline phosphatase of the calf (CIAP) and found a significant inhibitory potential (IC_{50} 0.25–4.25 μM) compared with standard potassium monophosphate (IC_{50} 4.32 μM). The pharmacokinetic evaluation of the synthesized compounds using the ADMET program and molecular docking for alkaline phosphatase confirmed the prospects of their further research as drug agents.

A synthesized new series of derivatives acylthiourea (**81**) containing the pyrazole cycle was evaluated for antitumor activity on colon, liver and human leukemia cancer cell lines [32]. Compounds **81** were obtained by "one-pot synthesis", namely by stepwise addition to 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl chloride (**80**) of ammonium thiocyanate and various aryl-(hetaryl-) amines (Fig. 23). Studies of compounds **81** in cell cultures have demonstrated their significant cytotoxicity. It is shown that they show antitumor activity at concentrations of 10^{-4} and 10^{-5} M. The authors note that, as a rule, the antitumor effect is expressed in compounds that contain an aryl substituent.

A series of derivatives *N*-(1-methyl-1*H*-pyrazole-4-carbonyl)thiourea (**86**) was synthesized by reacting substituted anilines with 1-methyl-1*H*-pyrazole-4-carbonylisothiocyanate (**84**) [33]. Approaches to the synthesis of the latter are classic and are shown in Fig. 24. However, the authors found that compounds 85 show moderate antimicrobial activity (MIC>250.0 μg/ml) against both gram-positive bacteria (*B. subtili, E. faecalis, S. aureus*) and gram-negative (*P. aeruginosa, A. baumannii, K. pneumoniae, E. coli*). The paper also discusses some correlations of the structure-activity relationship.

A series of novel acyl thiourea derivatives containing pyrazole moiety (**89**) were designed and synthesized from ethyl acetoacetate, triethyl orthoformate, methylhydrazine by multi-step reactions (Fig. 25) [34]. The target compounds were evaluated for their fungicidal activity. The results showed that some of these compounds did not show a high specific fungicidal effect against *Botryospuaeria berengeriana*. The results of molecular docking made it possible to assess the probable mechanism of action. It has been shown that the interaction of succinodehydrogenase with N- [2,6-diethylphenyl)carbamothioyl]-1,3-dimethyl-1*H*-pyrazole-4-carboxamide is realized through hydrogen bonding and donor-acceptor π (σ)-π-interactions.

A series of new acylthiourea derivatives (**95**) containing a difluoromethylpyrazole moiety was synthesized to search for fungicides [35]. The synthesis of the basic cycle with ethylcarboxyl group (**91**) was performed using ethyl 4,4-difluoro-3-oxobutanoate (**90**), triethylorthoformate and methylhydrazine. Subsequent hydrolysis, chlorination, isothiocyanation in methanol in the presence of a solid-phase catalyst (PEG-600) and interaction with substituted anilines led to the formation of target products (**95**) with a yield of 59.6–91 % (Fig. 26). The results of the study of the fungicidal activity of compounds **95** showed that the latter potentiate the growth of *Corynespora mazei* and *Fusarium oxysporum* at a concentration of 50 μg/ml. Whereas, according to the authors, they in this concentration have a fungicidal effect on *Pseudomonas syringae pv. Lachry-*

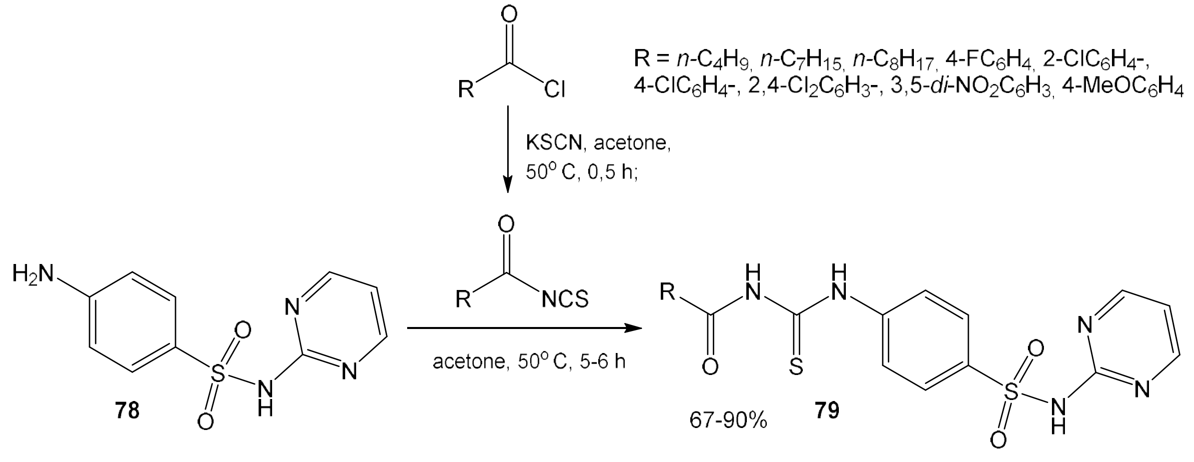


Fig. 22. Approaches to the synthesis of *N*-[(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)carbamothioyl]acylamides

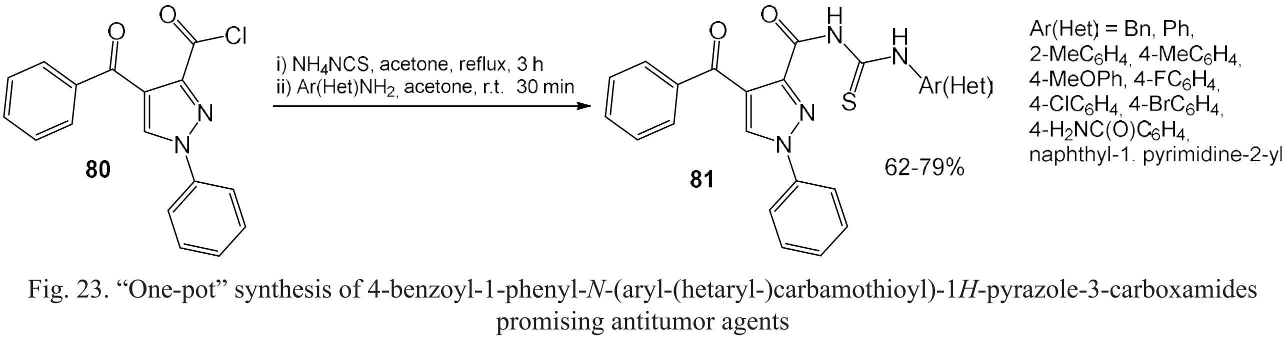
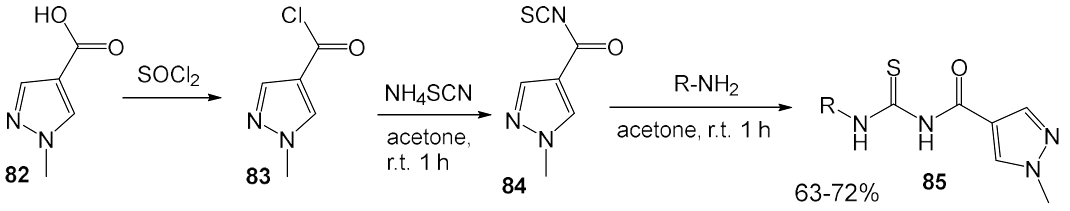


Fig. 23. "One-pot" synthesis of 4-benzoyl-1-phenyl-*N*-(aryl-(hetaryl-)carbamothioyl)-1*H*-pyrazole-3-carboxamides promising antitumor agents

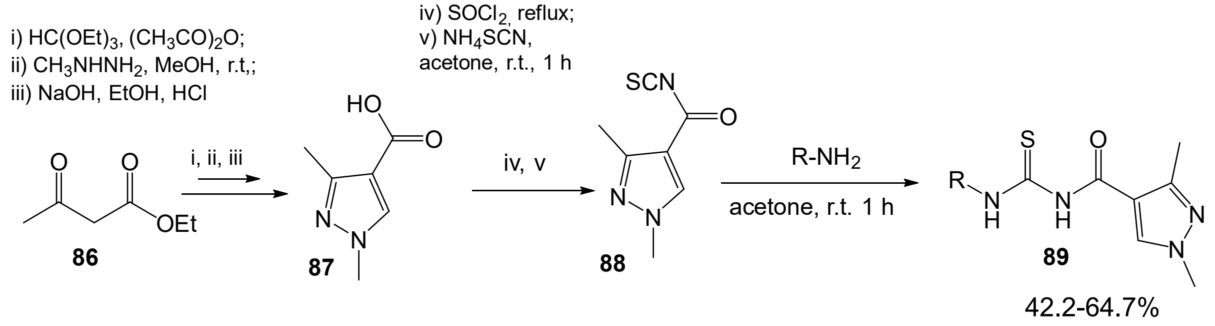
mans and *Botrytis cinerea*, exceeding the fungicide – "Fluxapiroxad". Preliminary analysis of the structure-activity relationship showed that the substituent in the phenyl substituent affects the fungicidal activity. For example, the introduction of fluorine to position 3 leads to an increase in activity, and its movement to position 2 leads to a significant decrease in relation to *Botrytis cinerea*.

A series of anthranylamides (**100**), which are linked via a «linker» carboxythioureid group to 1-(3-[chloropyridin-2-yl)-3-R-1*H*-pyrazole, has been synthesized to search for insecticides [36]. The search strategy was as follows, first, in the synthesis of acyl isothiocyanates (**97**), anthranylamides (**99**), and secondly, their subsequent interaction with each other with the formation of target products 100 with a yield of 68–84 % (Fig. 27). The authors conducted a detailed evaluation of the insecicidal activity of compounds **103** against the eastern armyworm (*Mythimna separata*), mosquito larvae (*Culex pipiens pallens*) and diamond moth (*Plutella xylostella*). It was found that most of the tested compounds **103** show high larvicidal activity at a concentration of 10 mg/l. The authors also note that the introduction into the structure of 103 bulky substituents (isoamyl, cyclohexyl) leads to a significant loss of activity. The most active compounds and "Chlorantraniliprole", using electrophysiological and fluorescent methods, were investigated for the release of calcium ions from neurons from *S. exigua*. It was found that the synthesized compounds, as well as "Chlorantraniliprol" affect the calcium channel and are potential activators of the insect ryanodine receptor (RyR).



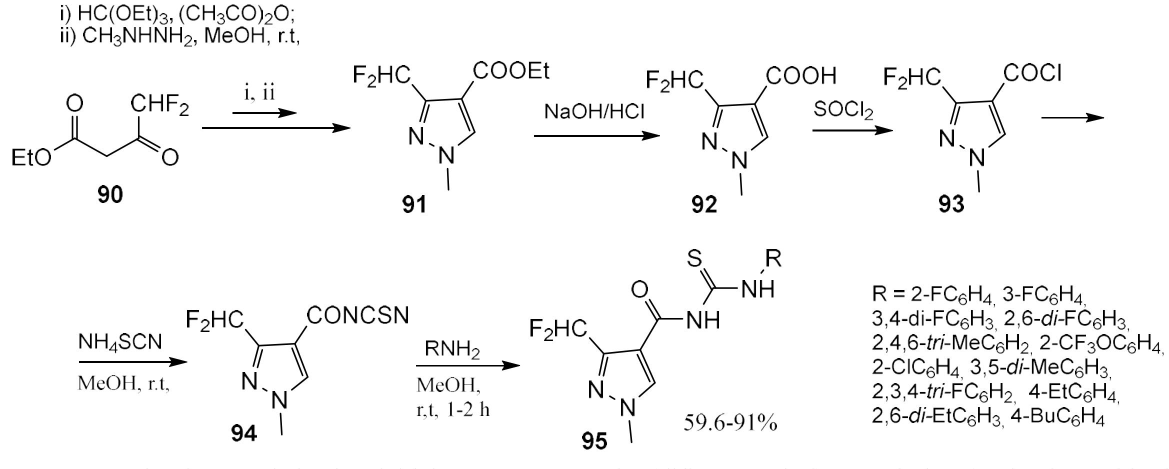
R = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-EtC_6H_4, 3-EtC_6H_4, 2-*n*-PrC_6H_4, 4-*n*-PrC_6H_4, 2-*i*-PrC_6H_4, 4-*i*-PrC_6H_4, 2-*s*-BuC_6H_4, 4-*s*-BuC_6H_4, 2-*t*-BuC_6H_4, 4-*t*-BuC_6H_4,

Fig. 24. Approaches to the synthesis of 1-methyl-*N*-(arylcarbamothioyl)-1*H*-pyrazole-4-carboxamides



R = 2-MeC_6H_4, 3,5-*di*-MeC_6H_3, 4-EtC_6H_4, 2,6-*di-Et*C_6H_3, 2-FC_6H_4, 3-FC_6H_4, 3,4-*di*-FC_6H_3, 2,6-*di*-FC_6H_3, 2,3,4-*tri*-FC_6H_2, 2-$CF_3C_6H_4$, 2-$OCF_3C_6H_4$,

Fig. 25. Strategy for the search for fungicidal agents among of *N*-(arylcarbamothioyl)-1,3-dimethyl-1*H*-pyrazole-4-carboxamides



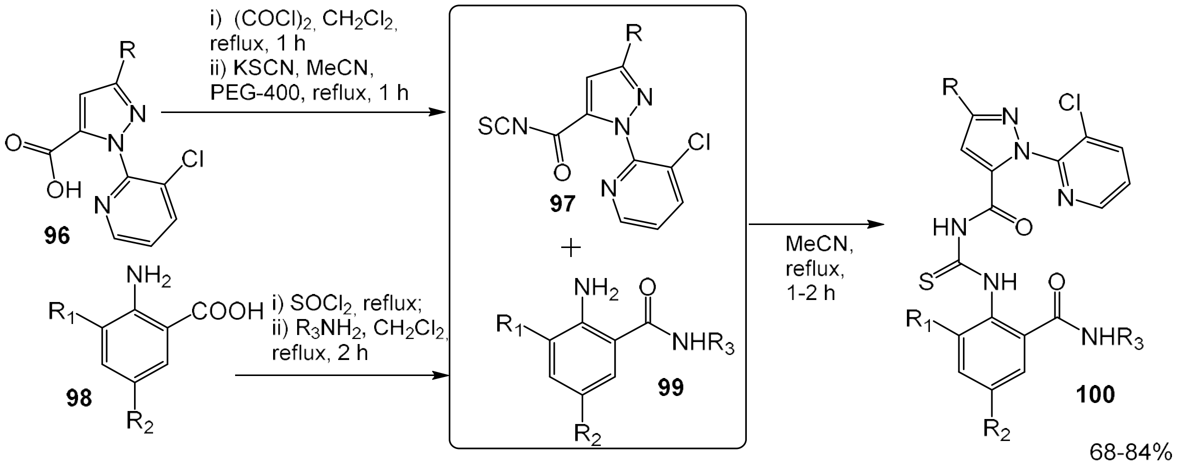
R = 2-FC_6H_4, 3-FC_6H_4, 3,4-di-FC_6H_3, 2,6-*di*-FC_6H_3, 2,4,6-*tri*-MeC_6H_2, 2-$CF_3OC_6H_4$, 2-ClC_6H_4, 3,5-*di*-MeC_6H_3, 2,3,4-*tri*-FC_6H_2, 4-EtC_6H_4, 2,6-*di*-EtC_6H_3, 4-BuC_6H_4

Fig. 26. Strategy for the search for fungicidal agents among of 3-(difluoromethyl)-1-methyl-*N*-(arylcarbamothioyl)-1*H*-pyrazole-4-carboxamides

Targeted search for antitumor agents is extended to other acylthioureas with a pyrimidine moiety, namely 1-ethyl-2-oxo-4-phenyl-*N*-(arylcarbamothioyl)-1,2-dihydropyrimidine-5-carboxamides (**104**) [37]. To implement the search strategy, the authors carried out a stepwise synthesis of acids, acid chlorides, acyl isocyanates and acylthioureas (**104**) from the original ethyl 1-ethyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**101**, Fig. 28). *In vitro* studies on the ability of compounds **104** to inhibit breast cancer cell lines (MCF-7) and human osteosarcoma (Saos-2) at various concentrations (**100** μM, 25μM, 12.5 μM, 6.25 μM, 3,125 μM) allowed to establish the effective inhibitory concentration (IC_{50}), which was 5.24–73.86 μM. Structure-activity analysis in this series showed that the potent cytotoxicity of the compounds was determined by a naphthyl-1-yl substituent. Whereas the introduction of a phenyl group or additional introduction of substituents (methyl-, methoxy, halogen) reduced the anti-cancer activity. The results of molecular docking have shown that compounds interact with the ATP pocket Hsp90 and inhibit ATPase function and, according to the authors, are promising for the treatment of breast cancer and osteosarcoma of the bones.

In should be mentioned that search of the biologically active agents among complexes of acylthioureas with transition metal ions (Pt(II), Pd(II), Ru(II)), Rh(III) and Ir(III) is still in the focus of modern medicinal chemistry [8, 9]. It was shown that compounds (**107**, **108**) that are formed on basis of *N*-mono- and *N,N′*-disubstituted-*N*-acyl thioureas (105) and $PdCl_2(PPh_3)_2$ are promising anticancer agents (Fig. 29) [38].

Ligands **105** were obtained by standard procedures starting from benzoyl chlorides, furan-2-(thiophene-2-)carbonyl chlorides, potassium thiocyanates and mono- or disubstituted amines. The crystalline structure of obtained complexes was studied by authors using physicochemical methods including X-ray diffraction methods. It was found that ligands form interactions with metal cations via Oxygen and Sulfur atoms in case of *N,N′*-disubstituted-*N*-acylthioureas (**107**) and via Sulfur and Nitrogen in case of *N*-substituted-*N*-acylthioureas (**108**). Revealed that the most active compounds against MDAMB-231 (human breast cancer cells) are complexes with thienyl and dimethylamine (IC_{50}=0.62±0.08 μM) and with benzoyl and aminomorpholine (IC_{50}=1.93±0.45 μM) moieties.



R=Cl, Br, CF_3; R_1=H, Me; R_2=H, Cl, Br; R_3=Me, Et, *i*-Pr, *n*-Pr, *n*-Bu, Cpr, Cy, *i*-Am, Bn

Fig. 27. Insecticide search strategy among 3-R-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acids with anthranylthioureides fragments

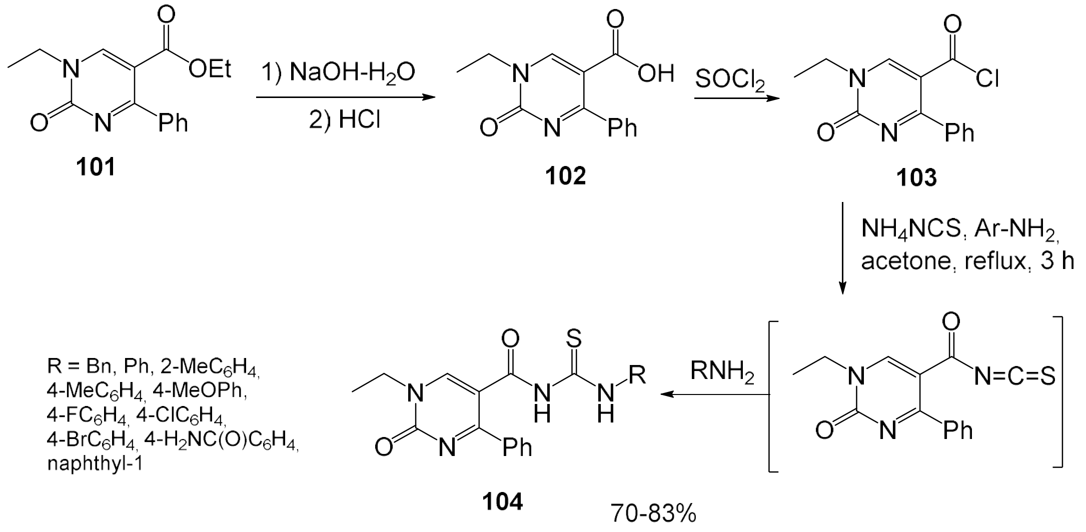


Fig. 28. Antitumor strategy among 1-ethyl-2-oxo-4-phenyl-*N*-(arylcarbamothioyl)-1,2-dihydropyrimidine-5-carboxamides

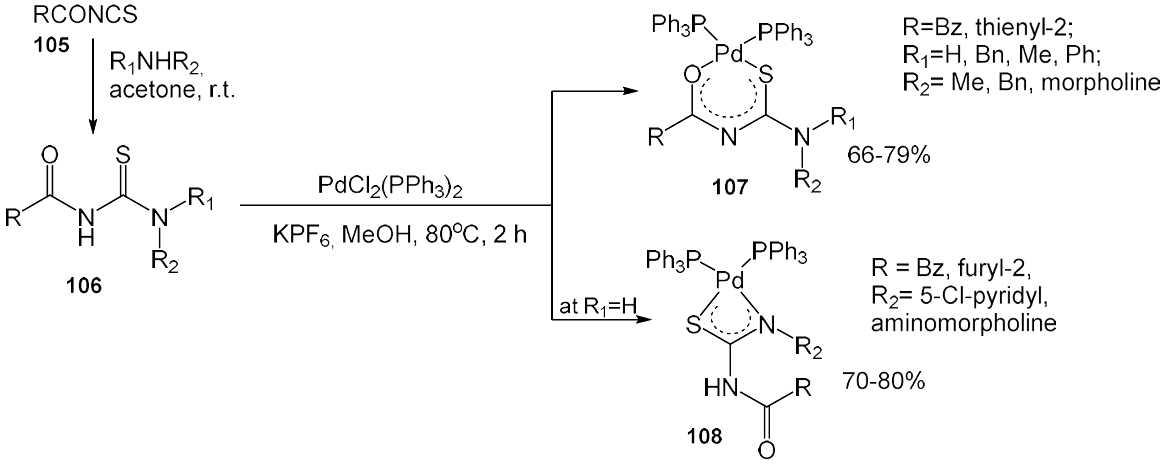


Fig. 29. Synthesis of Pd(II) complexes with *N,S* or *O,S* coordination modes of acylthiourea ligands promising antitumor agents

4. Conclusions

The analysis of literature data of recent years shows that alkanoyl-(aroyl-, hetaroyl)-isothiocyanates and products of their modification (substituted acyl thioureas, acyl thiosemicarbazides, complex compounds) are not sufficiently studied class of compounds, despite their usage in the field of chemistry, materials science and medical chemistry. These compounds exhibit antimicrobial, fungicidal, antitumor, antiviral, antifungal, antiradical, antioxidant, diuretic, anticonvulsant, insecticidal, larvicidal and other activities. Thus, alkanoyl-(aroyl-, heteroyl)-isothiocyanates and products of their modification remain reagents with undiscovered potential for molecular design and structural modification of biologically active compounds.

Conflict of interests

The authors declare that they have no conflicts of interest.

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