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The Synthesis of Isoxazolyl- and Isothiazolylcarbamides Exhibiting Antitumor Activity

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Abstract—Accessible 5-phenyl(*p*-tolyl)isoxazol-3-carboxylic, 4,5-dichlorothiazol-3-carboxylic and 5-(benzylsulfanyl)-4-chlorothiazol-3-carboxylic acids were converted via a series of cascade transformations into the corresponding (1,2-azolyl)-3-carbonyl azides whose reaction with slightly basic aryl(heteryl)amines led to generation of 1-(1,2-azolyl)-3-aryl(heteryl)carbamides. To obtain isoxazolyl(isothiazolyl)carbamides containing the residues of highly basic amines, (1,2-azolyl)-3-carbonyl azides were preliminary transformed into aryl (1,2-azol-3-yl)carbamates by the action of phenol or 4-fluorophenol. Carbamates then were introduced into reaction with aliphatic or heterocyclic amines. Some of the obtained compounds and their precursors show high antitumor activity and are capable to increase the effect of cytostatic drugs applied in the medical practice.

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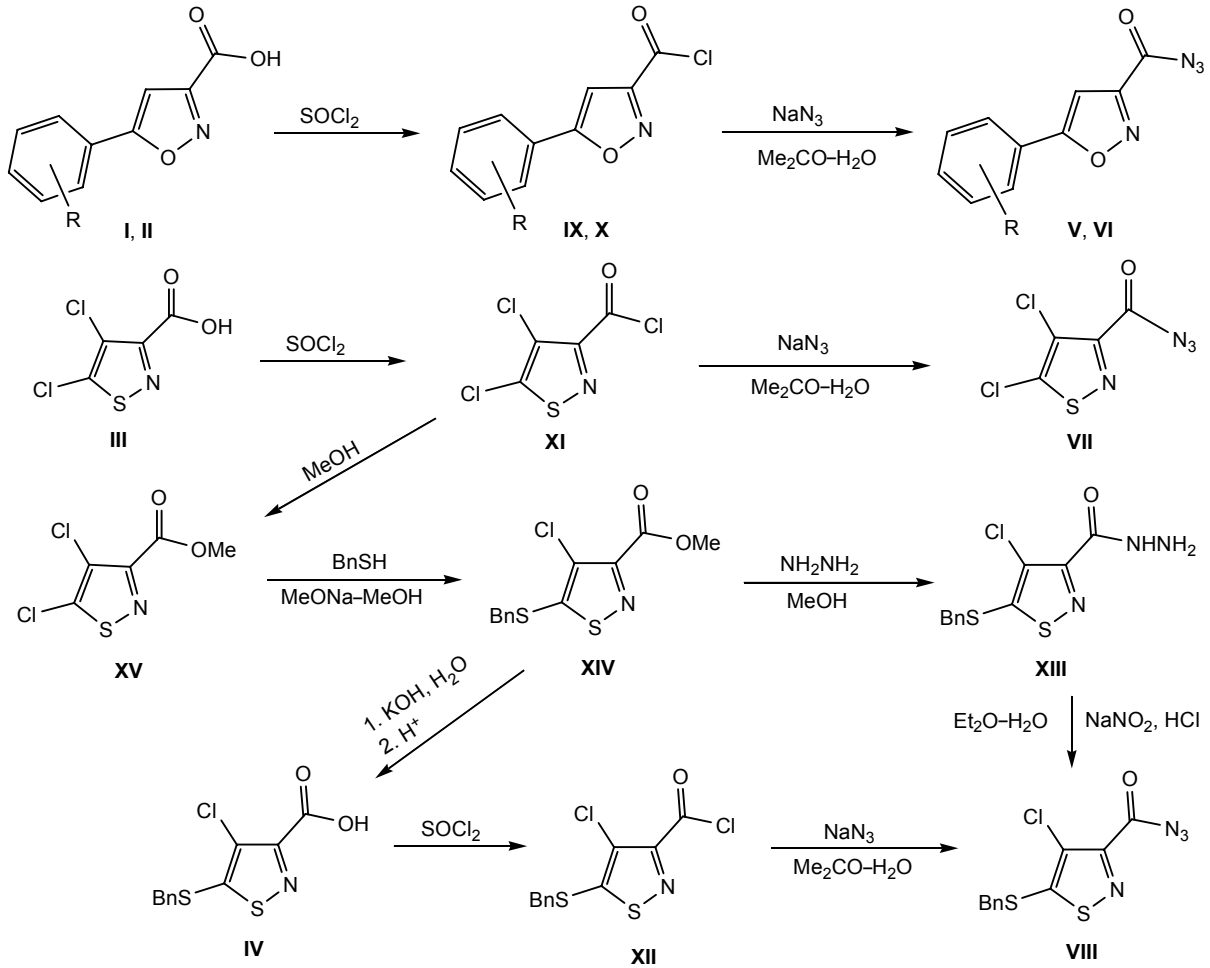
Isoxazoles and isothiazoles are the molecular fragments of a wide spectrum of bioactive compounds, among them the ureas with 1,2-azole groups also belong to new promising antitumor agents [1]. For instance, one of (5-benzyloxy-4-carbamoylisothiazol-3-yl)carbamides is an inhibitor of tyrosine kinase and is nowadays extensively tested in USA as antitumor substance CP-547.632 [2]. Among the isoxazolylcarbamides an effective inhibitor of Raf kinase was also discovered, which regulates the processes of cellular onkogenesis and apoptosis [3]. Hence the synthesis of new derivatives of urea, substituted by isoxazol or isothiazol heterocycle is still relevant.

There are quite a number of synthesis variations of substituted carbamides; from the ones recently published the carbonylation of aliphatic amines with *S*,*S*-dimethyldithiocarbonate and also with the carbon oxide should be mentioned [4, 5]. One of the general methods is the reaction of amines with acyl carbamates, which in turn are obtained from acyl azides. Various modifications of this method are known, differing in steps of preparating azides, acyl carbamates, and the participating reagents.

Basing on 5-phenyl(*p*-tolyl)isoxazole- and 4,5-dichlorothiazole-3-carboxylic acids **I–III** we worked out convenient procedures of synthesis of carbamides substituted with isoxazole or isothiazole rings, aiming to obtain compounds that were isosteres of antitumor agents and promising for biotesting. The initial 5-phenyl(*p*-tolyl)isoxazole- and 4,5-dichlorothiazole-3-carboxylic acids are easily obtained as a result of successive transformations of trichloroethylene dimer [7–9]. Along with 4,5-dichlorothiazole-3-carboxylic acid (**III**) as a starting compound 5-(benzylsulfanyl)-4-chlorothiazole-3-carboxylic acid (**IV**) was also used, which we had obtained earlier [10, 11]. Adding the acid **IV** to insecticides leads to increasing their bioactivity [11]. Besides, the presence of benzylsulfanyl group in the position *5* makes it possible to hope on obtaining the isosteric carbamide analog structurally closer to the substance CP-547.632.

The chosen approach to the synthesis of *N*-isoxazolyl(isothiazolyl)carbamides included the initial preparation of the corresponding 1,2-azolylcarbonyl azides **V–VIII**. The azides of 5-(*p*-tolyl)isoxazole- and 4,5-dichlorothiazole-3-carboxylic acids **VI** and **VII**

Scheme 1.



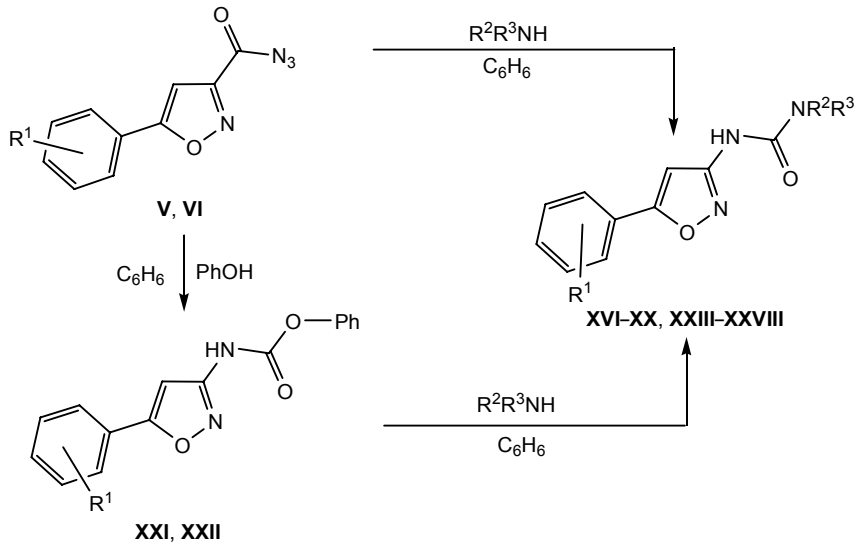
R = H (**I**, **V**, **IX**), 4-Me (**II**, **VI**, **X**).

were synthesized earlier by the reaction of 5-(*p*-tolyl)-isoxazole- and 4,5-dichlorothiazole-3-carbonyl chlorides **X** and **XI** with sodium azide [12, 13]. The azide of 5-phenylisoxazole-3-carboxylic acid (**V**) was synthesized in the same way from 5-phenylisoxazole-3-carbonyl chloride (**IX**). To obtain 5-(benzylsulfanyl)-4-chlorothiazole-3-carbonyl azide (**VIII**) acid chloride **XII** and hydrazide of 5-(benzylsulfanyl)-4-chlorothiazole-3-carboxylic acid (**XIII**) were used; their precursor was the methyl ester of that acid **XIV**.

We optimized the recently published method of synthesis of the initial acid **IV**, including the primary preparation of methyl dichlorothiazole-3-carboxylate (**XV**), the selective substitution of the chlorine atom in the position *5* of the heterocycle by treating with sodium benzylthiolate at 20°C, and the hydrolysis of methyl 5-(benzylsulfanyl)-4-chlorothiazole-3-carboxylate (**XIV**) [11]. Applying the double excess of benzylthiol in the step of nucleophilic substitution and boiling the mixture allows decreasing the time of the reaction from 8 to 2 h and increasing the yield of acid **IV** from 85 to 95%. The intermediate ether may be isolated in 97% yield by excluding the step of hydrolysis.

The hydrazide **XIII** was obtained in 95% yield by the action of hydrazine hydrate on ether **XIV** in methanol. The subsequent treatment of hydrazide **XIII** with nitrous acid (mixture of $NaNO_2$ and HCl) led to the target azide of 5-(benzylsulfanyl)-4-chlorothiazole-3-carboxylic acid (**VIII**). However as a result of low solubility of hydrazide **XIII** in acid medium the reaction proceeds slowly and the yield of azide **VIII** did not exceed 65%, whereas in the reaction of 5-(benzylsulfanyl)-4-chlorothiazolecarbonyl chloride (**XII**) with NaN_3 the target azide **VIII** was obtained in 82% yield (Scheme 1).

Scheme 2.



R^1 = H (**V**, **XVI**–**XIX**, **XXI**, **XXIII**–**XXVII**), 4-Me (**VI**, **XX**, **XXII**, **XXVIII**); R^2 = H, R^3 = 4-BrC_6H_4 (**XVI**), C_6H_4-4-COOH (**XVII**), C_6H_4-4-COOEt (**XVIII**), hexyl (**XXIII**), 6-hydroxyhexyl (**XXIV**), Bn (**XXV**); R^2R^3N = 3,5-dimethylpyrazol-1-yl (**XIX**), benzotriazol-1-yl (**XX**), piperazin-1-yl (**XXVI**), morpholin-4-yl (**XXVII**, **XXVIII**).

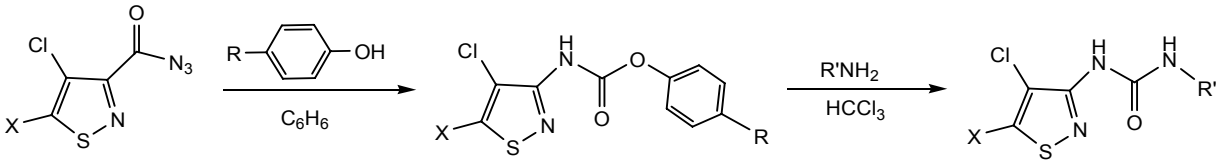
The azides **V**–**VIII** were used in syntheses of the corresponding (1,2-azol-3-yl)ureas. By the example of 5-aryl(*p*-tolyl)isoxazole-3-carbonyl azides **V** and **VI** we demonstrated that under the effect of weakly basic aromatic and heterocyclic amines (*p*-bromoaniline, *p*-aminobenzoic acid, its ethyl ether, 3,5-dimethylpyrazole, and benzotriazole) at boiling the mixture in benzene (5-aryl-isoxazol-3-yl)carbamides **XVI**–**XX** formed (yields 63–91%), containing the residues of the corresponding amines. However at the treatment with more basic amines of aliphatic, alkylaromatic, and heterocyclic series (hexylamine, 6-aminohexanol, benzylamine, piperazine, and morpholine) this way of synthesis of substitued isoxazolylureas is not realized since the corresponding amides are obtained as predominant products of the reaction. Therefore first the urethane derivatives of 5-arylisoxazol-3-ylcarbamates **XXI** and **XXII** [14] were synthesized. Phenyl [5-(*p*-tolyl)isoxazol-3-yl]carbamate (**XXII**) was obtained by reacting azide **VI** with phenol and used in the synthesis of a palladium complex [12]. Phenyl (5-phenylisoxazol-3-yl)carbamate (**XXI**) was obtained in the similar way from azide **V** (Scheme 2).

Isoxazolylcarbamates were introduced in the reaction with amines to obtain 5-arylisoxazolylureas **XXIII**–**XXVIII** in 61–82% yields.

The closest analogs of the tyrosine kinase inhibitor, the antitumor agent CP-547.632, are arylalkyl-substituted isothiazolylureas with aliphatic residue in the carbamide fragment. From the compounds we obtained these are the benzylsulfanylisothiazolylcarbamides. Taking into consideration the experimental data the isoxazolylureas were obtained through isothiazolylcarbamates. Some preparatively important features for obtaining the derivatives of 4,5-dichloronitroazole and 5-(benzylsulfanyl)-4-chlorothiazole series were found. Whereas phenyl (4,5-dichlorothiazol-3-yl)carbamate (**XXIX**) was obtained in similar way to compounds **XXI** and **XXII** by treating dichloroisothiazolyl azide **VII** with phenol in benzene, *p*-fluorophenol was applied to the synthesis of the carbamate from azide **VIII**, for phenylcarbamate possessed low solubility in benzene that prevented its further application in obtaining the carbamides, because the reaction proceeded too slow and with low conversion, and the formed compounds required additional purification. Moreover, *p*-fluorphenol has higher reactivity toward azides comparing to phenol and the formation of 5-(benzylsulfanyl)-4-chloroisothiazolylcarbamate (**XXX**) was finished in 30 min, while the reaction with phenol took 4 h.

Isothiazolylcarbamates **XXIX** and **XXX** were brought into reaction with aliphatic amines (hexylamine, 6-aminohexanol, 2-aminoethoxyethanol, *N*′,*N*′-dimethylpropane-1,3-diamine). Considering higher solubility of carbamate **XXX** in chloroform than in benzene, the reaction with amines was performed in boiling chloroform, and the excess of amine was used

Scheme 3.



VII, **VIII** **XXIX**, **XXX** **XXXI–XXXV**

X = Cl (**VII**, **XXIX**, **XXXI**), BnS (**VIII**, **XXX**, **XXXII**–**XXXV**); R = H (**XXIX**), F (**XXX**); R' = hexyl (**XXXI**, **XXXII**), 6-hydroxyhexyl (**XXXIII**), 2-(2-hydroxyethoxy)ethyl (**XXXIV**), 3-(dimethylamino)propyl (**XXXV**).

to compensate its binding in salt with liberating *p*-fluorphenol, possessing higher acidity compared to phenol. In the optimal conditions the reaction was complete within 1 h (Scheme 3).

As a result functionalized carbamides with different end groups were obtained, including the polar ones important for biotesting, since the latter increased the solubility of compounds in water.

The composition and structure of the obtained substances were determined basing on the elemental analysis data, IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

The presence of the N_3 fragment in molecules of azides **V** and **VIII** is confirmed by the strong characteristic absorption bands in the IR spectrum of these compounds in the region 2146–2214 cm^{-1}. In the mass spectra of azides **V** and **VIII** ion peaks $[M - N_2]^+$ possess the maximal intensity, no peaks of molecular ions are detected.

In IR spectrum of isothiazolylhydrazide **XIII** NH_2 and NH groups appear as broadened absorption bands in the interval 3202–3337 cm^{-1}, and in ^{1}H NMR spectrum they give rise to broadened singlets, δ 3.59 (NH_2) and 9.87 (NH) ppm.

Generation of carbamates **XXI**, **XXIX**, and **XXX** from the corresponding azides is confirmed by the absence of the absorption bands of the azide group in the region 2146–2214 cm^{-1} in their IR spectra and the appearance of stretching vibration bands of N−H in the interval 3198–3467 cm^{-1}. In ^{1}H NMR spectra of carbamates **XXI**, **XXIX**, and **XXX** the singlets at δ 7.60–9.21 ppm correspond to the NH groups.

In ^{1}H NMR spectra of 1,2-azolylureas **XVI–XVIII**, **XXIII–XXVI**, and **XXXI–XXXV** the groups of NH carbamide fragment appear as two singlets in the interval 6.51–9.88 ppm. In ^{1}H NMR spectra of isoxazolylureas **XIX**, **XX**, and **XXVI–XXVIII**, derivatives of heterocyclic amines, a singlet at δ 9.37–9.86 ppm corresponds to NH group of carbamide fragment.The C=O group of the carbamide residue in IR spectra of 1,2-azolylurea is characterized by a pair of strong absorption bands in the area 1547–1739 cm^{-1}. ^{13}C NMR spectra confirm the number of carbon atoms in the molecules of all synthesized compounds.

By the example of 1-[5-(benzylsulfanyl)-4-chloroisothiazol-3-yl]-3-hexylurea (**XXXII**) we carried out the computer simulation of the possibility of embedding this compound into the sites of cyclin-dependent protein kinase 2 (Cdk2) and tyrosine kinase VEGFR-2, for the conjugation with them regulates the cytostatic effect of the drugs. For optimization of the protein geometry the force field AMBER [15] was applied, charges of aminoacids were obtained from AMBER ff99SB and AM1-BCC [16]. The optimization of the ligand **XXXII** geometry was fulfilled within the framework of the method of molecular mechanics with application of the force field MMFF94 [17]. The distribution of charges for the optimized structure was obtained by the DFT method, theoretic level B3LYP1/6-311++G. The ligand was prepared using the program Avogadro [18], docking results were visualized within the program UCSF Chimera [19]. Calculations ab initio were made in the program package Firefly [20], partly basing on GAMESS (US) [21]. As graphic covering for preparing the input files program Gabedit [22] was applied. Docking was carried out in program complex UCSF Dock 6.4 [23].

In the course of the docking it was determined that the molecule of 1-[5-(benzylsulfanyl)-4-chlorothiazol-3-yl]-3-hexylurea (**XXXII**) is able to be embedded in kinase sites, while the amino groups of the carbamide fragment form bonds with the oxygen atoms of the aminoacid parts of kinase that facilitates stronger conjugation of the isothiazole agent and the kinase molecule.

The docking data fully correlated with the results of biotesting, carried out in the Institute of Physiology of National Academy of Sciences of Belarus. The research on isoxazole and isothiazole derivatives was carried out on various species of neuroepithelial primar tumors (medulloblastoma, glioblastoma). It was determined that the specimens of the synthesized compounds and their precursors (1,2-azolylcarbamates) demonstrate antitumor activity and, which is the most important point, can intensify the effect of practically applied protocol cytostatics: cisplatine, carboplatine, and citarabine. For the structure cytostatic–azolylureaderivative 1 : 1, at 10 grade dilution (in some cases at even higher) the efficiency of antitumor effect remains at the level of protocolly recommended doze of the individual drug. Hence a new way opens to reduction of the side effects and toxicity of chemical drugs at developing similar compositions.

EXPERIMENTAL

IR spectra were registered on Fourier-spectrophotometer Protege-460 Nicolet in tablets of KBr. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer Bruker Avance-500 in $CDCl_3$ (**V**, **VIII**, **XIV**, **XIX**, **XXI**, **XXIII**, **XXVI**, and **XXIX–XXXII**), in $(CD_3)_2CO$ (**XXV**), in $(CD_3)_2SO$ (**IV**, **XIII**, **XVI–XVIII**, **XX**, **XXIV**, **XXVII**, **XXVIII**, and **XXXIII–XXXV**). Chemical shifts were measured with respect to the residual proton and to carbon signals of deuterated solvents [$CDCl_3$, δ_H 7.26, δ_C 77.2 ppm; $(CD_3)_2CO$, δ_H 2.05, δ_C 30.2 ppm; $(CD_3)_2SO$, δ_H 2.50, δ_C 40.1 ppm]. Mass-spectra were obtained on aGC-MS instrument Hewlett Packard 5890/5972 (electron impact with electron energy 70 eV; capillary column HP-5MS 30 m × 0.25 mm, phase (5% PhMe Silicone) 0.25 μm, evaporator temperature 250°C).

5-benzylsulfanyl-4-chloroisothiazol-3-carboxylic acid chloride (**XII**) was obtained by the method [11].

5-Benzylsulfanyl-4-chlorothiazole-3-carboxylic acid (IV). In 50 mL of anhydrous methanol was dissolved 0.57 g (25 mmol) of metallic sodium, 5.85 g (47 mmol) of benzylthiol was added, the mixture was stirred for 15 min and a solution of 5 g (23 mmol) of methyl 4,5-dichlorothiazole-3-carboxylate (**XV**) in 30 mL anhydrous methanol was added. The reaction mixture was boiled for 2 h, solution of 5 g of KOH in 10 mL of water was added and the boiling was continued for 5 min more, then the solution was cooled to room temperature and 15 mL of concentrated HCl was added. The precipitate was filtered off, washed with water, hexane, and recrystallized from chloroform. Yield 6.38 g (95%). Physicochemical constants and IR and NMR spectra were consistent with the published data [11].

5-Phenylisoxazole-3-carbonyl azide (V). To solution of 8.62 g (41.52 mmol) of chloride of 5-phenylisoxazole-3-carboxylic acid (**IX**) in 40 mL of anhydrous acetone was added 3 g of sodium azide and the mixture was stirred for 3 h at 20°C, then it was poured into water, the precipitate was filtered off, washed with water, and dried in a vacuum over P_2O_5. Yield 8.45 g (95%), mp 105–106°C (decomp.). IR spectrum, cm^{-1}: 3147, 3129, 3062, 2214, 2165, 1693, 1612, 1592, 1573, 1497, 1438, 1229, 1172, 962, 946, 941, 856, 825, 762, 684, 673. ^{1}H NMR spectrum, δ, ppm: 6.94 s ($1H_{isoxazole}$), 7.48 m ($3H_{Ar}$), 7.79 m ($2H_{Ar}$). ^{13}C NMR spectrum, δ, ppm: 99.61 ($CH_{isoxazole}$), 126.10 ($2CH_{Ar}$), 129.32 ($2CH_{Ar}$), 131.19 (CH_{Ar}), 126.43, 157.45, 165.90 ($3C_{quat.}$), 172.57 (C=O). Found, %: C 56.18; H 3.04; N 26.15. $[M - N_2]^+$ 186 (I_{rel} 100%). $C_{10}H_6N_4O_2$. Calculated, %: C 56.08; H 2.82; N 26.16. *M* 214.18.

Methyl 5-(benzylsulfanyl)-4-chlorothiazole-3-carboxylate (XIV). In 50 mL of anhydrous methanol was dissolved 0.57 g (25 mmol) of metallic sodium, 5.85 g (47 mmol) of benzylthiol was added, the mixture was stirred for 15 min and a solution of 5 g (23 mmol) of methyl 4,5-dichlorothiazole-3-carboxylate (**XV**) in 30 mL of anhydrous methanol was added. The reaction mixture was boiled for 2 h, cooled to room temperature, and poured on ice. The solid reaction product was filtered off, washed with water, hexane, and dried in a vacuum. Yield 6.68 g (97%), mp 103–103.5°C. IR spectrum, cm^{-1}: 2951, 1724, 1439, 1345, 1230, 1200, 1083, 735, 717, 708. ^{1}H NMR spectrum, δ, ppm: 3.93 s (3H, CH_3), 4.19 s (2H, CH_2S), 7.29 m ($5H_{Ar}$). ^{13}C NMR spectrum, δ, ppm: 52.93 (OCH_3), 39.30 (CH_2S), 128.37 (CH_{Ar}), 128.99 ($2CH_{Ar}$), 129.04 ($2CH_{Ar}$), 125.34, 135.00, 154.10, 158.41 ($4C_{quat}$), 160.07 (C=O). Found, %: C 48.14; H 3.28; Cl 11.88; N 4.65; S 21.46. $[M]^+$ 299 (I_{rel} 100%). $C_{12}H_{10}ClNO_2S_2$. Calculated, %: C 48.08; H 3.36; Cl 11.83; N 4.67; S 21.39. *M* 299.80.

5-(Benzylsulfanyl)-4-chlorothiazole-3-carbonyl azide (VIII). To cooled to 0°C solution of 1 g (3.3 mmol) of acid chloride **XII** in 30 mL of acetone was added dropwise while stirring the solution of 0.23 g of sodium azide in 5 mL of water, then the mixture

was stirred at this temperature for 30 min and poured on ice. Solid reaction product was filtered off, washed with water, and dried in a vacuum above P_2O_5. Yield 0.98 g (82%), mp 36–38°C. IR spectrum, cm^{-1}: 3086, 3064, 3031, 3007, 2923, 2854, 2146, 1683, 1494, 1453, 1405, 1344, 1244, 1190, 1031, 946, 869, 744, 707, 695. ^1H NMR spectrum, δ, ppm: 4.21 s (2H, CH_2S), 7.31 m ($5H_{Ar}$).^{13}C NMR spectrum, δ, ppm: 39.33 (CH_2S), 128.50 (CH_{Ar}), 129.07 ($4CH_{Ar}$), 125.64, 134.87, 153.69, 159.45 ($4C_{quat}$), 165.50 (C=O). Found, %: C 42.42; H 2.33; Cl 11.35; N 18.12; S 20.57. $[M - N_2]^+$ 310 (I_{rel} 100%). $C_{11}H_7ClN_4OS_2$. Calculated, %: C 42.51; H 2.27; Cl 11.41; N 18.03; S 20.64. *M* 310.78.

5-(Benzylsulfanyl)-4-chlorothiazole-3-carbonyl hydrazide (XIII). To 1 g (3.3 mmol) of methyl 5-benzylsulfanyl-4-chlorothiazole-3-carboxylate (**XIV**) in 10 mL of methanol was added 0.165 mL of (3.3 mmol) of hydrazine hydrate, and the mixture was stirred at room temperature for 30 min. The formed precipitate was filtered off, washed with methanol, and dried in a vacuum over P_2O_5. Yield 0.94 g (95%), mp 135–137°C. IR spectrum, cm^{-1}: 3337, 3275, 3202, 3031, 2922, 2853, 1657, 1634, 1515, 1495, 1464, 1454, 1353, 1340, 1274, 1248, 1144, 1083, 874, 698, 653. ^1H NMR spectrum, δ, ppm: 3.59 br.s (2H, NH_2), 4.44 s (2H, CH_2S), 7.30 t ($1H_{Ar}$, ^3J 7.1 Hz), 7.35 t ($2H_{Ar}$, ^3J 7.1 Hz), 7.43 d ($2H_{Ar}$, ^3J 7.1 Hz), 9.87 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 38.44 (CH_2S), 128.60 (CH_{Ar}), 129.34 ($2CH_{Ar}$), 129.72 ($2CH_{Ar}$), 120.66, 136.35, 158.28, 158.92 ($4C_{quat}$), 160.16 (C=O). Found, %: C 43.90; H 3.51; Cl 11.80; N 14.05; S 21.44. $C_{11}H_{10}ClN_3OS_2$. Calculated, %: C 44.07; H 3.36; Cl 11.83; N 14.02; S 21.39.

Isoxazolylureas XVI–XX. General method. A solution of 20 mmol of amine and 20 mmol of the corresponding azide **V** and **VI** in 50 mL of anhydrous benzene was boiled for 4–10 h. The obtained precipitate was filtered off, washed with benzene, and dried in a vacuum.

1-(4-Bromophenyl)-3-(5-phenylisoxazol-3-yl)urea (XVI). Yield 78%, mp 238–239°C. IR spectrum, cm^{-1}: 3358, 3276, 3150, 3089, 3036, 2976, 2924, 2853, 1704, 1634, 1610, 1585, 1558, 1534, 1497, 1485, 1425, 1310, 1220, 1070, 764, 685, 500. ^1H NMR spectrum, δ, ppm: 7.27 s (1H, $CH_{isoxazol}$), 7.51 m ($7H_{Ar}$), 7.87 m ($2H_{Ar}$), 8.99 s (1H, NH), 9.71 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 93.76 ($CH_{isoxazol}$), 120.45 ($2CH_{Ar}$), 125.38 ($2CH_{Ar}$), 129.14 ($2CH_{Ar}$), 130.39 (CH_{Ar}), 131.54 ($2CH_{Ar}$), 113.99, 126.82, 138.26, 151.17, 159.06 ($5C_{quat}$), 168.42 (S=O). Found, %: C 61.83; H 5.79; Br 22.42; N 15.34. $C_{16}H_{12}BrN_3O_2$. Calculated, %: C 61.53; H 5.53; Br 22.31; N 15.38.

4-[3-(5-Phenylisoxazol-3-yl)ureido]benzoic acid (XVII). Yield 91%, mp 237–240°C (decomp.). IR spectrum, cm^{-1}: 3334, 3280, 3253, 3118, 3089, 3029, 2907, 2669, 2549, 1685, 1623, 1597, 1577, 1540, 1520, 1450, 1430, 1416, 1379, 1317, 1290, 1260, 1180, 946, 858, 763, 690. ^1H NMR spectrum, δ, ppm: 7.35 s (1H, $CH_{isoxazol}$), 7.52 d ($2H_{Ar}$, ^3J 6.8 Hz), 7.60 d ($2H_{Ar}$, ^3J 8.5 Hz), 7.88 d ($2H_{Ar}$, ^3J 6.8 Hz), 7.91 d ($2H_{Ar}$, ^3J 8.5 Hz), 7.97 m ($1H_{Ar}$), 9.22 s (1H, NH), 9.79 s (1H, NH), 12.75 br.s (1H, COOH). ^{13}C NMR spectrum, δ, ppm: 99.84 ($CH_{isoxazole}$), 117.61 ($2CH_{Ar}$), 125.46 ($2CH_{Ar}$), 129.21 ($2CH_{Ar}$), 130.29 (CH_{Ar}), 130.58 ($2CH_{Ar}$), 124.38, 126.87, 143.15, 151.13, 159.05 ($5C_{quat}$), 166.95 (S=O), 168.57 (S=O). Found, %: C 63.38; H 3.89; N 13.08. $C_{17}H_{13}N_3O_4$. Calculated, %: C 63.16; H 4.05; N 13.00.

Ethyl 4-[3-(5-phenylisoxazol-3-yl)ureido]-benzoate (XVIII). Yield 84%, mp 208–211°C. IR spectrum, cm^{-1}: 3370, 3321, 3300, 3274, 3132, 3068, 3034, 2996, 2959, 2857, 1734, 1679, 1627, 1595, 1580, 1562, 1536, 1495, 1481, 1421, 1372, 1309, 1291, 1200, 1177, 1139, 850, 769, 690, 666. ^1H NMR spectrum, δ, ppm: 1.30 t (3H, CH_3, ^3J 7 Hz), 4.27 q (2H, CH_2, ^3J 7 Hz), 7.31 s (1H, $CH_{isoxazol}$), 7.51 m ($3H_{Ar}$), 7.62 d ($2H_{Ar}$, ^3J 8.5 Hz), 7.87 d ($2H_{Ar}$, ^3J 6.5 Hz), 7.92 d ($2H_{Ar}$, ^3J 8.5 Hz), 9.24 s (1H, NH), 9.79 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.15 (CH_3), 60.31 (CH_2), 93.79 ($CH_{isoxazole}$), 117.62 ($2CH_{Ar}$), 125.42 ($2CH_{Ar}$), 128.25 (CH_{Ar}), 129.15 ($2CH_{Ar}$), 130.35 ($2CH_{Ar}$), 123.44, 126.86, 143.43, 151.05, 159.00 ($5C_{quat}$), 165.29 (S=O), 168.54 (S=O). Found, %: C 65.21; H 4.55; N 11.89. $C_{19}H_{17}N_3O_4$. Calculated, %: C 64.95; H 4.88; N 11.96.

3,5-Dimethyl-*N*-(5-phenylisoxazol-3-yl)-1*H*-pyrazole-1-carboxamide (XIX). Yield 63%, mp 155–158°C (decomp.). IR spectrum, cm^{-1}: 3363, 3178, 3059, 3046, 2996, 2927, 2853, 1739, 1621, 1595, 1577, 1541, 1494, 1442, 1426, 1339, 1249, 1092, 1029, 967, 947, 884, 803, 792, 765, 737, 686, 606. ^1H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 2.59 s (3H, CH_3), 5.97 c (1H, $CH_{pyrazole}$), 7.23 s (1H, $CH_{isoxazole}$), 7.45 m ($3H_{Ar}$), 7.79 d ($2H_{Ar}$, ^3J 7.8 Hz), 9.86 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 13.59 (CH_3), 13.89 (CH_3), 93.21 ($CH_{isoxazole}$), 110.99 ($CH_{pyrazole}$), 125.69 ($2CH_{Ar}$), 128.95 ($2CH_{Ar}$), 130.35 (CH_{Ar}), 127.36, 143.95, 148.01, 151.37, 157.78 ($5C_{quat}$), 170.21 (S=O).

Found, %: C 63.66; H 5.23; N 19.79. $C_{15}H_{14}N_4O_2$. Calculated, %: C 63.82; H 5.00; N 19.85.

***N*-[5-(4-Methylphenyl)isoxazol-3-yl]-1*H*-benzo-[*d*][1,2,3]triazole-1-carboxamide (XX)**. Yield 85%, mp 226–227°C (decomp.). IR spectrum, cm^{-1}: 3185, 3147, 3079, 3057, 3034, 2920, 2853, 1733, 1618, 1607, 1592, 1571, 1548, 1501, 1477, 1449, 1433, 1363, 1058, 1041, 1011, 923, 831, 791, 752, 745, 707. ^1H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 7.22 s (1H, $CH_{isoxazole}$), 7.32 d (2H_{Ar}, ^3J 7.6 Hz), 7.43 m (2H_{Ar}), 7.75 d (2H_{Ar}, ^3J 7.6 Hz), 7.91 m (2H_{Ar}), 9.79 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.96 (CH_3), 93.05 ($CH_{isoxazole}$), 125.14 (2CH_{Ar}), 125.40 (2CH_{Ar}), 129.50 (2CH_{Ar}), 129.74 (2CH_{Ar}), 124.16, 139.52, 140.43, 150.40, 158.72, 164.51 (6C_{quat}), 169.95 (S=O). Found, %: C 64.12; H 4.22; N 21.79. $C_{17}H_{13}N_5O_2$. Calculated, %: C 63.94; H 4.10; N 21.93.

Phenyl (1,2-azol-3-yl)carbamates (XXI and XXIX). General method. The solution of 20 mmol of phenol and 20 mmol of azide **V** and **VII** in 70 mL of anhydrous benzene was boiled for 4 h. Then the solvent was removed at a reduced pressure, solid precipitate was washed with 5% solution of sodium hydrogen carbonate, with water, dried in a vacuum, and crystallized from 70% methanol.

Phenyl (5-phenylisoxazol-3-yl)carbamate (XXI). Yield 79%, mp 176–178°C (decomp.). IR spectrum, cm^{-1}: 3264, 3218, 3087, 3033, 2966, 2867, 2799, 1748, 1636, 1596, 1582, 1558, 1485, 1429, 1267, 1240, 1209, 1165, 1070, 985, 793, 762, 727, 685. ^1H NMR spectrum, δ, ppm: 7.16 s (1$H_{isoxazole}$), 7.25 m (3H_{Ar}), 7.43 m (5H_{Ar}), 7.76 m (2H_{Ar}), 9.21 b.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 93.27 ($CH_{isoxazole}$), 121.56 (2CH_{Ar}), 125.80 (2CH_{Ar}), 126.07 (CH_{Ar}), 128.99 (2CH_{Ar}), 129.50 (2CH_{Ar}), 130.50 (CH_{Ar}), 127.21, 150.43, 151.55, 158.81 (5C_{quat}), 170.31 (C=O). Found, %: C 68.89; H 4.67; N 9.85. $C_{16}H_{12}N_2O_3$. Calculated, %: C 68.56; H 4.32; N 9.99.

Phenyl (4,5-dichlorothiazol-3-yl)carbamate (XXIX). Yield 80%, mp 125–127°C. IR spectrum, cm^{-1}: 3198, 3080, 3044, 3032, 2979, 2924, 1746, 1717, 1553, 1520, 1494, 1483, 1456, 1433, 1293, 1233, 1198, 1167, 1124, 1074, 1032, 995, 896, 780, 7561, 740, 687, 647, 519, 501. ^1H NMR spectrum, δ, ppm: 7.22 m (3H_{Ar}), 7.38 m (2H_{Ar}), 7.66 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 121.46 (2CH_{Ar}), 126.24 (CH_{Ar}), 129.62 (2CH_{Ar}), 114.11, 148.28, 149.81, 150.28 (4C_{quat}), 151.24 (S=O). Found, %: C 41.72; H 2.17; Cl 24.70; N 9.59; S 11.17. $C_{10}H_6Cl_2N_2O_2S$. Calculated, %: C 41.54; H 2.09; Cl 24.52; N 9.69; S 11.09.

4-Fluorphenyl (5-benzylsulfanyl-4-chloroisothiazol-3-yl)carbamate (XXX) was obtained in the similar way as carbamates **XXI** and **XXIX** from 4-fluorphenol and azide **VIII**, but the reaction mixture was boiled for 30 min. Yield 98%, mp 133–137°C. IR spectrum, cm^{-1}: 3467, 3417, 3263, 3061, 3032, 2924, 1736, 1597, 1536, 1496, 1455, 1435, 1402, 1227, 1189, 1152, 1113, 1026, 1003, 892, 851, 826, 770, 709, 696, 633, 513, 486. ^1H NMR spectrum, δ, ppm: 4.19 s (2H, CH_2S), 7.06 t (2H_{Ar}, ^3J 8.5 Hz), 7.17 m (2H_{Ar}), 7.31 m (5H_{Ar}), 7.60 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 39.24 (CH_2S), 116.11 (CH_{Ar}), 116.29 (CH_{Ar}), 122.94 (CH_{Ar}), 123.01 (CH_{Ar}), 128.37 (CH_{Ar}), 129.00 (2CH_{Ar}), 129.12 (2CH_{Ar}), 135.17, 146.18, 149.96, 151.43, 155.64, 159.41 (6C_{quat}), 161.36 (C=O). Found, %: C 51.92; H 3.28; Cl 8.77; N 7.12; S 16.38. $C_{17}H_{12}ClFN_2O_2S_2$. Calculated, %: C 51.71; H 3.06; Cl 8.98; N 7.09; S 16.24.

(1,2-Azol-3-yl)ureas XXIII–XXVIII and XXXI. General method. The solution of 20 mmol of amine and 20 mmol of phenyl (1,2-azol-3-yl)carbamate **XXI**, **XXII**, and **XXIX** in 50 mL of benzene was boiled for 7 h. The precipitate of the obtained carbamide was filtered off, washed with benzene, and dried in a vacuum.

1-Hexyl-3-(5-phenylisoxazol-3-yl)urea (XXIII). Yield 74%, mp 92–95°C. IR spectrum, cm^{-1}: 3324, 3257, 3137, 3068, 3015, 2955, 2925, 2855, 1682, 1623, 1598, 1578, 1517, 1500, 1469, 1450, 1375, 1315, 1265, 1233, 1204, 1068, 945, 761, 685. ^1H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, ^3J 7.1 Hz), 1.32 m (4H, 2CH_2), 1.40 quintet (2H, CH_2, ^3J 7.1 Hz), 1.61 quintet (2H, CH_2, ^3J 7.1 Hz), 3.37 q (2H, CH_2, ^3J 6.6 Hz), 6.57 s (1H, $CH_{isoxazole}$), 7.23 b.s (1H, NH), 7.43 m (3H_{Ar}), 7.74 m (2H_{Ar}), 9.88 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.16 (CH_3), 22.70 (CH_2), 22.75 (CH_2), 29.96 (CH_2), 31.65 (CH_2), 40.61 (CH_2N), 92.94 ($CH_{isoxazole}$), 125.92 (2CH_{Ar}), 129.06 (2CH_{Ar}), 130.55 (CH_{Ar}), 127.23, 155.63, 159.77 (3C_{quat}), 169.10 (S=O). Found, %: S 67.03; H 7.09; N 14.44. $C_{16}H_{21}N_3O_2$. Calculated, %: S 66.88; H 7.37; N 14.62.

1-(6-Hydroxyhexyl)-3-(5-phenylisoxazol-3-yl)urea (XXIV). Yield 89%, mp 126–128°C. IR spectrum, cm^{-1}: 3438, 3325, 3240, 3133, 3066, 3014, 2939, 2878, 2858, 1683, 1622, 1597, 1576, 1540, 1516, 1478, 1449, 1373, 1317, 1303, 1261, 1205, 1066, 945, 766, 689. ^1H NMR spectrum, δ, ppm: 1.28 m (4H, 2CH_2), 1.43 m (4H, 2CH_2), 3.12 m (2H, CH_2), 3.38 m (2H,

CH_2), 4.36 br.s (1H, OH), 6.51 br.s (1H, NH), 7.13 s (1H, $CH_{isoxazole}$), 7.50 m ($3H_{Ar}$), 7.83 m ($2H_{Ar}$), 9.42 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 25.85 (CH_2), 26.85 (CH_2), 30.23 (CH_2), 33.10 (CH_2), 39.83 (CH_2N), 61.27 (CH_2O), 94.26 ($CH_{isoxazole}$), 126.02 ($2CH_{Ar}$), 129.79 ($2CH_{Ar}$), 130.95 (CH_{Ar}), 127.61, 154.36, 160.34 ($3C_{quat}$), 168.58 (S=O). Found, %: S 63.47; H 7.05; N 13.79. $C_{16}H_{21}N_3O_3$. Calculated, %: S 63.35; H 6.98; N 13.85.

1-Benzyl-3-(5-phenylisoxazol-3-yl)urea (XXV). Yield 82%, mp 187–189°C. IR spectrum, cm^{-1}: 3284, 3226, 3178, 3088, 3065, 3034, 2920, 2852, 1686, 1659, 1630, 1604, 1585, 1566, 1514, 1496, 1453, 1280, 1259, 1051, 1027, 762, 749, 698, 688. ^1H NMR spectrum, δ, ppm: 4.50 d (2H, CH_2, ^3J 5.8 Hz), 7.06 s (1H, $CH_{isoxazole}$), 7.26 t (1H, NH, ^3J 7.2 Hz), 7.34 t ($3H_{Ar}$, ^3J 7.4 Hz), 7.38 d ($2H_{Ar}$, ^3J 7.4 Hz), 7.52 m ($3H_{Ar}$), 7.86 d.d ($2H_{Ar}$, ^3J 7.4 Hz), 8.87 b.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 45.36 (CH_2), 95.16 ($CH_{isoxazole}$), 127.39 ($2CH_{Ar}$), 128.82 (CH_{Ar}), 129.21 ($2CH_{Ar}$), 130.27 ($2CH_{Ar}$), 130.97 ($2CH_{Ar}$), 132.16 (CH_{Ar}), 129.42, 141.78, 155.73, 161.84 ($4C_{quat}$), 170.56 (S=O). Found, %: S 69.79; H 5.02; N 14.35. $C_{17}H_{15}N_3O_2$. Calculated, %: S 69.61; H 5.15; N 14.33.

***N*-(5-Phenylisoxazol-3-yl)piperazine-1-carboxamide (XXVI)**. Yield 78%, mp 238–241°C (decomp.). IR spectrum, cm^{-1}: 3257, 3192, 3091, 3000, 2923, 2865, 1673, 1626, 1598, 1579, 1549, 1500, 1471, 1426, 1382, 1264, 1234, 995, 947, 875, 765, 686, 642. ^1H NMR spectrum, δ, ppm: 3.00 t (4H, CH_2NCH_2, ^3J 5 Hz), 3.66 t (4H, CH_2NHCH_2, ^3J 5 Hz), 4.40 b.s (1H, NH), 7.36 s (1H, $CH_{isoxazole}$), 7.43 m ($3H_{Ar}$), 7.71 m ($2H_{Ar}$), 9.37 b.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 45.07 ($2CH_2N$), 45.71 ($2CH_2NH$), 94.73 ($CH_{isoxazole}$), 125.61 ($2CH_{Ar}$), 129.05 ($2CH_{Ar}$), 130.39 (CH_{Ar}), 127.35, 153.89, 160.71 ($3C_{quat}$), 169.26 (S=O). Found, %: S 61.98; H 5.85; N 20.51. $C_{14}H_{16}N_4O_2$. Calculated, %: S 61.75; H 5.92; N 20.58.

***N*-(5-Phenylisoxazol-3-yl)morpholine-4-carboxamide (XXVII)**. Yield 64%, mp 225–227°C. IR spectrum, cm^{-1}: 3257, 3217, 3201, 3176, 3095, 3068, 3040, 2976, 2958, 2922, 2866, 1682, 1628, 1601, 1581, 1553, 1501, 1431, 1279, 1267, 1251, 1120, 988, 875, 763, 683, 576. ^1H NMR spectrum, δ, ppm: 3.47 t (4H, CH_2NCH_2, ^3J 4.3 Hz), 3.60 t (4H, CH_2OCH_2, ^3J 4.3 Hz), 7.21 s (1H, $CH_{isoxazole}$), 7.51 m ($3H_{Ar}$), 7.85 d ($2H_{Ar}$, ^3J 6.6 Hz), 9.84 s (1H, NH). Spectrum NMR ^{13}C, δ, ppm: 44.10 ($2CH_2N$), 65.85 ($2CH_2O$), 95.00 ($CH_{isoxazole}$), 125.28 ($2CH_{Ar}$), 129.13 ($2CH_{Ar}$), 130.22 (CH_{Ar}), 127.00, 153.73, 160.48 ($3C_{quat}$), 167.73 (S=O). Found, %: S 61.70; H 5.41; N 15.35. $C_{14}H_{15}N_3O_3$. Calculated, %: S 61.53; H 5.53; N 15.38.

***N*-[5-(4-Methylphenyl)isoxazol-3-yl]morpholine-4-carboxamide (XXVIII)**. Yield 61%, mp 242–245°C. IR spectrum, cm^{-1}: 3251, 3212, 3157, 3096, 3070, 3039, 2956, 2926, 2860, 1676, 1625, 1616, 1573, 1556, 1509, 1428, 1366, 1305, 1267, 1247, 1218, 1185, 1117, 990, 945, 878, 807, 569. ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 3.47 t (4H, CH_2NCH_2, ^3J 4.4 Hz), 3.59 t (4H, CH_2OCH_2, ^3J 4.4 Hz), 7.14 s (1H, $CH_{isoxazole}$), 7.31 d ($2H_{Ar}$, ^3J 8 Hz), 7.72 d ($2H_{Ar}$, ^3J 8 Hz), 9.81 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.58 (CH_3), 44.78 ($2CH_2N$), 66.53 ($2CH_2O$), 95.04 ($CH_{isoxazole}$), 125.90 ($2CH_{Ar}$), 130.34 ($2CH_{Ar}$), 125.05, 140.73, 154.43, 161.12 ($4C_{quat}$), 168.59 (S=O). Found, %: S 62.87; H 5.64; N 14.72. $C_{15}H_{17}N_3O_3$. Calculated, %: S 62.71; H 5.96; N 14.63.

1-(4,5-Dichlorothiazol-3-yl)-3-hexylurea (XXXI). Yield 83%, mp 64–72°C. IR spectrum, ν, cm^{-1}: 3312, 3236, 3146, 3114, 2989, 2958, 2932, 2855, 1682, 1547, 1528, 1509, 1478, 1457, 1373, 1345, 1321, 1298, 1261, 1230, 1132, 1102, 1028, 701, 681, 555. ^1H NMR spectrum, δ, ppm: 0.84 m (3H, CH_3, ^3J 6.8 Hz), 1.29 m (6H, $3CH_2$), 1.54 quintet (2H, CH_2, ^3J 7.0 Hz), 3.31 q (2H, CH_2N, ^3J 6.5 Hz), 8.04 s (1H, NH), 8.19 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.04 (CH_3), 22.59 (CH_2), 26.63 (CH_2), 29.73 (CH_2), 31.50 (CH_2), 40.36 (CH_2), 111.69, 147.04, 153.61 ($3C_{isothiazole}$), 153.91 (C=O). Found, %: S 40.37; H 5.51; Cl 24.11; N 14.22; S 10.93. $C_{10}H_{15}Cl_2N_3OS$. Calculated, %: S 40.55; H 5.10; Cl 23.94; N 14.19; S 10.82.

1-[5-(Benzylsulfanyl)-4-chlorothiazol-3-yl]ureas XXXII–XXXV. General method. The solution of 0.94 g (2.3 mmol) of 4-fluorphenyl (5-benzyl-sulfanyl-4-chlorothiazol-3-yl)carbamate (**XXX**) and 4.6 mmol of amine in 10 mL of chloroform was boiled for 1 h. The solvent was removed at a reduced pressure, the precipitate was recrystallized from chloroform and dried in a vacuum.

1-[5-(Benzylsulfanyl)-4-chlorothiazol-3-yl]-3-hexylurea (XXXII). Yield 95%, mp 44–46°C. IR spectrum, cm^{-1}: 3262, 2925, 1663, 1572, 1519, 1506, 1322, 1101, 713, 694. ^1H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, ^3J 6.8 Hz), 1.31 m (6H, $3CH_2$), 1.57 m (2H, CH_2), 3.33 q (2H, CH_2, ^3J 6.6 Hz), 4.17 s (2H, CH_2S), 7.24 s (1H, NH), 7.32 m ($5H_{Ar}$), 8.26 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.16 (CH_3), 22.69 (CH_2), 26.73 (CH_2), 29.84 (CH_2), 31.61 (CH_2), 39.21 (CH_2S), 40.43 (CH_2N), 128.39 (CH_{Ar}), 129.02 ($2CH_{Ar}$), 129.12

($2CH_{Ar}$), 110.51, 135.33, 153.62, 154.08 ($4C_{quat}$), 154.20 (C=O). Found, %: C 53.41; H 5.99; Cl 8.97; N 10.98; S 16.85. $C_{17}H_{22}ClN_3OS_2$. Calculated, %: C 53.18; H 5.78; Cl 9.23; N 10.94; S 16.70.

1-[5-(Benzylsulfanyl)-4-chlorothiazol-3-yl]-3-(5-hydroxyhexyl)urea (XXXIII). Yield 95%, mp 122–125°C. IR spectrum, cm^{-1}: 3281, 3167, 3058, 2955, 2926, 2848, 1675, 1566, 1525, 1455, 1425, 1393, 1323, 1106, 1058, 715, 697. ^1H NMR spectrum, δ, ppm: 1.27 m (4H, $2CH_2$), 1.41 q (4H, $2CH_2$, ^3J 6.5 Hz), 3.13 d (2H, CH_2, ^3J 6.0 Hz), 3.37 t (2H, CH_2N, ^3J 6.2 Hz), 4.36 br.s (3H, CH_2 + OH), 7.29 t ($1H_{Ar}$, ^3J 7.1 Hz), 7.34 t ($2H_{Ar}$, ^3J 7.1 Hz), 7.41 d ($2H_{Ar}$, ^3J 7.1 Hz), 7.68 s (1H, NH), 8.88 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 25.85 (CH_2), 26.91 (CH_2), 30.12 (CH_2), 33.12 (CH_2), 38.07 (CH_2), 39.93 (CH_2S), 61.27 (CH_2N), 128.48 (CH_{Ar}), 129.24 ($2CH_{Ar}$), 129.65 ($2CH_{Ar}$), 111.21, 136.54, 153.87, 154.89 ($4C_{quat}$), 155.25 (C=O). Found, %: C 51.20; H 5.47; Cl 8.78; N 10.58; S 16.00. $C_{17}H_{22}ClN_3O_2S_2$. Calculated, %: C 51.05; H 5.54; Cl 8.86; N 10.51; S 16.03.

1-[5-(Benzylsulfanyl)-4-chlorothiazol-3-yl]-3-[2-(2-hydroxyethoxy)ethyl]urea (XXXIV). Yield 89%, mp 99–100°C. IR spectrum, cm^{-1}: 3482, 3343, 3253, 3135, 3095, 3068, 2987, 2923, 2892, 2862, 1664, 1568, 1520, 1508, 1454, 1454, 1413, 1324, 1279, 1105, 1083, 1073, 1049, 886, 779, 720, 693, 619. ^1H NMR spectrum, δ, ppm: 3.31 q (2H, CH_2, ^3J 5.2 Hz), 3.43 t (2H, CH_2, ^3J 5.2 Hz), 3.48 m (4H, $2CH_2$), 4.37 s (2H, CH_2S), 4.60 t (1H, OH, ^3J 5.4 Hz), 7.30 t ($1H_{Ar}$, ^3J 7.3 Hz), 7.35 t ($2H_{Ar}$, ^3J 7.3 Hz), 7.42 d ($2H_{Ar}$, ^3J 7.3 Hz), 7.73 b.s (1H, NH), 9.14 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 38.07 (CH_2), 39.93 (CH_2S), 60.82 (CH_2N), 69.88 (CH_2), 72.73 (CH_2), 128.48 (CH_{Ar}), 129.25 ($2CH_{Ar}$), 129.65 ($2CH_{Ar}$), 111.38, 136.54, 153.92, 154.94 ($4C_{quat}$), 155.14 (C=O). Found, %: C 46.35; H 4.77; Cl 9.07; N 10.88; S 16.48. $C_{15}H_{18}Cl{\cdot}N_3O_3S_2$. Calculated, %: C 46.44; H 4.68; Cl 9.14; N 10.83; S 16.53.

1-[5-(Benzylsulfanyl)-4-chlorothiazol-3-yl]-3-[3-(dimethylamino)propyl]urea (XXXV). Yield 92%, mp 95–96°C. IR spectrum, cm^{-1}: 3254, 3221, 3133, 3093, 3061, 2987, 2937, 2860, 2819, 2772, 1662, 1566, 1518, 1497, 1454, 1321, 1278, 1247, 1101, 716, 694. ^1H NMR spectrum, δ, ppm: 1.56 t (2H, ^3J 6.8 Hz), 2.10 s (6H, NMe_2), 2.22 t (2H, CH_2, ^3J 6.8 Hz), 3.17 q (2H, CH_2, ^3J 6.3 Hz), 4.38 s (2H, CH_2S), 7.30 t ($1H_{Ar}$, ^3J 7.3 Hz), 7.35 t ($2H_{Ar}$, ^3J 7.3 Hz), 7.41 d ($2H_{Ar}$, ^3J 7.3 Hz), 7.79 s (1H, NH), 9.04 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 45.76 ($2CH_3$), 27.76 (CH_2), 38.05 (CH_2), 38.46 (CH_2S), 57.36 (CH_2N), 128.44 (CH_{Ar}), 129.20 ($2CH_{Ar}$), 129.62 ($2CH_{Ar}$), 111.12, 136.49, 153.87, 154.87 ($4C_{quat}$), 155.23 (C=O). Found, %: C 49.87; H 5.61; Cl 9.14; N 14.58; S 16.59. $C_{16}H_{21}ClN_4OS_2$. Calculated, %: C 49.92; H 5.50; Cl 9.21; N 14.55; S 16.66.

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