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Fluorine-Containing Heterocycles: XVII.* (Tetrafluorobrnzoyl)thioureas in the Synthesis of Fluorine-Containing Azaheterocycles

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Abstract—Proceeding from (tetrafluorobenzoyl)thioureas fluorine-containing derivatives were synthesized of 1-aryl-2-ethylthioquinazolin-4-one, [1,3]benzothiazin-4-one, and also of thiazolidine and 1*H*-1,2,4-triazole.

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(Tetrafluorobenzoyl)thioureas are convenient synthons for preparation of versatile fluorine-containing heterocycles. We formerly reported on application of (tetrafluorobenzoyl)thioureas for building up fluorine-containing [1,3]benzothiazin-4-ones [1–5], but the synthesis of derivatives of quinazolin-4-one did not succeed [6]. Yet the interest to quinazoline derivatives, also to fluorine-containing, considerably grew recently owing to the wide range of biological activity inherent to this class compounds [7–12]. For instance, in the series of 4-anilinoquinazolinone inhibitors are found of neuraminidase of smallpox virus [13] and highly selective inhibitors of EGF receptor of thyrosine kinase [7, 8], 1-phenyl-4(1*H*)quinazolinones are active with respect to the receptor cholecystocholine [14], and 5-fluoro-3-(1,3,4-thiadiazol-5-yl)quinazolin-4-ones are proved to be antiviral and antitumor agents [15]; 6-fluoro-3-(4-fluorophenyl-ethyl)-quinazolin-4-ones are promising for treating diseases originating from the disfunction of MC4-R receptor, like obesity and diabetes [16].

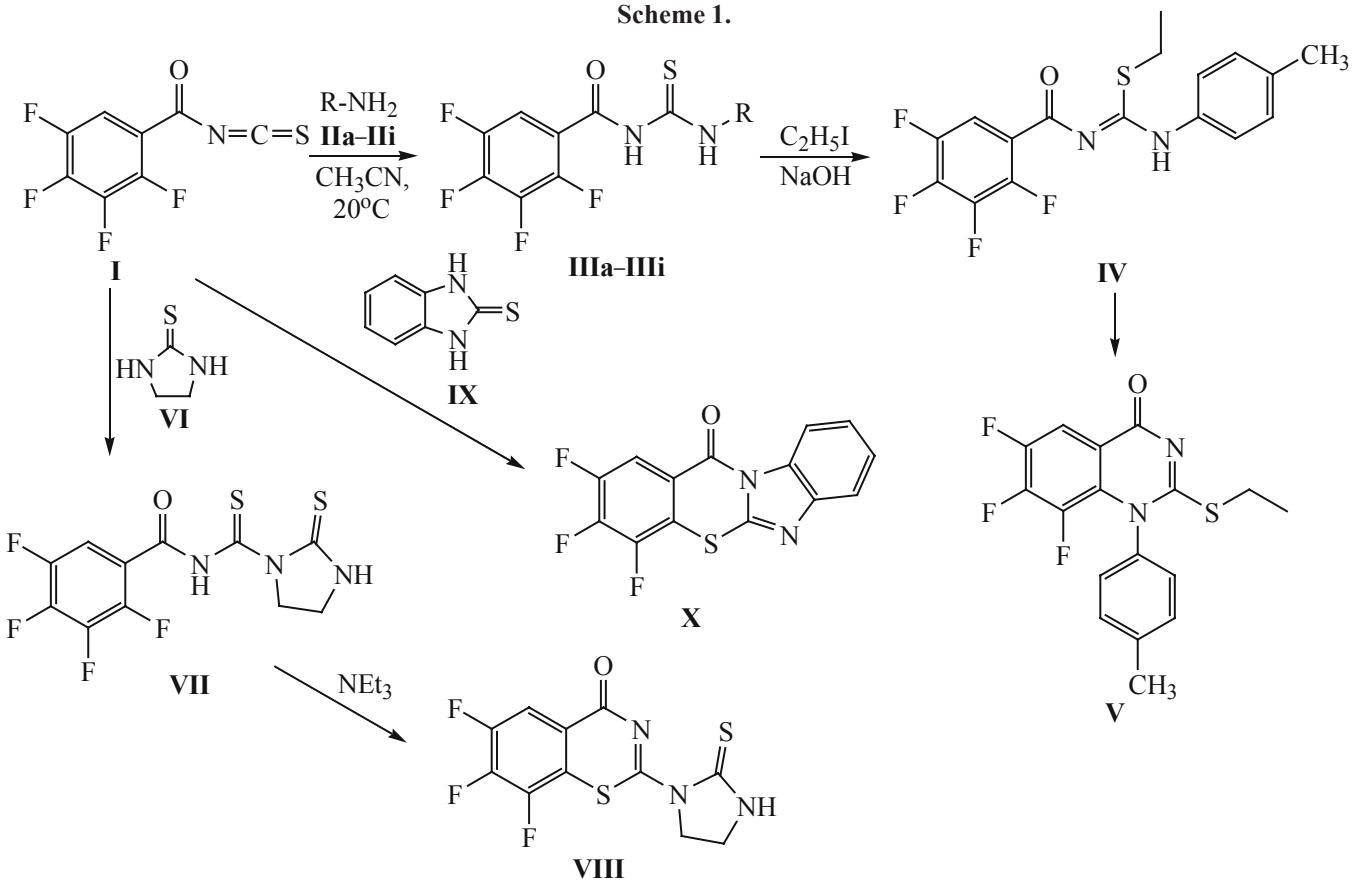
We were interested in developing conditions for alkylation of *N*-tetrafluorobenzoyl-N'-arylthioureas at the sulfur atom aiming at cyclizing the derivatives obtained into 1-aryl-2-alkylthioquinazolin-4-ones for the preparation of 1-aryl-2-mercaptoquinazolin-4-ones by intramolecular cyclization of *N*-tetrafluorobenzoyl-*N′*-arylthioureas under basic conditions proved to be difficult [6].

Initial (tetrafluorobenzoyl)thioureas **IIIa–IIIi** were obtained by the reaction of (tetrafluorobenzoyl) isothiocyanate (**I**) with aromatic or heterocyclic amines **II** in acetonitrile at room temperature (Scheme 1). Synthesis of thioureas **IIIe–IIIi** was described in [2]. We formerly prepared compounds **IIIa–IIIc** from tetrafluorobenzoyl chloride and the appropriate phenylthioureas [6], but the synthesis of (tetrafluorobenzoyl)thioureas based on (tetrafluorobenzoyl) isothiocyanate (**I**) proved to be more feasible as seen from the higher yields of target products. The structure of *N*-tetrafluorobenzoyl-*N′*-arylthioureas **IIIa**–**IIId** was confirmed by NMR spectra (see EXPERIMENTAL).

The attempt at S-alkylation of thioureas **III** and cyclocondensation of the derivative obtained into 6,7,8-trifluoroquinazolin-4-one was successful only in the case of compound **IIIb** (Scheme 1). The reaction of compound **IIIb** with ethyl iodide in ethanol in the presence of sodium hydroxide at room temperature in 2 days led to the formation S-ethyl derivative **IV** whose structure was confirmed by ^{1}H NMR spectrum, and heating of it in toluene in the presence of triethylamine for 3 h resulted in quinazolinone **V**. The reaction of compound **IIIb** with ethyl iodide in the presence of NaOH at 80^{0}C for 5 h also yielded quinazolinone **V**. The closure of the ring is confirmed by the appearance in the ^{1}H NMR spectrum of compound **V** of a characteristic d.d.d signal at 7.43 ppm. In the ^{19}F NMR spectrum of quinazolinone **V**

* For communication XVI, see [1].

Scheme 1.



R = Ph (**a**), 4-$CH_3C_6H_4$ (**b**), 2-ClC_6H_4 (**c**), 2,4-$Cl_2C_6H_3$ (**d**), 2-pyridyl (**e**), 6-methyl-2-pyridyl (**f**), pyrimidin-2-yl (**g**), 4,6-dimethylpyrimidin-2-yl (**h**), 5-methylpyrazol-3-yl (**i**).

the signals of three fluorine atoms are observed as d.d.d. Mass spectrum of compound **V** contains a peak of molecular ion (*m/z* 350) of low intensity (8%), and also fragment peaks resulting from elimination from the molecular ions of CO (*m/z* 322), SEt (*m/z* 289), and EtSCN (*m/z* 263).

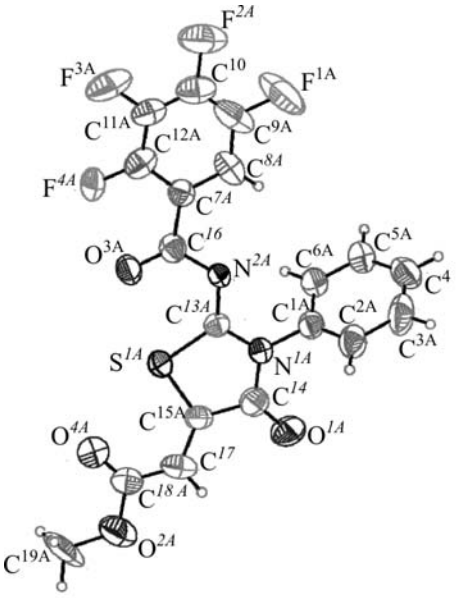
In order to obtain new fluorine-containing derivatives of [1,3]benzothiazin-4-one we investigated the reaction between tetrafluorobenzoyl isothiocyanate (**I**) with azolylthiones. The mixing of solutions of imidazolidinethione **VI** and isothiocyanate **I** initiated an addition reaction resulting in benzamide **VII** (Scheme 1) (see EXPERIMENTAL). The cyclization of compound **VII** into [1,3]benzothiazin-4-one **VIII** occurred at boiling in toluene in the presence of triethylamine for 2.5 h. The structure of [1,3]benzothiazin-4-one **VIII** was confirmed by ^{1}H NMR and mass spectra. Thus in the ^{1}H NMR spectrum of compound VIII the signals of the protons of imidazolidine fragment were conserved, one signal of NH group disappeared, and the multiplicity of H^5 signal simplified to d.d.d in the region δ 7.62 ppm. The most abundant peak in the mass spectrum of benzothiazinone **VIII** *m/z* 258 corresponds to the fragment ion $[M - HSCN]^+$, and peak *m/z* 190 (63%) is consistent with the data on fragmentation of 6,7,8-trifluoro-2-R-[1,3]benzothiazin-4-ones [2].

The reaction of tetrafluorobenzoyl isothiocyanate (**I**) with benzimidazole-2-thione **IX** in boiling acetone takes another route leading to benzimidazo[2,1-*b*]benzothiazinone **X** that proved to be identical to the compound obtained from tetrafluorobenzoyl chloride and thione **IX** [17]. At keeping the dispersion of compounds **IX** and **I** the yield of compound **X** is significantly lower due to the low solubility of thione **IX**. Evidently the derivatives of benzimidazole-2-thione do not react with the N=C bond of isothiocyanate **I** but substitute the N=C=S moiety. The replacement of the fragment N=C=S of tetrafluorobenzoyl isothiocyanate by the residue of 2-aminothiazole was reported in [2].

We also studied reactions of (tetrafluorobenzoyl)thioureas **III** proceeding without involvement of the fluorine atom in the *ortho*-position to the benzoyl group.

Actually, the reaction of thioureas **IIIa, IIIb, IIIe–IIIi** with dimethyl acetylenedicarboxylate (**XI**) is a convenient procedure for preparation of new fluorine-containing heterocycles (Scheme 2). The treatment of methanol solutions of thioureas **III** with ester **XI** at room temperature for 12 h led to cyclocondensation providing thiazolidinones **XII** in 73–82% yield.

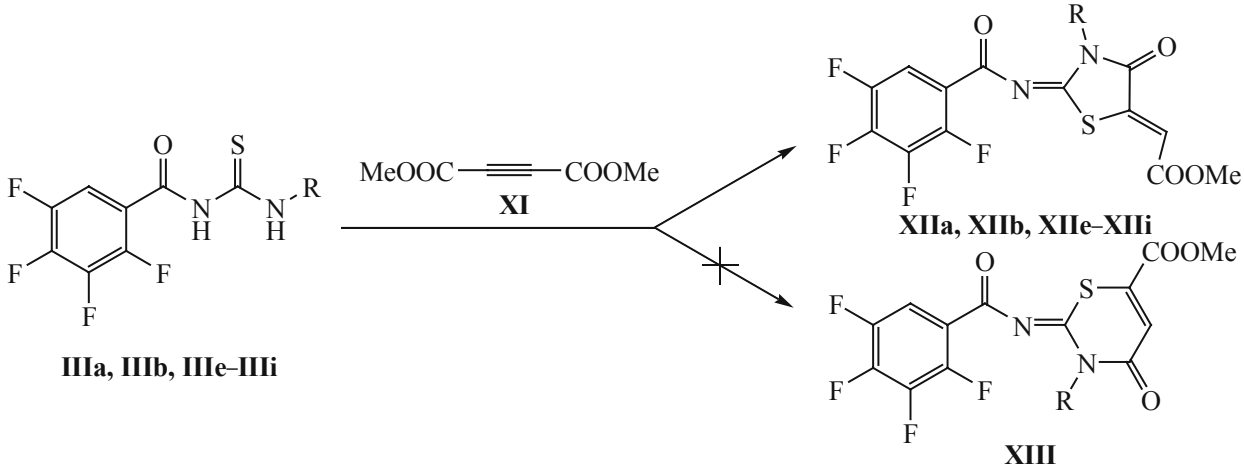
In the ^{1}H NMR spectra of reaction products of thioureas **III** and ester **XI** appeared signals of protons from aryl(heteryl) fragments, multiplet from the tetrafluorobenzoyl fragment at δ 7.47–7.64 ppm, also a singlet of the proton of thiazolidine moiety in the region δ 6.98–7.07 ppm, and a three-proton singlet of the methoxycarbonyl group at δ 3.88–3.90 ppm. The mass spectra of compounds **XII** contain the peak of molecular ion of intensity 9–29%, whereas the most abundant is the peak of *m/z* 177 corresponding to the fluoroaryl fragment C_6HF_4. Although published data indicated the formation of 4-thiazolidinones derivatives in reaction of thioureas (or thioamides) with ester **XI** [18–20], we subjected compound **XIIa** to XRD analysis in order to exclude the formation of an alternative product, methyl 3-aryl(heteryl)-4-oxo-2-(2,3,4,5-tetrafluorobenzoylimino)-3,4-dihydro-2*H*-[1,3]thiazine-6-carboxylate **XIII**. According to XRD data (see the figure) compound **XIIa** really has a structure of a thiazolidinone.



Structure of methyl [4-oxo-3-phenyl-2-(2,3,4,5-tetrafluorobenzoylimino)thiazolidin-5-ylidene]acetate (**XIIa**).

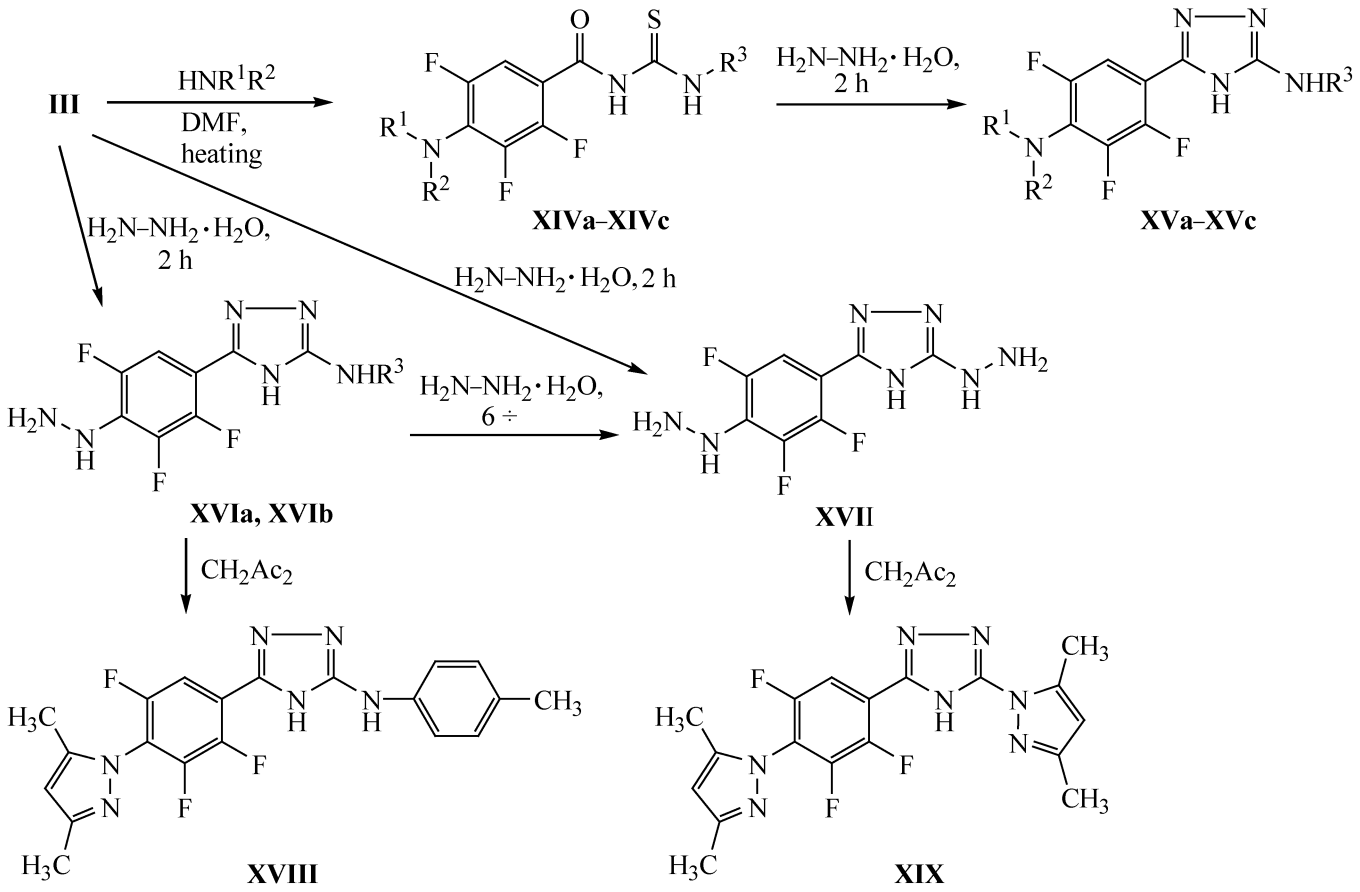
The (tetrafluorobenzoyl)thioureas **III** can be also involved into reactions at carbonyl and thiocarbonyl groups situated in the β-position to each other. The investigation of reactions between compounds **III** and dinucleophiles, e.g., hydrazine, is more convenient to perform using derivatives where the fluorine atom located in the *para*-position to the amide group is substituted with a residue of cycloalkylamine thus preventing the concurrent reaction at the fragment C(O)NHC(S) and the fluorine atom in the aromatic ring. To this end by boiling thioureas **IIIc** and **IIId** with pyrrolidine or morpholine in DMF we obtained derivatives **XIVa–XIVc** (Scheme 3). Thioureas **IIIa** and **IIIb** at heating in DMF underwent cyclization giving a mixture of benzothiazinone and quinazolinone [6], and compound **IIIe–IIIi** suffered cyclization into benzothiazinones [2]. The structure of thioureas **XIV** was confirmed by ^{1}H NMR spectra.

Scheme 2.



R = Ph (**a**), 4-$CH_3C_6H_4$ (**b**), 2-pyridyl (**e**), 6-methyl-2-pyridyl (**f**), pyrimidin-2-yl (**g**), 4,6-dimethylpyrimidin-2-yl (**h**), 5-methylpyrazol-3-yl (**i**).

Scheme 3.



XIV, XV, NR^1R^2 = pyrrolidin-1-yl, R^3 = 2-ClC_6H_4 (**a**), 2,4-$Cl_2C_6H_3$ (**b**); NR^1R^2 = morpholino, R^3 = 2-ClC_6H_4 (**c**); **XVI**, R^3 = C_6H_5 (a), 4-$CH_3C_6H_4$ (**b**).

In the reaction of thioureas **XIVa–XIVc** with hydrazine hydrate within 2 h a closure 4*H*-1,2,4-triazole ring occurred with the formation of derivatives **XVa–XVc** whose structure is consistent with the ^{1}H NMR spectra. As expected, in the reaction of thioureas **IIIa** and **IIIb** with hydrazine hydrate for 2 h occurred both the closure of the triazole ring and the substitution of F^4 aton by the hydrazine group. The structure of obtained compounds **XVIa** and **XVIb** was confirmed by spectral data. In reaction with hydrazine hydrate of heteryl-substituted thioureas **IIIe** and **IIIg** in 2 h occurred both cyclization and substitution of the heteryl moiety by the hydrazine as showed the lack in the ^{1}H NMR spectrum of derivative **XVII** the signals from protons of the pyridine or pyrimidine moieties and appearance of $NHNH_2$ signals. Compound **XVII** was also obtained in reaction of benzamide **VII** with hydrazine hydrate within 2 h. The prolongation of the reaction between thiourea **IIIb** and hydrazine hydrate from 2 to 8 h resulted in the formation of dihydrazino derivative **XVII**. Thus also the arylamino moiety in the position *3* of triazole ring is capable of being replaced by hydrazine group. This was confirmed by the reaction of compound **XVIb** with hydrazine hydrate for 6 h that yielded derivative **XVII**. Hydrazino derivative **XVI** and dihydrazino derivative **XVII** on heating with acetylacetone in acetonitrile in the presence of acetic acid were converted into derivatives **XVIII** and **XIX**.

Thus the study demonstrated that nucleophilic reactions of N-tetrafluorobenzoyl-N'-aryl-(heteryl)thioureas **III** involved the fluorine atom in the ortho-position and also the C(O)–NH–C(S) fragment of compounds **III**.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker WM-250 and Bruker DRX-400 at operating

frequencies 250.14 and 400.13 MHz (internal reference TMS); ^{19}F NMR spectra were recorded on a spectrometer Bruker DRX-500 at operating frequency 376.45 MHz (internal reference hexafluorobenzene). DMSO-d_6 was used as solvent. Mass spectra were measured on Varian MAT 311A instrument at following parameters: accelerating voltage 3 kV, cathode emission current 300 μA, ionizing electrons energy 70 eV, direct admission of the sample into the ion source. XRD analysis of compound **XIIa** was performed on single-crystal X-ray diffractometer Xcalibur 3 with a CCD-detector with the use of software package SHELXL-97 [21]. The wavelength of radiation λ 0.71073 (MoK_α), temperature at the experiment 295 K. Crystals 0.5 × 0.4 × 0.3 mm, colorless, triclinic, space group P1 (pseudo P-1), unit cell parameters: *a* 10.6311(18), *b* 14.028(3), *C* 14.6841(13) Å, α 64.041(16), β 81.001(16), γ 76.935(16)°. The cell includes 4 molecular units with a coplanar location of thiazole and tetrafluorophenyl rings The structure was solved by the direct method in isotropic approximation and refined in anisotropic approximation. The atomic coordinates and thermal factors are given in the table.

***N*-(2,3,4,5-Tetrafluorobenzoyl)-*N'*-phenylthiourea (IIIa).** To a solution of 6.0 g (28 mmol) of tetrafluorobenzoyl chloride in 6.5 ml of toluene was added a solution of 2.17 g (28 mmol) of ammonium thiocyanate in 35 ml of anhydrous acetonitrile. The mixture was heated for 5 min at 40°C, the ammonium chloride was filtered off, and the filtrate was added to the solution of 2.5 ml (2.55 g, 27.4 mmol) of aniline in 5 ml of anhydrous acetonitrile. The reaction mixture was kept for 3 h at room temperature, the separated precipitate was filtered off and recrystallized from ethanol. Yield 8.2 g (91%), mp 118–120°C. ^1H NMR spectrum, δ, ppm: 7.09 m ($1H_{arom}$), 7.32 m ($2H_{arom}$), 7.57 m (1H, $H^{6'}$), 7.67 m ($1H_{arom}$), 10.4 br.s (1H, NH), 14.0–15.0 br.s (1H, NH). Found, %: C 51.27; H 2.38; N 8.49. $C_{14}H_8F_4N_2OS$. Calculated, %: C 51.22; H 2.46; N 8.53.

Compounds **IIIb–IIId** were prepared similarly.

***N*-(2,3,4,5-Tetrafluorobenzoyl)-*N'*-(*p*-tolyl)thiourea (IIIb)**. Yield 92%, mp 120–122°C. ^1H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 7.11 m ($2H_{arom}$), 7.54 m ($2H_{arom}$), 7.60 m (1H, $H^{6'}$), 10.3 br.s (1H, NH), 14.0–15.0 br.s (1H, NH). Found, %: C 52.58; H 2.99; N 8.23. $C_{15}H_{10}F_4N_2OS$. Calculated, %: C 52.63, H 2.94, N 8.18.

***N*-(2,3,4,5-Tetrafluorobenzoyl)-*N'*-(2-chlorophenyl)-thiourea (IIIc)**. Yield 89%, mp 123–125°C. ^1H NMR spectrum, δ, ppm: 7.24 m ($1H_{arom}$), 7.36 m ($1H_{arom}$), 7.49 m ($1H_{arom}$), 7.65 m (1H, $H^{6'}$), 7.85 m ($1H_{arom}$),

Atomic coordinates (in fractions of unit cell axes) and thermal factors U_{iso}/U_{eq} for methyl [4-oxo-2-(2,3,4,5-tetrafluorobenzoylimino)-3-phenylthiazolidin-5-ylidene]acetate (**XIIa**)

Atom	*x*	*y*	*y*	U_{iso}/U_{eq}
S^1	–0.5695(2)	2.03011(18)	–0.58917(18)	0.0447(6)
O^1	–0.8497(8)	1.9036(6)	–0.5957(7)	0.070(2)
C^1	–0.9561(9)	2.0978(8)	–0.5757(8)	0.048(2)
N^1	–0.8208(7)	2.0529(7)	–0.5846(7)	0.046(2)
F^1	–0.9966(10)	2.5199(10)	–0.5339(11)	0.147(5)
O^4	–0.3848(10)	1.7297(8)	–0.6292(9)	0.091(3)
F^2	–0.8230(11)	2.6437(8)	–0.5548(9)	0.119(4)
C^2	–1.0331(11)	2.1223(10)	–0.6523(10)	0.067(3)
H^{2a}	–0.9994	2.1099	–0.7093	0.080
N^2	–0.7550(7)	2.1990(6)	–0.5815(6)	0.0387(18)
O^2	–0.5410(7)	2.1946(6)	–0.5623(7)	0.062(2)
F^3	–0.5661(11)	2.5732(7)	–0.5831(7)	0.106(3)
C^3	–1.1679(12)	2.1677(11)	–0.6423(13)	0.087(4)
H^{3a}	–1.2223	2.1863	–0.6935	0.104
O^3	–0.3631(8)	1.8720(8)	–0.6089(7)	0.075(3)
F^4	–0.4846(5)	2.3843(6)	–0.5900(6)	0.0720(18)
C^4	–1.2155(10)	2.1833(10)	–0.5549(10)	0.076(4)
H^{4a}	–1.3024	2.2116	–0.5471	0.091
C^5	–1.1327(9)	2.1564(10)	–0.4789)9)	0.066(3)
H^{5a}	–1.1653	2.1665	–0.4206	0.080
C^6	–1.0037(10)	2.1152(9)	–0.4889(10)	0.060
H^{6a}	–0.9488	2.0992	–0.4387	0.072
C^7	–0.7024(10)	2.3506(9)	–0.5682(9)	0.049(3)
C^8	–0.8357(12)	2.3843(10)	–0.5540(9)	0.067(3)
H^{8a}	–0.8971	2.3438	–0.5486	0.081
C^9	–0.8681(14)	2.4843(13)	–0.5487(13)	0.095(5)
C^{10}	–0.7836(17)	2.5481(11)	–0.5616(10)	0.079(4)
C^{11}	–0.6557(13)	2.5133(10)	–0.5737(11)	0.066(3)
C^{12}	–0.6136(12)	2.4122(10)	–0.5742(9)	0.064(3)
C^{13}	–0.7248(9)	2.1034(7)	–0.5835(7)	0.039(2)
C^{14}	–0.7819(11)	1.9574(10)	–0.5920(9)	0.056(3)
C^{15}	–0.6386(10)	1.9310(8)	–0.5970(8)	0.047(2)
C^{16}	–0.6553(10)	2.2399(9)	–0.5683(8)	0.048(2)
C^{17}	–0.5651(11)	1.8419(8)	–0.6079(8)	0.059(3)
H^{17a}	–0.6092	1.7925	–0.6096	0.071
C^{18}	–0.4308(10)	1.8194(9)	–0.6167(8)	0.056(3)
C^{19}	–0.2424(13)	1.7033(12)	–0.6397(15)	0.121(6)
H^{19a}	–0.2174	1.6386	–0.6504	0.182
H^{19b}	–0.2070	1.6927	–0.5790	0.182
H^{19c}	–0.2100	1.7614	–0.6966	0.182

9.9 br.s (1H, NH), 14.0–15.0 br.s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 7.47 m (1F), 10.38 m (1F), 23.84 m (2F). Found, %: C 46.39; H 2.09; N 7.53. $C_{14}H_7ClF_4N_2OS$. Calculated, %: C 46.36; H 1.95; N 7.72.

***N*-(2,4-Dichlorophenyl)-*N′*-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIId)**. Yield 93%, mp 136–138°C. ^{1}H NMR spectrum, δ, ppm: 7.18 d.d (1H, H$^{4''}$, ^3J 8.8, ^4J 2.5 Hz), 7.41 m (1H, H$^{6'}$), 7.52 d (1H, H$^{3''}$, ^3J 8.8 Hz), 8.35 d (1H, H$^{6''}$, ^4J 2.5 Hz), 9.2 br.s (1H, NH), 13.5–14.0 br.s (1H, NH). Found, %: C 42.38; H 1.59; N 7.03. $C_{14}H_6Cl_2F_4N_2OS$. Calculated, %: C 42.32; H 1.51; N 7.05.

2-Ethyl-1-(2,3,4,5-tetrafluorobenzoyl)-3-(*p*-tolyl)-isothiourea (IV). To a solution of 2.0 g (5.8 mmol) of thiourea **IIIb** was added 1.8 ml of ethyl iodide and 1.8 ml of 30% NaOH solution. The reaction mixture was left standing for 2 days at room temperature, then the precipitate was filtered off, the mother liquor was evaporated, and the residue was recrystallized from ethanol. Yield 1.7 g (79%), mp 125–127°C. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3), 2.31 s (3H, CH_3), 4.31 q (2H, SCH_2), 7.10 d (2H$_{arom}$, ^3J 8.5 Hz), 7.32 m (1H, H$^{6'}$), 7.54 d (2H$_{arom}$, ^3J 8.5 Hz), 10.1 br.s (1H, NH). Found, %: C 55.24; H 3.47; N 7.63. $C_{17}H_{13}F_4N_2OS$. Calculated, %: C 55.28; H 3.52; N 7.59.

1-(*p*-Tolyl)-6,7,8-trifluoro-2-ethylsulfanyl-1*H*-quinazolin-4-one (V). *a*. To a solution of 2.0 g (5.8 mmol) of thiourea **IIIb** was added 1.8 ml of ethyl iodide and 1.8 ml of 30% NaOH solution. The reaction mixture was for 5 h heated to 80°C, then it was evaporated, the residue was washed with water, then with a mixture hexane–ethanol, 2:1, and recrystallized from ethanol. Yield 1.35 g (67%), mp 212–214°C. ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, CH_3), 3.00 s (3H, CH_3), 3.07 q (2H, SCH_2), 7.35 d (2H$_{arom}$, ^3J 8.5 Hz), 7.42 d (2H$_{arom}$, ^3J 8.5 Hz), 7.82 d.d.d (1H, H^5, ^3J 10.0, ^4J 7.8, ^5J 2.3 Hz). ^{19}F NMR spectrum, δ, ppm: 11.06 d.d.d (1F, F^7, ^3J 23.0, ^3J 19.6, ^4J 8.0 Hz), 20.46 d.d.d (1F, F^8, ^3J 19.6, ^4J 4.0, ^5J 2.5 Hz), 25.54 d.d.d (1F, F^6, ^3J 23.0, ^3J 9.8, ^4J 4.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 350 (8) $[M]^+$, 322 (26), 321 (12), 289 (3), 264 (11), 263 (64), 262 (18), 234 (21), 173 (13), 120 (10), 119 (100). Found, %: C 58.30; H 3.81; N 8.04. $C_{17}H_{13}F_3N_2OS$. Calculated, %: C 58.28; H 3.74; N 7.99. *M* 350.36.

b. To a solution of 0.5 g (1.35 mmol) of compound **IV** in 15 ml of anhydrous toluene was added 0.45 ml (3 mmol) of triethylamine. The reaction mixture was boiled for 3 h, then evaporated, the residue was washed with water and recrystallized from ethanol. Yield 0.28 g (60%).

***N*-(2-Thioxoimidazolidine-1-carbothioyl)-2,3,4,5-tetrafluorobenzamide (VII).** To a solution of 12 mmol of imidazolidine-2-thione (**VI**) in a mixture of 15 ml of dioxane and 15 ml of acetonitrile was added 24 mmol of isothiocyanate solution in acetonitrile (the solution was prepared as described in the procedure of the synthesis of compound **IIIa**). The reaction mixture was maintained at room temperature for 24 h. The yellow-green precipitate was filtered off and recrystallized from acetonitrile. Yield 3.3 g (83%), mp 202–204°C. ^{1}H NMR spectrum, δ, ppm: 3.56 m (2H, CH_2), 4.44 m (2H, CH_2), 7.62 m (1H, H$^{6'}$), 10.4 br.s (1H, NH), 14.8 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 337 (35) $[M]^+$, 278 (49) $[M - HSCN]^+$, 177 (100), 149 (28). Found, %: C 39.24; H 2.13; N 12.42. $C_{11}H_7F_4N_3OS_2$. Calculated, %: C 39.17; H 2.08; N 12.46. *M* 337.32.

2-(2-Thioxoimidazolidin-1-yl)-6,7,8-trifluoro-[1,3]benzothiazin-4-one (VIII). To a dispersion of 0.7 g (2.1 mmol) of benzamide **VII** in 10 ml of toluene was added 0.6 ml (4.2 mmol) of triethylamine. The reaction mixture was boiled for 2.5 h, then it was evaporated, the residue was washed with water and dilute acetic acid, then it was recrystallized from ethanol. Yield 0.45 g (67%), mp 130–132°C. ^{1}H NMR spectrum, δ, ppm: 3.95 m (4H, $2CH_2$), 7.62 d.d.d (1H, H^5, ^3J 10.3, ^4J 7.6, ^5J 2.1 Hz), 12.1 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 258 (100) $[M - HSCN]^+$, 190 (63), 172 (13), 162 (18), 69 (22). Found, %: C 41.68; H 1.95; N 13.20. $C_{11}H_6F_3N_3OS_2$. Calculated, %: C 41.64; H 1.89; N 13.25.

2,3,4-Trifluoro-6a,10a-dihydro-12*H*-benzo[*e*]-benzo[4,5]imidazo[2,1-*b*][1,3]thiazin-12-one (X). To 1.2 g (8 mmol) of benzimidazole -2-thione (**IX**) in 15 ml of anhydrous acetonitrile was added a solution of 12 mmol of tetrafluorobenzoyl isothiocyanate (**I**), the reaction mixture was boiled for 2 h, then it was cooled. The settled precipitate was filtered off and recrystallized from DMSO. Yield 2.2 g (90%), mp 224–226°C. ^{1}H NMR spectrum, δ, ppm: 7.50 m (2H, H^8, H^9), 7.76 m (1H, H^{10}), 8.34 d.d.d (1H, H^5, ^3J 10.7, ^4J 7.3, ^5J 1.2 Hz), 8.48 m (1H, H^7). ^{19}F NMR spectrum, δ, ppm: 12.78 d.d.d (1F, F^3, ^3J 22.5, ^3J 20.9, ^4J 7.3 Hz), 28.83 d.d.d (1F, F^2, ^3J 22.5, ^3J 10.7, ^4J 5.6 Hz), 29.65 d.d.d (1F, F^4, ^3J 20.8, ^4J 5.6, ^5J 1.5 Hz). Mass spectrum, *m/z* (I_{rel}, %): 306 (100) $[M]^+$, 274 (10), 190 (13), 162 (9). Found, %: C 55.00; H 1.30; N 9.19. $C_{14}H_5F_3N_2OS$. Calculated, %: C 54.91; H 1.65; N 9.15. *M* 306.26.

Methyl [4-oxo-2-(2,3,4,5-tetrafluorobenzoylimino)-3-phenylthiazolidin-5-ylidene]acetate (XIIa).

To a solution of 0.45 g (1.37 mmol) of thiourea **IIIa** in 20 ml of methanol was added 0.3 ml (2.38 mmol) of dimethyl acetylenedicarboxylate (**XI**). The reaction mixture was stirred at room temperature for 12 h, the separated colorless precipitate was filtered off and recrystallized from DMSO. Yield 0.48 g (80%), mp 168–170°C. ^{1}H NMR spectrum, δ, ppm: 3.89 s (3H, COOMe), 6.99 s (1H, CH), 7.54 m (2H, Ph), 7.57 m (4H, Ph, CHF_4). Mass spectrum, *m/z* (I_{rel}, %): 438 (15) $[M]^+$, 289 (11), 177 (100), 149 (19). Found, %: C 52.15; H 2.19; N 6.43. $C_{19}H_{10}F_4N_2O_4S$. Calculated, %: C 52.06; H 2.30; N 6.39. *M* 438.35.

Compounds **XIIb, XIIe–XIIi** were analogously obtained.

Methyl [4-oxo-2-(2,3,4,5-tetrafluoro-benzoylimino)-3-(*p*-tolyl)thiazolidin-5-ylidene]acetate (XIIb). Yield 82%, mp 155–157°C. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 3.90 s (3H, COOMe), 6.98 s (1H, CH), 7.33 d ($4H_{arom}$, ^3J 2.8 Hz), 7.52 m (1H, CHF_4). Mass spectrum, *m/z* (I_{rel}, %): 452 (15) $[M]^+$, 303 (7), 177 (100), 149 (17). Found, %: C 53.09; H 2.62; N 6.15. $C_{20}H_{12}F_4N_2O_4S$. Calculated, %: C 53.10; H 2.67; N 6.19. *M* 452.38.

Methyl [4-oxo-3-(2-pyridyl)-2-(2,3,4,5-tetrafluorobenzoylimino)thiazolidin-5-ylidene]acetate (XIIe). Yield 79%, mp 205–210°C. ^{1}H NMR spectrum, δ, ppm: 3.89 s (3H, COOMe), 7.02 s (1H, CH), 7.47 m (1H, CHF_4), 7.60 m (2H, Py), 8.07 m (1H, Py), 8.65 (1H, Py). Mass spectrum, *m/z* (I_{rel}, %): 439 (10) $[M]^+$, 407 (10), 290 (7), 262 (21), 177 (100), 149 (24), 144 (11), 116 (18), 85 (10), 78 (11). Found, %: C 49.18; H 2.12; N 9.53. $C_{18}H_9F_4N_3O_4S$. Calculated, %: C 49.19; H 2.06; N 9.56. *M* 439.34.

Methyl [4-oxo-3-(6-methyl-2-pyridyl)-2-(2,3,4,5-tetrafluorobenzoylimino)thiazolidin-5-ylidene]-acetate (XIIf). Yield 76%, mp 203–205°C. ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 3.90 s (3H, COOMe), 7.01 s (1H, CH), 7.41 d.d (2H, H$^{3'}$, H$^{5'}$, ^3J 7.8, ^4J 4.6 Hz), 7.51 m (1H, CHF_4), 7.94 t (1H, H$^{4'}$, ^3J 7.8 Hz). Mass spectrum, *m/z* (I_{rel}, %): 453 (9) $[M]^+$, 421 (7), 276 (27), 177 (100), 149 (21), 116 (13). Found, %: C 50.44; H 2.36; N 9.28. $C_{19}H_{11}F_4N_3O_4S$. Calculated, %: C 50.34; H 2.45; N 9.27. *M* 453.37.

Methyl [4-oxo-3-(pyrimidin-2-yl)-2-(2,3,4,5-tetrafluorobenzoylimino)thiazolidin-5-ylidene]-acetate (XIIg). Yield 73%, mp 210–212°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H, COOMe), 7.07 s (1H, CH), 7.47 m (1H, CHF_4), 7.81 t (1H, H$^{4'}$, ^3J 4.9 Hz), 9.08 d (2H, H$^{3'}$, H$^{5'}$, ^3J 4.9 Hz). Mass spectrum, *m/z* (I_{rel}, %): 440 (22) $[M]^+$, 297 (9), 291 (10), 177 (100), 149 (30), 144 (57), 116 (42), 85 (18). Found, %: C 46.29; H 1.84; N 12.67. $C_{17}H_8F_4N_4O_4S$. Calculated, %: C 46.37; H 1.83; N 12.72.

Methyl [4-oxo-3-(4,6-dimethylpyrimidin-2-yl)-2-(2,3,4,5-tetrafluorobenzoylimino)thiazolidin-5-ylidene]acetate (XIIh). Yield 75%, mp 240–242°C. ^{1}H NMR spectrum, δ, ppm: 2.59 s (6H, $2CH_3$), 3.89 s (3H, COOMe), 7.05 s (1H, CH), 7.49 s (1H, H$^{4'}$), 7.52 m (1H, CHF_4). Mass spectrum, *m/z* (I_{rel}, %): 468 (29) $[M]^+$, 325 (12), 177 (100), 149 (22), 144 (44), 116 (34), 85 (12). Found, %: C 48.66; H 2.58; N 11.87. $C_{19}H_{12}F_4N_4O_4S$. Calculated, %: C 48.72; H 2.58; N 11.96.

Methyl [4-oxo-3-(5-methylpyrazol-3-yl)-2-(2,3,4,5-tetrafluorobenzoylimino)thiazolidin-5-ylidene]-acetate (XIIi). Yield 75%, mp 218–220°C. ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 3.88 s (3H, COOMe), 6.09 s (1H, H$^{4'}$), 6.99 s (1H, CH), 7.64 m (1H, CHF_4), 12.9 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 442 (15) $[M]^+$, 293 (7), 177 (100), 149 (19). Found, %: C 46.20; H 2.32; N 12.62. $C_{17}H_{10}F_4N_4O_4S$. Calculated, %: C 46.16; H 2.28; N 12.67.

***N*-(2,4-Dichlorophenyl)-*N*'-[4-(pyrrolidin-1-yl)-2,3,5-trifluorobenzoyl]thiourea (XIVb).** To 2.0 g (5.0 mmol) of compound **IIId** in 12 ml of DMF was added 1.7 g (24 mmol) of pyrrolidine, the mixture was boiled for 5 h, on cooling the colorless precipitate was filtered off and recrystallized from DMSO. Yield 1.9 g (83%), mp 166–168°C. ^{1}H NMR spectrum, δ, ppm: 1.93 m [4H, $(CH_2)_2$], 3.68 m [4H, $N(CH_2)_2$], 7.17 d.d (1H, H$^{4''}$, ^3J 8.8, ^4J 2.5 Hz), 7.34 d.d.d (1H, H$^{6'}$, ^3J 14.0, ^4J 7.1, ^5J 2.0 Hz), 7.48 d (1H, H$^{3''}$, ^3J 8.8 Hz), 8.32 d (1H, H$^{6''}$, ^4J 2.5 Hz), 9.2 br.s (1H, NH), 12.1 br.s (1H, NH). Found, %: C 48.27; H 3.19; N 9.33. $C_{18}H_{14}Cl_2F_3N_3OS$. Calculated, %: C 48.21; H 3.13; N 9.38.

Compounds **XIVa** and **XIVc** were obtained similarly and recrystallized from ethanol.

***N*-[4-(Pyrrolidin-1-yl)-2,3,5-trifluorobenzoyl]-*N*'-(2-chlorophenyl)thiourea (XIVa).** Yield 79%, mp 98–100°C. ^{1}H NMR spectrum, δ, ppm: 1.92 m [4H, $(CH_2)_2$], 3.66 m [4H, $N(CH_2)_2$], 7.17 m ($1H_{arom}$), 7.34 m ($1H_{arom}$), 7.36 d.d.d (1H, H$^{6'}$, ^3J 14.2, ^4J 7.2, ^5J 2.2 Hz), 7.47 m ($1H_{arom}$), 8.13 m ($1H_{arom}$), 9.2 br.s (1H, NH), 14.0 br.s (1H, NH). Found, %: C 52.28; H 3.71; N 10.09. $C_{18}H_{15}ClF_3N_3OS$. Calculated, %: C 52.24; H 3.65; N 10.15.

***N*-(4-Morpholino-2,3,5-trifluorobenzoyl)-*N*'-(2-chlorophenyl)thiourea (XIVc).** Yield 77%, mp 111–

113°C. ^{1}H NMR spectrum, δ, ppm: 3.31 m [4H, $N(CH_2)_2$], 3.75 m [4H, $O(CH_2)_2$], 7.20 m ($1H_{arom}$), 7.36 m ($1H_{arom}$), 7.47 d.d.d (1H, H*6′*, ^3J 13.9, ^4J 7.1, ^5J 2.2 Hz), 7.50 m ($1H_{arom}$), 8.11 m ($1H_{arom}$), 9.4 br.s (1H, NH), 14.0 br.s (1H, NH). Found, %: C 50.34; H 3.49; N 9.72. $C_{18}H_{15}ClF_3N_3O_2S$. Calculated, %: C 50.29; H 3.42; N 9.78.

[4-(Pyrrolidin-1-yl)-5-(2,3,5-trifluorophenyl)-4*H*-1,2,4-triazol-3-yl]-2-chlorophenylamine (XVa). To 0.2 g (0.48 mmol) of thiourea **XIVa** in 20 ml of ethanol was added 1 ml (20 mmol) of hydrazine hydrate, the mixture was boiled for 2 h, on cooling the precipitate was filtered off and recrystallized from ethanol. Yield 0.16 g (84%), mp 109–111°C. ^{1}H NMR spectrum, δ, ppm: 1.92 m [4H, $(CH_2)_2$], 3.65 m [4H, $N(CH_2)_2$], 7.13 m ($1H_{arom}$), 7.32 m ($1H_{arom}$), 7.39 d.d.d (1H, H*6′*, ^3J 12.5, ^4J 6.2, ^5J 2.2 Hz), 7.48 m ($1H_{arom}$), 8.24 m ($1H_{arom}$), 9.1 br.s (1H, NH), 13.0 br.s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 12.08 d.d (1F, F*2′*, ^3J 18.1, ^4J 6.2 Hz), 22.58 d.d.d (1F, F*3′*, ^3J 18.1, ^4J 6.6, ^5J 2.2 Hz), 34.63 d.d (1F, F*5′*, ^3J 12.3, ^4J 6.6 Hz). Found, %: C 54.88; H 3.83; N 17.73. $C_{18}H_{15}ClF_3N_5$. Calculated, %: C 54.85; H 3.81; N 17.78.

Compound **XVb** and **XVc** were similarly obtained.

(2,4-Dichlorophenyl)-[4-(pyrrolidin-1-yl)-5-(2,3,5-trifluorophenyl)-4*H*-1,2,4-triazol-3-yl]-amine (XVb). Yield 81%, mp 178–180°C. ^{1}H NMR spectrum, δ, ppm: 1.94 m [4H, $(CH_2)_2$], 3.68 m [4H, $N(CH_2)_2$], 7.15 d.d (1H, H*4″*, ^3J 8.8, ^4J 2.5 Hz), 7.34 d.d.d (1H, H*6′*, ^3J 12.5, ^4J 6.4, ^5J 2.1 Hz), 7.47 d (1H, H*3″*, ^3J 8.8 Hz), 8.36 d (1H, H*6″*, ^4J 2.5 Hz), 9.1 br.s (1H, NH), 12.8 br.s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 11.98 m (1F), 21.89 m (1F), 34.64 m (1F). Found, %: C 50.51; H 3.32; N 16.31. $C_{18}H_{14}Cl_2F_3N_5$. Calculated, %: C 50.74; H 3.27; N 16.36.

[5-(4-Morpholino-2,3,5-trifluorophenyl)-4*H*-1,2,4-triazol-3-yl](2-chlorophenyl)amine (XVc). Yield 79%, mp 167–169°C. ^{1}H NMR spectrum, δ, ppm: 3.30 m [4H, $N(CH_2)_2$], 3.73 m [4H, $O(CH_2)_2$], 7.21 m ($1H_{arom}$), 7.37 m ($1H_{arom}$), 7.43 d.d.d (1H, H*6′* , ^3J 12.3, ^4J 6.5, ^5J 2.0 Hz), 7.49 m ($1H_{arom}$), 8.07 m ($1H_{arom}$), 9.4 br.s (1H, NH), 12.7 br.s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 17.98 d.d (1F, F*2′*, ^3J 21.2, ^4J 6.2 Hz), 21.66 d.d.d (1F, F*3′*, ^3J 21.2, ^4J 6.5, ^5J 2.1 Hz), 37.89 d.d (1F, F*5′*, ^3J 12.7, ^4J 6.5 Hz). Found, %: C 52.79; H 3.71; N 17.06. $C_{18}H_{15}ClF_3N_5O$. Calculated, %: C 52.75; H 3.66; N 17.09.

Phenyl[5-(4-hydrazino-2,3,5-trifluorophenyl)-4*H*-1,2,4-triazol-3-yl]amine (XVIa). To 0.3 g (0.91 mmol) of thiourea **IIIa** in 20 ml of ethanol was added 1 ml (20 mmol) of hydrazine hydrate, the mixture was boiled for 2 h, on cooling the precipitate was filtered off and recrystallized from ethanol. Yield 0.25 g (86%), mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 4.31 br.s (2H, NH_2), 6.75 br.s (1H, NH), 7.02 m ($1H_{arom}$), 7.16 d.d.d (1H, H*6′*, ^3J 12.5, ^4J 6.2, ^5J 2.2 Hz), 7.26 m ($2H_{arom}$), 7.64 m ($2H_{arom}$), 9.8 br.s (1H, NH), 12.9 br.s (1H, NH). Found, %: C 52.47; H 3.42; N 26.27. $C_{14}H_{11}F_3N_6$. Calculated, %: C 52.50; H 3.46; N 26.24. Likewise was obtained compound **XVIb**.

[5-(4-Hydrazino-2,3,5-trifluorophenyl)-4*H*-1,2,4-triazol-3-yl](*p*-tolyl)amine (XVIb). Yield 83%, mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 2.31 C (3H, CH_3), 4.33 br.s (2H, NH_2), 6.76 br.s (1H, NH), 7.08 d ($2H_{arom}$, ^3J 8.8 Hz), 7.14 d.d.d (1H, H*6′,* ^3J 12.3, ^4J 6.1, ^5J 2.1 Hz), 7.54 d ($2H_{arom}$, ^3J 8.8 Hz), 9.7 br.s (1H, NH), 12.5 br.s (1H, NH). Found, %: C 53.93; H 3.96; N 25.09. $C_{15}H_{13}F_3N_6$. Calculated, %: C 53.89; H 3.92; N 25.14.

[5-(4-Hydrazino-2,3,5-trifluorophenyl)-4*H*-1,2,4-triazol-3-yl]hydrazine (XVII). To 0.5 g (1.5 mmol) of thiourea **III**g in 20 ml of ethanol was added 2.5 ml (50 mmol) of hydrazine hydrate, the mixture was boiled for 2 h, on cooling the precipitate was filtered off and recrystallized from ethanol. Yield 0.32 g (82%), mp 195–197°C. ^{1}H NMR spectrum, δ, ppm: 4.37 br.s (4H, $2NH_2$), 6.7 br.s (1H, NH), 7.14 d.d.d (1H, H*6′*, ^3J 12.5, ^4J 7.1, ^5J 2.5 Hz), 9.1 br.s (1H, NH), 12.4 br.s (1H, NH). Found, %: C 37.11; H 3.14; N 37.78. $C_8H_8F_3N_7$. Calculated, %: C 37.07; H 3.09; N 37.84.

Likewise compound **XVII** was obtained from thiourea **IIIe** (yield 76%), benzamide **VII** (yield 74%), thiourea **IIIb** at reaction duration 8 h (yield 71%) or compound **XVIb** at reaction duration 6 h (yield 77%).

{5-[4-(3,5-Dimethylpyrazol-1-yl)-2,3,5-trifluorophenyl]-4*H*-1,2,4-triazol-3-yl}(*p*-tolyl)-amine (XVIII). To a solution of 0.65 g (1.9 mmol) of compound **XVIb** in 12 ml of anhydrous acetonitrile was added 0.39 ml (0.39 g, 3.8 mmol) of acetylacetone and 0.4 ml of acetic acid. The reaction mixture was boiled for 2 h, then it was evaporated, the residue was washed with water and recrystallized from ethanol. Yield 0.55 g (73%), mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: 2.22 s (6H, $2CH_3$), 2.64 s (3H, CH_3), 6.06 s (1H, CH), 7.11 d ($2H_{arom}$, ^3J 8.2 Hz), 7.52 m (1H, H*6′*), 7.57 d ($2H_{arom}$, ^3J 8.2 Hz), 10.3 br.s (1H, NH), 13.5 br.s (1H, NH). Found, %: C 60.39; H 4.32; N 21.06. $C_{20}H_{17}F_3N_6$. Calculated, %: C 60.33; H 4.27; N 21.11.

3-(3,5-Dimethylpyrazol-1-yl)-5-[4-(3,5-dimethylpyrazol-1-yl)-2,3,5-trifluorophenyl]-4*H*-1,2,4-triazole

(XIX). To a solution of 0.4 g (1.5 mmol) of compound **XVII** in 12 ml of anhydrous acetonitrile was added 0.39 ml (0.39 g, 3.8 mmol) of acetylacetone and 0.4 ml of acetic acid. The reaction mixture was boiled for 2 h, then it was evaporated, the residue was dissolved in 5 ml of ethanol, the product was reprecipitated with water, filtered off, and recrystallized from ethanol. Yield 0.4 g (69%), mp 120–122°C. ^{1}H NMR spectrum, δ, ppm: 2.18 s (3H, CH_3), 2.21 s (3H, CH_3), 2.21 s (3H, CH_3), 2.64 s (3H, CH_3), 6.07 s (1H, CH), 6.24 s (1H, CH), 7.51 d.d.d (1H, H$^{6'}$, ^3J 11.3, ^4J 6.1, ^5J 1.8 Hz), 12.5 br.s (1H, NH). Found, %: C 55.75; H 4.17; N 25.24. $C_{18}H_{16}F_3N_7$. Calculated, %: C 55.70; H 4.13; N 25.30.

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