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Fluorine-Containing Heterocycles: XV.* Reactions of Polyfluorobenzoyl Isothiocyanates with Aminoazines and Aminoazoles

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Abstract—Reactions of tetra- and pentafluorobenzoyl isothiocyanates with aminoazoles and aminoazines led to the formation of fluorinated 1,3-benzothiazin-4-ones which reacted with cyclic amines in different ways. Replacement of the N=C=S fragment was observed in some reactions of polyfluorobenzoyl isothiocyanates with nucleophiles.

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Acyl isothiocyanates are characterized by high reactivity toward nucleophiles, including difunctional ones, so that such reactions are widely used in the synthesis of heterocycles [2]. Due to the presence of a halogen atom in the *ortho*-position of the benzene ring in benzoyl isothiocyanates, nucleophilic attack on the carbonyl or isothiocyanato group may be followed by intramolecular replacement of the *ortho*-halogen atom to give 2-substituted 1,3-benzothiazin-4-ones [3]. We previously showed that readily accessible polyfluorobenzoyl isothiocyanates **I** react with nucleophiles (e.g., cyclic amines and CH-active benzimidazoles), yielding fluorinated 1,3-benzothiazin-4-ones [4, 5]. In the present work we examined reactions of 2,3,4,5-tetra- and pentafluorobenzoyl isothiocyanates **Ia** and **Ib** with aminoazines and aminoazoles.

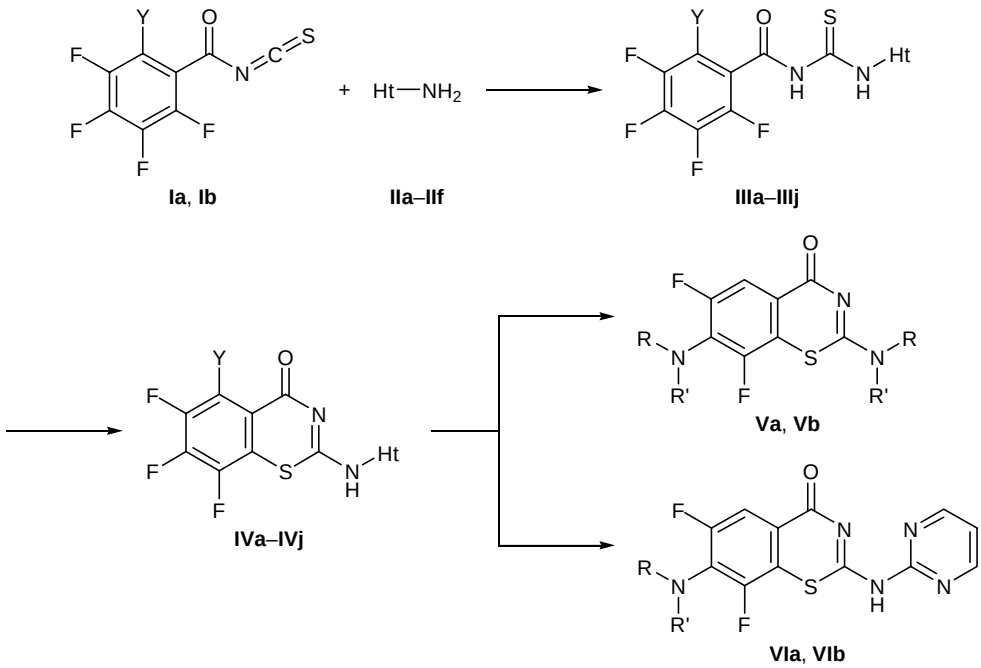
Polyfluorobenzoyl isothiocyanates **Ia** and **Ib** smoothly reacted with 2-aminopyridines **IIa** and **IIb**, 2-aminopyrimidines **IIc** and **IId**, and 3-aminopyrazoles **IIe** and **IIf** in acetonitrile at room temperature (reaction time 3 h) to give 69–89% of the corresponding addition products **IIIa**–**IIIj** (Scheme 1). The ^{1}H NMR spectra of **IIIa**–**IIIj** confirmed the presence in their molecules of heterocyclic fragments and NH groups (broadened signals at δ 11.5–13.9 ppm); a one-proton multiplet at δ 7.61–7.69 ppm in the spectra of compounds **IIIa**, **IIIc**, **IIIe**, **IIIg**, **IIIi**, and **IIIj** was typical of the tetrafluorobenzoyl moiety.

Polyfluorobenzoyl-substituted thioureas **IIIa**, **IIIc**, and **IIId** underwent intramolecular cyclization to 1,3-benzothiazin-4-ones **IVa**, **IVc**, and **IVd** on heating for 3 h in boiling toluene in the presence of triethylamine; analogous transformation of azolylamino derivatives **IIIi** and **IIIj** required a longer reaction time, 6 h. The cyclization of pyridyl- and pyrimidinyl-substituted thioureas **IIIa**–**IIIh** to the corresponding fluorinated 1,3-benzothiazin-4-ones **IVa**–**IVh** in boiling DMSO was complete within 3 min (yield 84–90%), whereas pyrazolyl derivatives **IIIi** and **IIIj** failed to react even on prolonged heating in the same solvent.

The structure of 1,3-benzothiazin-4-ones **IVa**–**IVj** was confirmed by the ^{1}H and ^{19}F NMR and mass spectra. The ^{1}H NMR spectra of **IVa**–**IVj** contained signals from protons in the heterocyclic fragment (as in the spectra of the initial thioureas), one NH signal disappeared from the spectra, and the multiplicity of the 5-H signal of **IVa**, **IVc**, **IVe**, **IVg**, **IVi**, and **IVj** changed to a double doublet of doublets (δ 7.97–8.02 ppm). In the ^{19}F NMR spectra of these compounds we observed multiplet signals from three (**IVa**, **IVe**, **IVg**) or four fluorine atoms (**IVb**, **IVf**). The molecular ion peaks in the mass spectra of 2-hetarylamino-1,3-benzothiazin-4-ones **IVa**–**IVj** had a relative

* For communication XIV, see [1].

Scheme 1.



I, Y = H (**a**), F (**b**); **II**, Ht = 2-pyridyl (**a**), 6-methylpyridin-2-yl (**b**), pyrimidin-2-yl (**c**), 4,6-dimethylpyrimidin-2-yl (**d**), 5-methyl-1*H*-pyrazol-3-yl (**e**), 5-phenyl-1*H*-pyrazol-3-yl (**f**); **III**, **IV**, Ht = 2-pyridyl, Y = H (**a**), F (**b**); Ht = 6-methylpyridin-2-yl, Y = H (**c**), F (**d**); Ht = pyrimidin-2-yl, Y = H (**e**), F (**f**); Ht = 4,6-dimethylpyrimidin-2-yl, Y = H (**g**), F (**h**); Ht = 5-methyl-1*H*-pyrazol-3-yl, Y = H (**i**); Ht = 5-phenyl-1*H*-pyrazol-3-yl, Y = H (**j**); **V**, **VI**, RR'N = morpholino (**a**), 4-ethoxycarbonylpiperazin-1-yl (**b**).

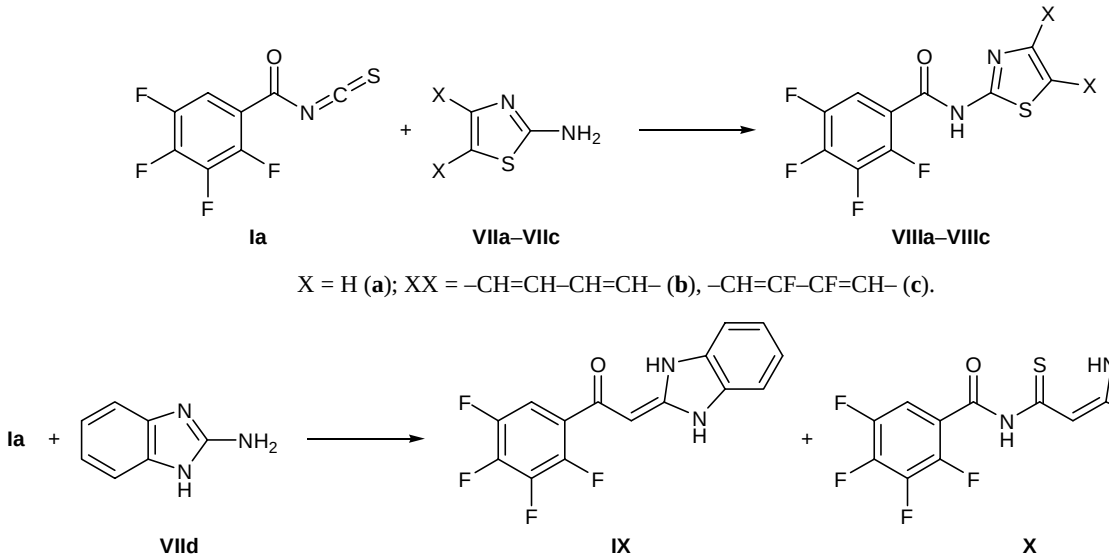
intensity of 17–45%. The most abundant ions were $[HtNHCN]^+$ (**IVa**–**IVd**, **IVg**–**IVj**) or $[M - HtNHCN]^+$ (*m*/*z* 190 or 208; **IVe**, **IVf**). It should be noted that the base peak in the mass spectra of 2-substituted 6,7,8-trifluoro-1,3-benzothiazin-4-ones corresponded to elimination of RCN from the molecular ion [4, 5]; elimination of the RNHCN fragment as the main decomposition pathway of 2-aminopyrido[3,2-*e*]thiazin-4-ones under electron impact was reported in [3].

The reaction of benzothiazinones **IVa** and **IVc** with morpholine in boiling DMF (5 h) involved replacement of both fluorine atom in position *7* and the amino group in position *2*; as a result, 6,8-difluoro-2,7-dimorpholino-1,3-benzothiazin-4-one (**Va**) was obtained. The product structure follows from the ^{1}H NMR spectrum which contained no signals from the pyridylamino fragment, but those belonging to two morpholine residues were present. Compound **Va** showed the molecular ion peak in the mass spectrum, and that corresponding to loss of the $O(CH_2)_4NCN$ fragment from the molecular ion was the most intense, in keeping with published data for fragmentation of benzothiazinones. Likewise, benzothiazinones **IVa** and **IVc** reacted with ethyl piperazine-1-carboxylate to give compound **Vb**. Replacement of substituent in position *2* of fluorine-containing 1,3-benzothiazin-4-ones by morpholino and 4-ethoxycarbonylpiperazin-1-yl groups was reported for the first time in [4]. Examples of replacement of an azolyl substituent in thiazoles are well known (see, e.g., [6]).

In the reactions of benzothiazinone **IVe** with morpholine or ethyl piperazine-1-carboxylate in DMF, only the 7-fluorine atom was replaced, while the pyrimidin-2-ylamino group in position *2* remained unchanged. The ^{1}H NMR spectra of compounds **VIa** and **VIb** thus formed contained signals from protons in the pyrimidinylamino fragment and cyclic amine moiety, as well as a doublet of doublets at δ 7.70–7.75 ppm from the 5-H proton (as in the spectra of **Va** and **Vb**).

2,3,4,5-Tetrafluorobenzoyl isothiocyanate (**Ia**) reacted with 2-aminothiazole (**VIIa**), 2-aminobenzothiazole (**VIIb**), and 2-amino-5,6-difluorobenzothiazole (**VIIc**) in acetonitrile at room temperature (3 h) in a different way. Here, the products were benzamides **VIIIa**–**VIIIc** rather than thioureas **III** (Scheme 2). Compounds **VIIIa**–**VIIIc** were identical to those obtained previously from 2,3,4,5-tetrafluorobenzoyl chloride and aminothiazoles **VIIa**–**VIIc** [7]. Obviously, the reaction involves substitution of the N=C=S group in **Ia** rather than nucleophilic addition of

Scheme 2.



2-aminothiazole at the N=C bond. Analogous replacement of the N=C=S fragment in benzoyl isothiocyanate by methyl- and benzylhydrazine residues was described in [8]. In the reaction of isothiocyanate **Ia** with 2-aminobenzimidazole (**VIId**), a mixture of the nucleophilic substitution and addition products **IX** and **X** was formed at a ratio of 10:3 (according to the ^{1}H NMR data). *N*-(2,3-Dihydro-1*H*-benzimidazol-2-ylidene)-2,3,4,5-tetrafluorobenzamide (**IX**) was identical to the product obtained by reaction of tetrafluorobenzoyl chloride with aminobenzimidazole **VIId** [7].

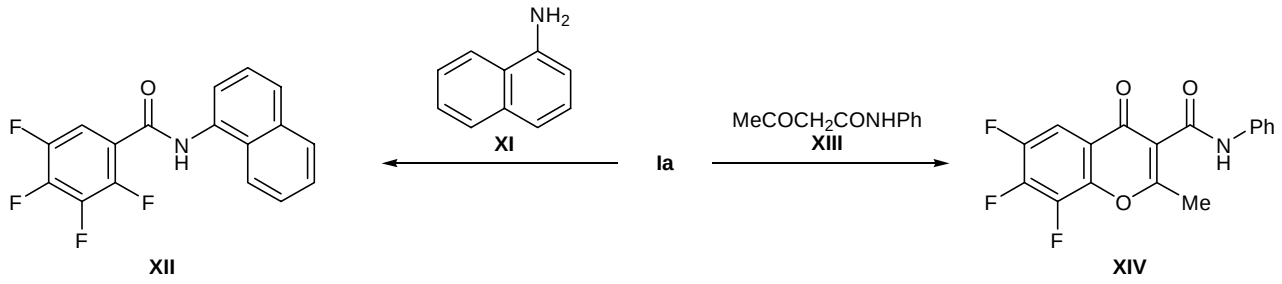
Likewise, the reaction of **Ia** with α-naphthylamine (**XI**) followed the replacement rather than addition pattern, leading to *N*-naphthylbenzamide **XII** (Scheme 3). One more example of substitution of the N=C=S group in tetrafluorobenzoyl isothiocyanate is the reaction of **Ia** with acetoacetanilide (**XIII**), which was performed in acetonitrile at room temperature (reaction time 3 h). From the reaction mixture we isolated 6,7,8-trifluoro-2-methyl-4-oxo-*N*-phenyl-4*H*-chromene-3-carboxamide (**XIV**); it was identical to the product obtained from tetrafluorobenzoyl chloride and compound **XIII** [9]. Obviously, in this case the isothiocyanato group is replaced by C-centered nucleophile, followed by intramolecular nucleophilic substitution of the *ortho*-fluorine atom.

Thus we have demonstrated that 2-hetarylamino-substituted fluorinated 1,3-benzothiazin-4-ones **IV** can be synthesized from tetra(penta)fluorobenzoyl isothiocyanate and the corresponding hetarylamine and revealed some specificity of the aminodefluorination of compounds **IV**. In addition, examples of facile replacement of the isothiocyanato group by aminoazoles have been described.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker WM-250 (250.14 MHz) and Bruker DRX-400 spectrometers (400.13 MHz). The ^{19}F NMR spectra were obtained on a Bruker DRX-500 instrument at 376.45 MHz. The chemical shifts were measured relative to tetramethylsilane (^{1}H) and hexafluorobenzene (^{19}F) as intermal references; DMSO-d_6 was used

Scheme 3.



as solvent. The mass spectra were run on a Varian MAT 311A spectrometer (electron impact, 70 eV; accelerating voltage 3 kV; cathode emission current 300 μA; direct sample admission into the ion source).

1-(2-Pyridyl)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIIa). A solution of 0.23 g (3 mmol) of ammonium thiocyanate in 7 ml of acetonitrile was added to a solution of 0.64 g (3 mmol) of tetrafluorobenzoyl chloride in 2.5 ml of toluene. The mixture was heated for 5 min at 40°C and filtered from ammonium chloride, the filtrate was added to a solution of 0.28 g (3 mmol) of pyridin-2-amine in 5 ml of acetonitrile, the mixture was stirred for 3 h at room temperature and evaporated, and the residue was washed with ethanol and recrystallized from ethanol. Yield 0.88 g (89%), mp 142–144°C. ^{1}H NMR spectrum, δ, ppm: 7.22 d.d (5-H, ^3J = 8.2, 5.0 Hz), 7.65 m (6'-H), 7.84 t.d (4-H, ^3J = 8.2, ^4J = 1.8 Hz), 8.38 d (6-H, ^3J = 5.0 Hz), 8.73 m (3-H), 11.9 br.s (1H, NH), 12.7 br.s (1H, NH). Found, %: C 47.38; H 2.10; N 12.81. $C_{13}H_7F_4N_3OS$. Calculated, %: C 47.42; H 2.13; N 12.77.

Compounds **IIIb**–**IIIj** were synthesized in a similar way.

3-Pentafluorobenzoyl-1-(2-pyridyl)thiourea (IIIb). Yield 87%, mp 138–140°C. ^{1}H NMR spectrum, δ, ppm: 7.24 d.d (5-H, ^3J = 7.3, 6.0 Hz), 7.86 t.d (4-H, ^3J = 7.3, ^4J = 2.3 Hz), 8.42 d (6-H, ^3J = 6.0 Hz), 8.75 m (3-H), 12.5 br.s (2H, NH). Found, %: C 45.00; H 1.76; N 12.08. $C_{13}H_6F_5N_3OS$. Calculated, %: C 44.96; H 1.73; N 12.10.

1-(6-Methylpyridin-2-yl)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIIc). Yield 82%, mp 120–122°C. ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 7.06 d (5-H, ^3J = 7.0 Hz), 7.64 m (6'-H), 7.70 t (4-H, ^3J = 7.5 Hz), 8.63 m (3-H), 11.8 br.s (1H, NH), 12.6 br.s (1H, NH). Found, %: C 46.84; H 2.54; N 11.68. $C_{14}H_9F_4N_3OS$. Calculated, %: C 46.80; H 2.51; N 11.70.

1-(6-Methylpyridin-2-yl)-3-pentafluorobenzoylthiourea (IIId). Yield 81%, mp 124–126°C. ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 7.17 d (5-H, ^3J = 7.0 Hz), 7.83 t (4-H, ^3J = 7.9 Hz), 8.51 m (3-H), 12.3 br.s (1H, NH), 12.7 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 361 $[M]^+$ (21), 341 (22), 195 (100), 167 (42), 151 (14), 150 (22), 134 (37), 133 (95), 117 (22), 108 (70), 93 (12), 92 (66), 91 (16), 81 (29), 80 (26), 66 (13), 65 (40). Found, %: C 46.51; H 2.19; N 11.66. $C_{14}H_8F_5N_3OS$. Calculated, %: C 46.54; H 2.22; N 11.63.

1-(Pyrimidin-2-yl)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIIe). Yield 84%, mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 7.28 t (5-H, ^3J = 4.8 Hz), 7.66 m (6'-H), 8.71 d (4-H, 6-H, ^3J = 4.8 Hz), 12.1 br.s (1H, NH), 13.0 br.s (1H, NH). Found, %: C 43.61; H 1.79; N 17.01. $C_{12}H_6F_4N_4OS$. Calculated, %: C 43.64; H 1.82; N 16.97.

1-Pentafluorobenzoyl-3-(pyrimidin-2-yl)thiourea (IIIf). Yield 69%, mp 242–244°C. ^{1}H NMR spectrum, δ, ppm: 7.30 t (5-H, ^3J = 5.0 Hz), 8.76 d (4-H, 6-H, ^3J = 5.0 Hz), 12.2 br.s (1H, NH), 13.2 br.s (1H, NH). Found, %: C 41.41; H 1.39; N 16.06. $C_{12}H_5F_5N_4OS$. Calculated, %: C 41.38; H 1.44; N 16.09.

1-(4,6-Dimethylpyrimidin-2-yl)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIIg). Yield 89%, mp 165–167°C. ^{1}H NMR spectrum, δ, ppm: 2.44 s (6H, CH_3), 6.99 s (5-H), 7.69 m (6'-H), 11.5 br.s (1H, NH), 13.8 br.s (1H, NH). Found, %: C 46.90; H 2.75; N 15.66. $C_{14}H_{10}F_4N_4OS$. Calculated, %: C 46.93; H 2.79; N 15.64.

1-(4,6-Dimethylpyrimidin-2-yl)-3-pentafluorobenzoylthiourea (IIIh). Yield 86%, mp 241–243°C. ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 2.47 s (3H, CH_3), 7.03 s (5-H), 11.7 br.s (1H, NH), 13.9 br.s (1H, NH). Found, %: C 44.71; H 2.42; N 14.87. $C_{14}H_9F_5N_4OS$. Calculated, %: C 44.68; H 2.39; N 14.89.

1-(5-Methyl-1*H*-pyrazol-3-yl)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIIi). Yield 87%, mp 202–204°C. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 6.82 s (4-H), 7.61 m (6'-H), 11.7 br.s (1H, NH), 12.3 br.s (1H, NH), 12.5 br.s (1H, NH). Found, %: C 43.40; H 2.42; N 16.85. $C_{12}H_8F_4N_4OS$. Calculated, %: C 43.37; H 2.41; N 16.87.

1-(5-Phenyl-1*H*-pyrazol-3-yl)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (IIIj). Yield 75%, mp 226–228°C. ^{1}H NMR spectrum, δ, ppm: 6.47 s (4-H), 7.34 m (1H, C_6H_5), 7.43 m (2H, C_6H_5), 7.68 m (6'-H), 7.72 m (2H, C_6H_5), 11.8 br.s (1H, NH), 12.7 br.s (1H, NH), 13.2 br.s (1H, NH). Found, %: C 51.82; H 2.57; N 14.18. $C_{17}H_{10}F_4N_4OS$. Calculated, %: C 51.78; H 2.54; N 14.21.

6,7,8-Trifluoro-2-(pyridin-2-ylamino)-1,3-benzothiazin-4-one (IVa). *a*. Thiourea **IIIa**, 0.25 g (0.8 mmol), was dispersed in 6 ml of toluene, 0.22 ml (1.6 mmol) of triethylamine was added, the mixture was heated for 3 h under reflux and evaporated, and the residue was washed with water and recrystallized from ethanol. Yield 0.15 g (61%), mp 202–204°C.

^{1}H NMR spectrum, δ, ppm: 7.16 d.d.d (5'-H, ^3J = 8.0, 5.0, ^4J = 0.5 Hz), 7.29 d.d (3'-H, ^3J = 8.0, ^4J = 0.5 Hz), 7.81 t.d (4'-H, ^3J = 8.0, ^4J = 1.5 Hz), 7.97 d.d.d (5-H, ^3J = 9.8, ^4J = 7.5, ^5J = 2.3 Hz), 8.41 d.d (6'-H, ^3J = 5.0, ^4J = 1.5 Hz), 12.2 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: 10.12 m (1F), 26.20 m (1F), 27.37 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$ (30), 308 (19), 190 (19), 162 (23), 119 (100), 78 (35). Found, %: C 50.53; H 1.97; N 13.55. $C_{13}H_6F_3N_3OS$. Calculated, %: C 50.49; H 1.94; N 13.59.

Compounds **IVc**, **IVd**, **IVi**, and **IVj** were synthesized in a similar way. In the synthesis of **IVi** and **IVj**, the reaction mixture was heated under reflux for 6 h. Compounds **IVd** and **IVj** were recrystallized from DMSO.

6,7,8-Trifluoro-2-(6-methylpyridin-2-ylamino)-1,3-benzothiazin-4-one (IVc). Yield 70%, mp 216–218°C. ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 7.00 d (5'-H, ^3J = 7.8 Hz), 7.10 d (3'-H, ^3J = 4.6 Hz), 7.69 d.d (4'-H, ^3J = 7.8, 4.6 Hz), 7.97 d.d.d (5-H, ^3J = 10.0, ^4J = 7.6, ^5J = 2.1 Hz), 11.7 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 323 $[M]^+$ (21), 322 (14), 190 (9), 162 (13), 134 (9), 133 (100), 92 (24), 91 (10), 69 (11), 65 (14). Found, %: C 52.04; H 2.52; N 12.97. $C_{14}H_8F_3N_3OS$. Calculated, %: C 52.01; H 2.48; N 13.00.

5,6,7,8-Tetrafluoro-2-(6-methylpyridin-2-ylamino)-1,3-benzothiazin-4-one (IVd). Yield 73%, mp 217–219°C. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 6.96 d (5'-H, ^3J = 7.7 Hz), 7.17 d (3'-H, ^3J = 4.5 Hz), 7.67 d.d (4'-H, ^3J = 7.7, 4.5 Hz), 12.1 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 341 $[M]^+$ (17), 133 (100), 92 (24), 65 (13). Found, %: C 49.31; H 2.08; N 12.29. $C_{14}H_7F_4N_3OS$. Calculated, %: C 49.27; H 2.05; N 12.32.

6,7,8-Trifluoro-2-(5-methyl-1*H*-pyrazol-3-ylamino)-1,3-benzothiazin-4-one (IVi). Yield 66%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 5.79 s (4'-H), 7.98 d.d.d (5-H, ^3J = 9.8, ^4J = 6.8, ^5J = 2.0 Hz), 12.0 br.s (1H, NH), 12.2 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 312 $[M]^+$ (45), 191 (13), 190 (13), 162 (15), 122 (100), 121 (11). Found, %: C 46.13; H 2.22; N 17.99. $C_{12}H_7F_3N_4OS$. Calculated, %: C 46.15; H 2.24; N 17.95.

6,7,8-Trifluoro-2-(5-phenyl-1*H*-pyrazol-3-ylamino)-1,3-benzothiazin-4-one (IVj). Yield 66%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 6.43 s (4'-H), 7.32 m (1H, C_6H_5), 7.42 m (2H, C_6H_5), 7.72 m (2H, C_6H_5), 7.98 d.d.d (5-H, ^3J = 9.9, ^4J = 7.8, ^5J = 2.2 Hz), 11.8 br.s (1H, NH), 13.2 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 374 $[M]^+$ (42), 185 (13), 184 (100), 162 (11), 77 (10). Found, %: C 54.51; H 2.38; N 14.96. $C_{17}H_9F_3N_4OS$. Calculated, %: C 54.55; H 2.41; N 14.97.

b. A solution of 0.3 g (0.9 mmol) of thiourea **IIIa** in 3 ml of DMSO was heated for 3 min at the boiling point, and the precipitate of **IVa** was filtered off and recrystallized from DMSO. Yield 0.25 g (90%).

Compounds **IVb**–**IVh** were synthesized in a similar way. Yield of **IVc** 87%, yield of **IVd** 88%.

5,6,7,8-Tetrafluoro-2-(pyridin-2-ylamino)-1,3-benzothiazin-4-one (IVb). Yield 88%, mp 220–222°C. ^{1}H NMR spectrum, δ, ppm: 7.14 d.d.d (5'-H, ^3J = 7.8, 5.0, ^4J = 0.8 Hz), 7.29 d.d (3'-H, ^3J = 7.8, ^4J = 0.8 Hz), 7.79 t.d (4'-H, ^3J = 7.8, ^4J = 1.5 Hz), 8.38 d.d (6'-H, ^3J = 5.0, ^4J = 1.5 Hz), 12.2 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: 5.52 m (1F), 13.11 m (1F), 20.97 m (1F), 25.40 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 327 $[M]^+$ (28), 326 (15), 208 (21), 180 (22), 120 (12), 119 (100), 78 (56), 51 (12). Found, %: C 47.73; H 1.55; N 12.80. $C_{13}H_5F_4N_3OS$. Calculated, %: C 47.71; H 1.53; N 12.84.

6,7,8-Trifluoro-2-(pyrimidin-2-ylamino)-1,3-benzothiazin-4-one (IVe). Yield 89%, mp 262–264°C. ^{1}H NMR spectrum, δ, ppm: 7.27 t (5'-H, ^3J = 4.9 Hz), 8.02 d.d.d (5-H, ^3J = 10.0, ^4J = 7.7, ^5J = 2.2 Hz), 8.78 d (4'-H, 6'-H, ^3J = 4.9 Hz), 12.5 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: 10.09 m (1F), 27.35 m (1F), 27.92 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 310 $[M]^+$ (40), 191 (13), 190 (100), 162 (43), 120 (25). Found, %: C 46.39; H 1.58; N 18.08. $C_{12}H_5F_3N_4OS$. Calculated, %: C 46.41; H 1.61; N 18.05.

5,6,7,8-Tetrafluoro-2-(pyrimidin-2-ylamino)-1,3-benzothiazin-4-one (IVf). Yield 87%, mp 279–281°C. ^{1}H NMR spectrum, δ, ppm: 7.25 t (5'-H, ^3J = 5.0 Hz), 8.75 d (4'-H, 6'-H, ^3J = 5.0 Hz), 12.4 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: 6.05 m (1F), 13.78 m (1F), 21.19 m (1F), 25.52 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 328 $[M]^+$ (40), 209 (12), 208 (100), 180 (38), 148 (12), 120 (54). Found, %: C 43.90; H 1.26; N 17.05. $C_{12}H_4F_4N_4OS$. Calculated, %: C 43.87; H 1.23; N 17.06.

2-(4,6-Dimethylpyrimidin-2-ylamino)-6,7,8-trifluoro-1,3-benzothiazin-4-one (IVg). Yield 85%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 2.48 s (3H, CH_3), 2.51 s (3H, CH_3), 6.96 s (5'-H), 7.98 d.d.d (5-H, ^3J = 9.8, ^4J = 6.8, ^5J = 2.0 Hz), 12.2 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: 9.45 m (1F), 25.27 m (1F), 27.68 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 338 $[M]^+$ (39), 190 (63), 162 (30), 149 (10), 148 (100), 107

(16), 68 (12), 67 (15). Found, %: C 49.73; H 2.68; N 16.54. $C_{14}H_9F_3N_4OS$. Calculated, %: C 49.70; H 2.66; N 16.57.

2-(4,6-Dimethylpyrimidin-2-ylamino)-5,6,7,8-tetrafluoro-1,3-benzothiazin-4-one (IVh). Yield 84%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 2.62 s (3H, CH_3), 6.95 s (5'-H), 12.2 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 356 $[M]^+$ (31), 208 (65), 180 (21), 148 (100), 107 (15), 68 (12), 67 (16). Found, %: C 47.21; H 2.28; N 15.70. $C_{14}H_8F_4N_4OS$. Calculated, %: C 47.19; H 2.25; N 15.73.

6,8-Difluoro-2,7-dimorpholino-1,3-benzothiazin-4-one (Va). Benzothiazinone **IVa**, 0.28 g (0.89 mmol), was dissolved in 5 ml of DMF, 0.35 ml (0.35 g, 4 mmol) of morpholine was added to the solution, the mixture was heated for 5 h under reflux, cooled, and diluted with water, and the precipitate was filtered off and recrystallized from DMSO. Yield 0.25 g (77%), mp >250°C. ^{1}H NMR spectrum, δ, ppm: 3.27 m (4H, NCH_2), 3.72 m (8H, NCH_2, OCH_2), 3.83 m (4H, OCH_2), 7.70 d.d (5-H, ^3J = 12.5, ^5J = 1.8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 369 $[M]^+$ (55), 327 (10), 257 (100), 215 (10), 199 (55). Found, %: C 51.94; H 4.58; N 11.44. $C_{16}H_{17}F_2N_3O_3S$. Calculated, %: C 52.03; H 4.64; N 11.38.

Diethyl 4,4'-(6,8-difluoro-4-oxo-4*H*-1,3-benzothiazine-2,7-diyl)bis(piperazine-1-carboxylate) (Vb) was synthesized in a similar way. Yield 67%, mp 245–247°C. ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3), 1.25 t (3H, CH_3), 3.28 m (4H, NCH_2), 3.53 m (4H, NCH_2), 3.58 m (4H, NCH_2), 3.87 m (4H, NCH_2), 4.07 q (2H, OCH_2), 4.11 q (2H, OCH_2), 7.72 d.d (5-H, ^3J = 12.5, ^5J = 1.8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 511 $[M]^+$ (35), 398 (14), 397 (24), 396 (43), 384 (15), 383 (71), 328 (21), 313 (14), 308 (17), 226 (18), 214 (21), 213 (17), 199 (22), 141 (17), 128 (16), 115 (15), 84 (12), 70 (14), 57 (11), 56 (100). Found, %: C 51.72; H 5.37; N 13.61. $C_{22}H_{27}F_2N_5O_5S$. Calculated, %: C 51.66; H 5.32; N 13.69.

The reaction of benzothiazinone **IVc** with morpholine gave compound **Va** in 74% yield, and with ethyl piperazine-1-carboxylate, compound **Vb** in 71% yield.

6,8-Difluoro-7-morpholino-2-(pyrimidin-2-ylamino)-1,3-benzothiazin-4-one (VIa). Morpholine, 0.35 ml (0.35 g, 4 mmol), was added to a solution of 0.31 g (1.0 mmol) of compound **IVe** in 5 ml of DMF, the mixture was heated for 5 h under reflux, cooled, and diluted with water, and the precipitate was filtered off and recrystallized from DMSO. Yield 0.29 g (77%), mp >250°C. ^{1}H NMR spectrum, δ, ppm: 3.33 m (4H, NCH_2), 3.74 m (4H, OCH_2), 3.83 m (4H, OCH_2), 6.76 t (5'-H, ^3J = 4.9 Hz), 7.72 d.d (5-H, ^3J = 12.3, ^5J = 1.6 Hz), 8.47 d (4'-H, 6'-H, ^3J = 4.9 Hz), 12.8 br.s (1H, NH). Found, %: C 50.96; H 5.48; N 18.53. $C_{16}H_{13}F_2N_5O_2S$. Calculated, %: C 50.93; H 3.45; N 18.57.

Ethyl 4-[6,8-difluoro-4-oxo-2-(pyrimidin-2-ylamino)-4*H*-1,3-benzothiazin-7-yl]piperazine-1-carboxylate (VIb) was synthesized in a similar way. Yield 79%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3), 3.30 m (4H, NCH_2), 3.52 m (4H, NCH_2), 4.08 q (2H, OCH_2), 6.77 t (5'-H, ^3J = 4.9 Hz), 7.75 d.d (5-H, ^3J = 12.3, ^5J = 1.6 Hz), 8.43 d (4'-H, 6'-H, ^3J = 4.9 Hz), 12.4 br.s (1H, NH). Found, %: C 50.86; H 3.99; N 18.77. $C_{19}H_{18}F_2N_6O_3S$. Calculated, %: C 50.89; H 4.02; N 18.75.

2,3,4,5-Tetrafluoro-*N*-(1,3-thiazol-2-yl)benzamide (VIIIa). A solution of 3 mmol of isothiocyanate **Ia** in acetonitrile (prepared as described above) was added to a solution of 0.32 g (3 mmol) of 1,3-thiazol-2-amine (**VIIa**) in 5 ml of acetonitrile, the mixture was stirred for 3 h at room temperature and evaporated, and the residue was recrystallized from ethanol. Yield 0.60 g (71%), mp 128–130°C. ^{1}H NMR spectrum, δ, ppm: 7.35 d (1H, 5-H, ^3J = 3.7 Hz), 7.58 d (1H, 4-H, ^3J = 3.7 Hz), 7.85 m (1H, 6'-H), 12.9 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 276 $[M]^+$ (19%), 257 (11), 248 (10), 177 (100), 149 (35), 99 (17). Found, %: C 43.55; H 1.52; N 10.08. $C_{10}H_4F_4N_2OS$. Calculated, %: C 43.49; H 1.46; N 10.14.

Compounds **VIIIb** and **VIIIc** were synthesized in a similar way.

***N*-(1,3-Benzothiazol-2-yl)-2,3,4,5-tetrafluorobenzamide (VIIIb).** Yield 75%, mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 7.37 m (1H, benzothiazole), 7.79 m (1H, benzothiazole), 7.92 m (1H, 6'-H), 7.99 m (1H, benzothiazole), 8.04 m (1H, benzothiazole), 13.2 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 326 $[M]^+$ (27%), 298 (11), 177 (100), 149 (29). Found, %: C 51.45; H 1.92; N 8.63. $C_{14}H_6F_4N_2OS$. Calculated, %: C 51.54; H 1.85; N 8.58.

***N*-(5,6-Difluoro-1,3-benzothiazol-2-yl)-2,3,4,5-tetrafluorobenzamide (VIIIc).** Yield 70%, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 7.91 d.d (1H, 4-H or 7-H, ^3J = 10.8, ^4J = 7.1 Hz), 8.21 d.d (1H, 7-H or 4-H, ^3J = 10.1, ^4J = 8.2 Hz), 7.92 m (1H, 6'-H), 13.3 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 362 (22) $[M]^+$, 177 (100), 149 (25). Found, %: C 46.47;

H 1.09; N 7.65. $C_{14}H_4F_6N_2OS$. Calculated, %: C 46.42; H 1.11; N 7.73.

***N*-(2,3-Dihydro-1*H*-benzimidazol-2-ylidene)-2,3,4,5-tetrafluorobenzamide (IX) and 1-(2,3-dihydro-1*H*-benzimidazol-2-ylidene)-3-(2,3,4,5-tetrafluorobenzoyl)thiourea (X).** A solution of 3 mmol of isothiocyanate **Ia** in acetonitrile (prepared as described above) was added to a solution of 0.4 g (3 mmol) of 1*H*-benzimidazol-2-amine (**VIId**) in 5 ml of acetonitrile, the mixture was stirred for 3 h at room temperature, and the precipitate (a mixture of compounds **IX** and **X**) was filtered off. Yield 0.62 g. ^{1}H NMR spectrum, δ, ppm: 7.08 m (2H, 5-H, 6-H in **X**), 7.15 m (2H, 5-H, 6-H in **IX**), 7.29 m (2H, 4-H, 7-H in **X**), 7.41 m (2H, 4-H, 7-H in **IX**), 7.56 m (1H, 6'-H in **X**), 7.75 m (1H, 6'-H in **IX**), 12.4 br.s (2H, NH in **IX**), 12.8 br.s (2H, NH in **X**), 14.1 br.s (1H, NH in **X**). Product ratio **IX**:**X** = 10:3.

2,3,4,5-Tetrafluoro-*N*-(1-naphthyl)benzamide (XII) was synthesized as described above for compound **VIIIa**. Yield 78%, mp 174–176°C. ^{1}H NMR spectrum, δ, ppm: 7.49 m (3H, naphthyl), 7.77 m (1H, 6'-H), 7.80 m (2H, naphthyl), 7.93 m (1H, naphthyl), 8.05 m (1H, naphthyl), 10.4 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 319 (44) $[M]^+$, 177 (100), 149 (20), 144 (38), 142 (17), 115 (61). Found, %: C 63.98; H 2.86; N 4.35. $C_{17}H_9F_4NO$. Calculated, %: C 63.95; H 2.82; N 4.39.

6,7,8-Trifluoro-2-methyl-4-oxo-*N*-phenyl-4*H*-chromene-3-carboxamide (XIV). A solution of 3 mmol of isothiocyanate **Ia** in acetonitrile (prepared as described above) was added to a solution of 0.53 g (3 mmol) of acetoacetanilide (**XI**) in 5 ml of acetonitrile, the mixture was stirred for 3 h at room temperature and evaporated, and the residue was recrystallized from ethanol. Yield 0.73 g (73%), mp 202–204°C. ^{1}H NMR spectrum, δ, ppm: 3.04 s (3H, CH_3), 7.13 t.t (1H, 4'-H, ^3J = 7.5, ^4J = 1.2 Hz), 7.35 m (2H, 3'-H, 5'-H, ^3J = 8.5, 7.5 Hz), 7.65 m (2H, 2'-H, 6'-H, ^3J = 8.5, ^4J = 1.2 Hz), 7.83 d.d.d (1H, 5-H, ^3J = 9.5, ^4J = 7.7, ^5J = 2.4 Hz), 11.32 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 333 (48) $[M]^+$, 316 (10), 242 (12), 241 (100), 175 (10), 93 (42), 67 (99). Found, %: C 61.24; H 3.05; N 4.32. $C_{17}H_{10}F_3NO_3$. Calculated, %: C 61.27; H 3.02; N 4.20.

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