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Fluoro-containing Heterocycles: XIII. Fluoro-containing Derivatives of Thiazolo[3,2-*a*]-, Benzothiazolo[3,2-*a*]-, and Benzimidazo[3,2-*a*]quinazolinones

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Abstract—Reactions of 2-aminothiazole, derivatives of 2-aminobenzothiazole and 2-aminobenzoimidazole with polyfluorobenzoyl chlorides gave rise to acylation products that at heating in the diphenyl ether formed fluoro-containing derivatives of thiazolo[3,2-*a*]-, benzothiazolo[3,2-*a*]-, and benzimidazo[3,2-*a*]quinazolinone.

In the last two decades the chemistry of fluoroquinolones and other fluoro-containing heterocycles has vigorously developed [2–6]. In the series of thiazolo-[3,2-*a*]-annelated fluoroquinolones and 1,8-naphthiridin-4-ones compounds were found possessing high antibacterial [7, 8], and also antitumor and antiviral activity [9]. [*a*]-Annelated quinazolinones which may be regarded as azaanalogs of [*a*]-annelated quinolones also demonstrated a wide range of biological activity [10, 11]. In the series of benzimidazo-annelated quinazolinones highly active immunosuppressors are also known [12].

The reaction of 2-halobenzoyl chlorides with *N,N*-dinucleo-philes is a convenient method of building up [*a*]- and [*b*]-annelated quinazolinones [13]. In publications [14–17] was described the application of this method to the synthesis of benzimidazo[3,2-*a*]-, benzothiazolo-[3,2-*a*]-, benzoxazolo[3,2-*a*]quinazolin-4-ones, and also of thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinazolin-4-ones, azaanalogs of thiazoloquinazolinones. We described the fluorinated imidazo[1,2-*a*]quinazoline-1,2-dicarbonitriles in [1]. However up till now no fluoro-containing derivatives of thiazolo-, benzothiazolo-, and benzimidazo-[*a*]-annelated quinazolinones were synthesized.

We demonstrated that acylation of 2-aminobenzothiazole derivatives **IIa–IIc** with polyfluorobenzoyl chlorides **Ia** and **Ib** in boiling toluene afforded polyfluoro-*N*-(benzothiazol-2-yl)benzamides **IIIa–IIIf** (Scheme 1). ^{1}H NMR spectra of compounds **IIIa–IIIf** confirm the presence of protons belonging to the benzothiazole fragment, NH group (broadened signal at δ 13.0–13.5 ppm), and also possess the characteristic multiplet of the singtle proton from the tetrafluorobenzene fragment (7.9 ppm) in the spectra of amides **IIIa**, **IIIc**, and **IIIe**. We failed to perform the cyclization of compounds **IIIa–IIIf** into tetracyclic derivatives **IVa–IVf** by heating in toluene with triethylamine, in dimethylformamide in the presence of cycloalkyl imines, or in acetonitrile using a strong base like 1,8-diazabicyclo[5.4.0]undec-1-ene, i.e., under conditions we had previously used in the synthesis of polycyclic fluoroquinolones and quinazolinones [1, 18, 19]. For instance, the heating of amide **IIIe** in DMF in the presence of cycloalkyl imines resulted only in the replacement of the $F^{4'}$ atom to yield compounds **VIa** and **VIb** whose stucture was confirmed by ^{1}H NMR and mass spectra (see EXPERIMENTAL).

However the heating of compounds **IIIa–IIIf** in the diphenyl ether proved to be an efficient procedure for the preparation of tetracyclic quinazolinones **IVa–IVf**. The structure of fluoro-containing benzothiazolo[3,2-*a*]quinazolin-4-ones **IVa–IVf** was confirmed by ^{1}H, ^{19}F NMR, and mass spectra. Thus in the ^{1}H NMR spectra are retained proton signals from the benzothiazole fragment, and a signal from the NH group is lacking; in the spectra of derivatives **IVa, IVc**, and **IVe** (Y = H) the multiplicity of the signal from H^5 is reduced to two doublets of doublets in the region of δ 8.0 ppm, and the ^{19}F NMR spectrum of compound **IVa** contains characteristic d.d.d from three fluorine atoms. The mass spectra of tetracyclic aromatic compounds **IVa–IVf** contain strong peaks of the molecular ions.

The boiling of compound **IVd** with pyrrolidine in DMF for 5 h resulted in formation of amino derivative **V** whose mass spectrum contained the molecular ion (100%), and in the ^{1}H NMR spectrum the signals from two pyrrolidine

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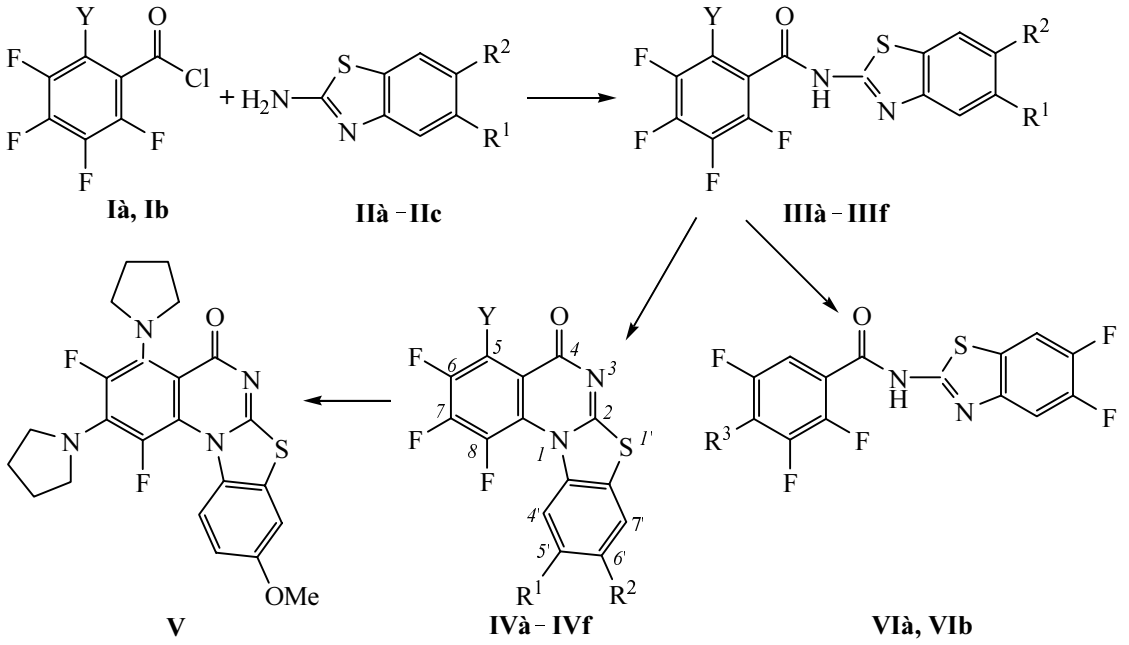
Scheme 1.

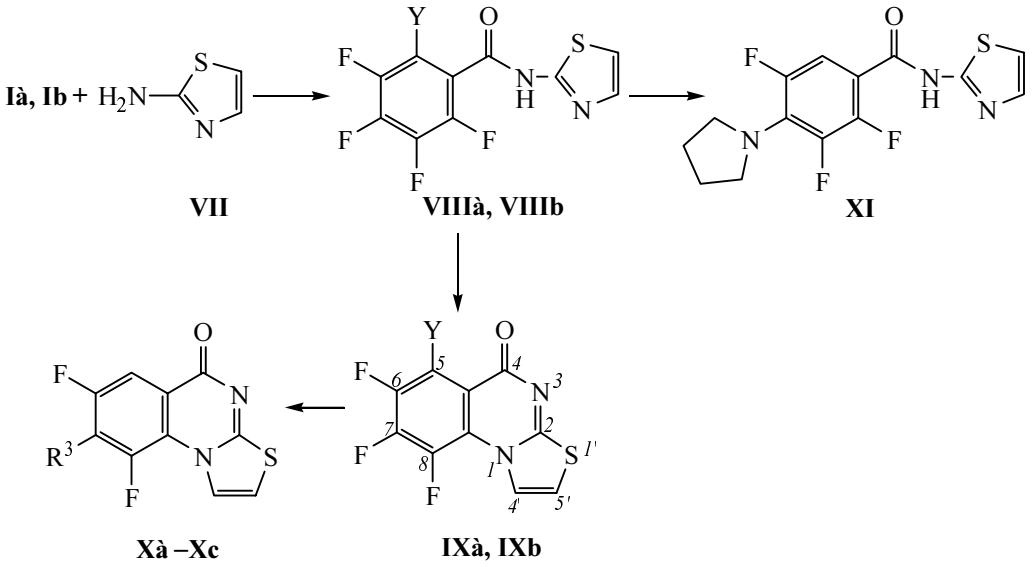


Ià, Ib **IIà – IIc** **IIIà – IIIf**

V **IVà – IVf** **VIà, VIb**

I, Y = H (**a**), F (**b**); **II**, $R^1 = R^2 = H$ (**a**), $R^1 = H$, $R^2 = OCH_3$ (**b**), $R^1 = R^2 = F$ (**c**); **III, IV**, $R^1 = R^2 = H$, Y = H (**a**), F (**b**); $R^1 = H$, $R^2 = OCH_3$, Y = H (**c**), F (**d**); $R^1 = R^2 = F$, Y = H (**e**), F (**f**); **VI**, R^3 = pyrrolidin-1-yl (**a**), morpholin-4-yl (**b**).

Scheme 2.



VII **VIIIà, VIIIb** **XI**

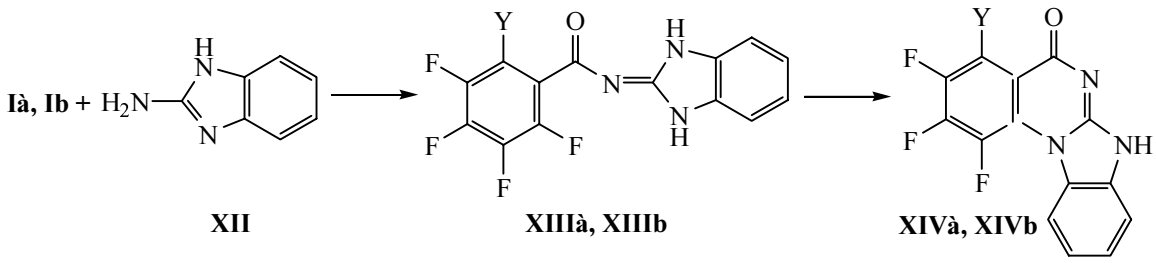
Xà –Xc **IXà, IXb**

VIII, IX, Y = H (**a**), F (**b**); X, R^3 = pyrrolidin-1-yl (**a**), morpholin-4-yl (**b**), 4-ethoxycarbonylpiperazin-1-yl (**c**).

moieties were observed. The substitution of F^5 and F^7 atoms in the tetrafluoro-substituted tetracyclic heterocycles we already mentioned in [20].

To annelate a thiazole ring to the [*a*]-edge of the quinazoline skeleton 2-aminothiazol (**VII**) was subjected to acylation with polyfluorobenzoyl chlorides **Ia** and **Ib** in boiling toluene yielding polyfluoro-*N*-(thiazol-2-yl)benzamides **VIIIa** and **VIIIb** (Scheme 2). The ^{1}H NMR spectra of amides **VIIIa** and **VIIIb** contain characteristic doublet signals from the protons of the thiazole fragment,

Scheme 2.



and a broadened one-proton singlet from the NH group; in the spectrum of amide **VIIIa** a characteristic multiplet from H^6 is present.

Heating of amides **VIIIa** and **VIIIb** in the diphenyl ether for 2 h same as in the case of benzothiazolyl derivatives of polyfluorinated benzamides **IIIa–IIIf** resulted in a thermal intramolecular cyclization to afford thiazolo-[3,2-*a*]quinazolin-4-ones **IXa** and **IXb**. In the ^{1}H NMR spectrum of compound **IXa** appeared a characteristic signal from H^5 as two doublets of doublets at δ 7.99 ppm, and in the spectra of compounds **IXa** and **IXb** were present the doublets belonging to the thiazole fragments and were absent the signals of NH groups. The intensity of molecular ions in their mass spectra reached 100%.

It was established that the boiling of (thiazol-2-yl)-benzamide **VIIIa** in DMF in the presence of pyrrolidine led not only to replacement of the F^4 atom by the amine moiety but also to an intramolecular cyclization. As a result a mixture of compounds **Xa** and **XI** was obtained in a ratio 5:4 (as shown by the ^{1}H NMR spectrum). Apparently due to the lower melting point of amide **VIIIa** compared to those of benzothiazolyl derivatives **IIIa–IIIf** the thermal cyclization of the former becomes possible in a lower boiling solvent than the diphenyl ether. Individual pyrrolidinyl drivative **Xa** was obtained at boiling thiazoloquinazolinone **IXa** with pyrrolidine in DMF. The other cycloalkylamines also are readily involved into the amino-defluorination reaction. The structures of the derivatives **Xa–Xc** obtained are confirmed by their ^{1}H NMR and mass spectra; the substitution of the F^7 atom is confirmed by appearance of the H^5 signal as a doublet of doublets with the coupling constants ^3J 11.6–13.8 and ^5J 1.5–1.8 Hz.

We applied one more *N,N*-dinucleophile: 2-aminobenzimidazole. The reaction of tetrafluorobenzoyl chloride (**Ia**) with 2-aminobenzimidazole (**XII**) in boiling toluene for 2 h or in dichloromethane in the presence of triethylamine at room temperature for 24 h afforded acyl derivative **XIIIa** (Scheme 3). The ^{1}H NMR spectrum of compound **XIIIa** contains a broadened singlet from two NH groups and two symmetric multiplets from the protons of the benzimidazole fragment in the region δ 7.15 and 7.41 ppm; basing on these data we ascribed an ylidene structure to compound **XIIIa**.

The heating of *N*-(1,3-dihydrobenzimidazol-2-ylidene)-2,3,4,5-tetrafluorobenzamide (**XIIIa**) in diphenyl ether for 3 h as previously had occurred with thiazolyl derivatives of polyfluorobenzamides **IIIa–IIIf** and **VIIIa, VIIIb** resulted in the thermal intramolecular cyclization affording benzimidazo[3,2-*a*]quinazolin-4-one **XIVa**. The reaction of pentafluorobenzoyl chloride (**Ib**) with aminobenzimidazole **XII** in dichloromethane in the presence of triethylamine at room temperature for 24 h resulted directly in tetracyclic derivative **XIVb**. Apparently intermediate **XIIIb** is very prone to cyclization. The higher reactivity in intramolecular cyclization of pentafluoro derivatives of benzoic acids compared to tetrafluoro derivatives was reported in [21, 22].

^{1}H NMR spectrum of compound **XIVa** contained a characteristic signal from H^5 as a doublet of doublets at δ 8.02 ppm. In the spectra of tetracylic derivatives **XIVa** and **XIVb** are observed the signals from a single NH group in the region 12.9–13.0 ppm; the signals from aromatic protons of the benzimidazole fragment are asymmetric, and in the spectrum of **XIVa** these signals are displaced downfield as compared to the corresponding peaks in the spectrum of the intermediate **XIIIa**. Molecular ion peaks are the most abundant in the mass spectra of compounds **XIVa** and **XIVb** (*m/z* 289 and 307 for compounds **XIVa** and **XIVb** respectively). No strong peaks of fragment ions are observed testifying to the stability of the tetracyclic aromatic system.

Hence this study led to preparation of new fluoro-containing thiazolo-, benzothiazolo-, and benzimidazo[*a*]-annelated quinazolinones.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker WM-250 and Bruker DRX-400 with operting frequencies 250.14 and 400.13 MHz respectively, ^{19}F NMR spectra were recorded on spectrometer Bruker DRX-500 at operating frequency 376.45 MHz. As internal references served TMS (^{1}H) and hexafluorobenzene (^{19}F), as solvent was used DMSO-d_6. Mass spectra were measured on Varian MAT 311A instrument at accelerating voltage 3kV, cathode emission current 300 μA, ionizing electrons energy 70 eV, direct sample admission into the ion source.

2,3,4,5-Tetrafluoro(benzothiazol-2-yl)benzamide (IIIa). To a dispersion of 0.7 g (4.7 mmol) of 2-aminobenzothiazole **IIa** in 10 ml of dry toluene was added 1.49 g (7 mmol) of 2,3,4,5-tetrafluorobenzoyl chloride (**Ia**). The reaction mixture was heated at reflux for 2 h, and on cooling the precipitate of compound **IIIa** was filtered off and recrystallized from ethanol. Yield 1.2 g (82%), mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 7.37 m (1H, benzothiazole), 7.79 m (1H, benzothiazole), 7.92 m (1H, C_6HF_4), 7.99 m (1H, benzothiazole), 8.04 m (1H, benzothiazole), 13.2 br.s (1H, NH). 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.

Compounds **IIIb–IIIf** were obtained similarly.

Pentafluoro(benzothiazol-2-yl)benzamide (IIIb). Yield 86%, mp > 230°C. ^{1}H NMR spectrum, δ, ppm: 7.39 m (1H, benzothiazole), 7.51 m (1H, benzothiazole), 7.81 m (1H, benzothiazole), 8.07 m (1H, benzothiazole), 13.5 br.s (1H, NH). Found, %: C 48.94; H… N 8.06. $C_{14}H_5F_5N_2OS$. Calculated, %: C 48.85; H 1.46; N 8.14.

2,3,4,5-Tetrafluoro(6-methoxybenzothiazol-2-yl)-benzamide (IIIc). Yield 77%, mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (3H, OCH_3), 7.08 d.d (1H, H^5, $^3J_{5,4}$ 8.8, $^4J_{5,7}$ 2.6 Hz), 7.63 d (1H, H^7, $^4J_{7,5}$ 2.6 Hz), 7.69 d (1H, H^4, $^3J_{4,5}$ 8.8 Hz), 7.91 m (1H, H^6), 13.0 br.s (1H, NH). Found, %: C 50.49; H 2.22; N 7.93. $C_{15}H_8F_4N_2O_2S$. Calculated, %: C 50.57; H 2.26; N 7.86.

Pentafluoro(6-methoxybenzothiazol-2-yl)benzamide (IIId). Yield 81%, mp 147–149°C. ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, OCH_3), 7.10 d.d (1H, H^5, $^3J_{5,4}$ 8.9, $^4J_{5,7}$ 2.6 Hz), 7.65 d (1H, H^7, $^4J_{7,5}$ 2.6 Hz), 7.72 d (1H, H^4, $^3J_{4,5}$ 8.9 Hz), 13.4 br.s (1H, NH). Found, %: C 48.21; H 1.95; N 7.39. $C_{15}H_7F_5N_2O_2S$. Calculated, %: C 48.14; H 1.89; N 7.48.

2,3,4,5-Tetrafluoro(5,6-difluorobenzothiazol-2-yl)-benzamide (IIIe). Yield 78%, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 7.91 d.d (1H, H^4 or H^7, ^3J 10.8, ^4J 7.1 Hz), 8.21 d.d (1H, H^7 or H^4, ^3J 10.1, ^4J 8.2 Hz), 7.92 m (1H, H^6), 13.3 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 362 (22) $[M]^+$, 177 (100), 149 (25.2). Found, %: C 46.47; H.… N 7.65. $C_{14}H_4F_6N_2OS$. Calculated, %: C 46.42; H 1.11; N 7.73.

Pentafluoro(5,6-difluorobenzothiazol-2-yl)-benzamide (IIIf). Yield 84%, mp 220–222°C. ^{1}H NMR spectrum, δ, ppm: 8.06 d.d (1H, H^4 or H^7, ^3J 10.3, ^4J 7.9 Hz), 8.25 d.d (1H, H^7 or H^4, ^3J 10.1, ^4J 8.0 Hz), 13.2 br.s (1H, NH). Found, %: C 44.29; H... N 7.31. $C_{14}H_3F_7N_2OS$. Calculated, %: C 44.22; H 0.79; N 7.37.

6,7,8-Trifluorobenzothiazolo[3,2-*a*]quinazolin-4-one (IVa). To 1.0 g (3.1 mmol) of amide **IIIa** was added 3 g of diphenyl ether, and the reaction mixture was boiled for 2 h. On cooling the precipitate of thiazoloquinazolinone **IVa** was filtered off, washed with 2-propanol, and recrystallized from DMSO. Yield 0.67 g (71%), mp 202–204°C. ^{1}H NMR spectrum, δ, ppm: 7.50 m (1H, benzothiazole), 7.59 m (1H, benzothiazole), 7.87 m (1H, benzothiazole), 8.04 m (2H, H^5, benzothiazole). Mass spectrum, *m/z* (I_{rel}, %): 306 (100) $[M]^+$, 305 (63), 278 (40), 220 (16), 139 (13). ^{19}F NMR spectrum, δ, ppm: 11.48 d.d.d (1F, F^7, $^3J_{FF}$ 22.9, $^3J_{FF}$ 20.2, $^4J_{FH}$ 8.0 Hz), 27.64 d.d.d (1F, F^6, $^3J_{FF}$ 22.9, $^3J_{FH}$ 9.7, $^4J_{FF}$ 6.5 Hz), 35.69 m (1F, F^8). Found, %: C 54.83; H 1.72; N 9.06. $C_{14}H_5F_3N_2OS$. Calculated, %: C 54.91; H 1.65; N 9.15.

Compounds **IVb–IVf** were obtained similarly.

5,6,7,8-Tetrafluorobenzothiazolo[3,2-*a*]quinazolin-4-one (IVb). Yield 72%, mp 218–220°C. ^{1}H NMR spectrum, δ, ppm: 7.49 m (1H, benzothiazole), 7.57 m (1H, benzothiazole), 7.78 m (1H, benzothiazole), 8.03 m (1H, benzothiazole). Mass spectrum, *m/z* (I_{rel}, %): 324 (100) $[M]^+$, 325 (19), 323 (45), 305 (19), 296 (37), 238 (20). ^{19}F NMR spectrum, δ, ppm: 4.05 m (1F), 14.46 m (1F), 21.02 m (1F), 29.18 m (1F). Found, %: C 51.79; H...N 8.71. $C_{14}H_4F_4N_2OS$. Calculated, %: C 51.86; H 1.24; N 8.64.

6,7,8-Trifluoro-62 -methoxybenzothiazolo[3,2-*a*]-quinazolin-4-one (IVc). Yield 76%, mp 230–232°C. ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OCH_3), 7.15 d.d (1H, H^{52}, $^3J_{52,42}$ 9.3, $^4J_{52,72}$ 2.7 Hz), 7.69 d (1H, H^{72}, $^4J_{72,52}$ 2.7 Hz), 7.80 d.d (1H, H^{42}, $^3J_{42,52}$ 9.3, $^5J_{42,72}$ 2.1 Hz), 8.03 d.d.d (H^5, ^3J 9.8, ^4J 7.8, ^5J 2.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 336 (100) $[M]^+$, 337 (19), 335 (25), 321 (11), 293 (15), 278 (15), 207 (12). Found, %: C 53.51; H 2.04; N 8.38. $C_{15}H_7F_3N_2O_2S$. Calculated, %: C 53.57; H 2.10; N 8.33.

5,6,7,8-Tetrafluoro-62 -methoxybenzothiazolo-[3,2-*a*]-quinazolin-4-one (IVd). Yield 69%, mp 216–

218°C. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H, OCH_3), 7.14 m (1H), 7.72 m (2H). Mass spectrum, *m/z* (I_{rel}, %): 354 (100) $[M]^+$, 353 (21), 339 (13), 311 (23), 148 (15). Found, %: C 50.92; H 1.76; N 7.85. $C_{15}H_6F_4N_2O_2S$. Calculated, %: C 50.85; H 1.71; N 7.91.

6,7,8,52,62-Pentafluorobenzothiazolo[3,2-*a*]-quinazolin-4-one (IVe). Yield 67%, mp 226–228°C. ^{1}H NMR spectrum, δ, ppm: 8.04 d.d.d (H^5, ^3J 9.8, ^4J 7.6, ^5J 1.9 Hz), 8.17 d.d (1H, H^{42}, $^3J_{42,52}$ 10.5, $^4J_{42,62}$ 6.9, $^3J_{42,1}$ 1.5 Hz), 8.24 d.d (1H, H^{72}, $^3J_{72,62}$ 9.8, $^4J_{72,52}$ 8.0 Hz). Found, %: C 49.08; H...N 8.24. $C_{14}H_3F_5N_2OS$. Calculated, %: C 49.13; H 0.88; N 8.18.

5,6,7,8,52 ,62-Hexafluorobenzothiazolo[3,2-*a*]-quinazolin-4-one (IVf). Yield 65%, mp 165–167°C. ^{1}H NMR spectrum, δ, ppm: 8.12 m (1H, H^{42}), 8.23 d.d (1H, H^{72}, $^3J_{72,62}$ 10.0, $^4J_{72,52}$ 8.0 Hz). Found, %: C 46.64; H...N 7.83. $C_{14}H_2F_6N_2OS$. Calculated, %: C 46.68; H 0.66; N 7.78.

2,4-Bis(pyrrolidin-1-yl)-1,3-difluoro-62-methoxythiazol[3,2-*a*]quinazolin-4-one (V). To 0.45 g (1.3 mmol) of compound **IVa** in 5 ml of DMF was added 0.36 g (5.2 mmol) of pyrrolidine. The reaction mixture was boiled for 5 h, on cooling the solution was diluted with 15 ml of water, the precipitate of compound **V** was filtered off and recrystallized from acetonitrile. Yield 0.43 g (73%), mp 212–214°C. ^{1}H NMR spectrum, δ, ppm: 1.88 m [4H, $(CH_2)_2$], 1.95 m [4H, $(CH_2)_2$], 3.32 m [4H, $N(CH_2)_2$], 3.66 m [4H, $N(CH_2)_2$], 3.83 s (3H, OCH_3), 7.08 d.d (1H, H^{52}, $^3J_{52,42}$ 9.2, $^4J_{52,72}$ 2.7 Hz), 7.59 d (1H, H^{72}, $^4J_{72,52}$ 2.7 Hz), 8.73 d (1H, H^{42}, $^3J_{42,52}$ 9.2 Hz). Mass spectrum, *m/z* (I_{rel}, %): 456 (100) $[M]^+$, 428 (44), 413 (16), 387 (34), 386 (46), 228 (40), 70 (17). Found, %: C 60.62; H 4.93; N 12.19. $C_{23}H_{22}F_2N_4O_2S$. Calculated, %: C 60.51; H 4.86; N 12.27.

***N*-(5,6-Difluorobenzothiazol-2-yl)-2,3,5-trifluoro-4-(pyrrolidin-1-yl)benzamide (VIa).** To 0.8 g (2.2 mmol) of amide **IIIe** in 5 ml of DMF was added 0.62 ml (8.8 mmol) of pyrrolidine. The reaction mixture was boiled for 5 h and then cooled. The separated precipitate of compound **VIa** was filtered off and recrystallized from DMSO. Yield 0.67 g (81%), mp 265–267°C. ^{1}H NMR spectrum, δ, ppm: 1.93 m [4H, $(CH_2)_2$], 3.68 m [4H, $N(CH_2)_2$], 7.39 d.d.d (1H, $H^{6'}$, ^3J 14.8, ^4J 6.8, ^5J 2.3 Hz), 7.65 d. d (1H, H^4 or H^7, ^3J 11.5, ^4J 7.5 Hz), 7.95 d.d (1H, H^7 or H^4, ^3J 11.5, ^4J 7.5 Hz), 12.4 br.s (1H, NH). Found, %: C 57.67; H 3.27; N 11.12. $C_{18}H_{12}F_3N_3OS$. Calculated, %: C 57.59; H 3.22; N 11.19.

***N*-(5,6-Difluorobenzothiazol-2-yl)-2,3,5-trifluoro-4-(morpholin-4-yl)benzamide (VIb)** was obtained in the same way. Yield 79%, mp 257–259°C. ^{1}H NMR spectrum, δ, ppm: 3.29 m [4H, $N(CH_2)_2$], 3.73 m [4H, $O(CH_2)_2$], 7.44 d.d.d (1H, $H^{6'}$, ^3J 12.5, ^4J 6.3, ^5J 2.5 Hz), 7.67 d.d (1H, H^4 or H^7, ^3J 11.3, ^4J 7.5 Hz), 7.97 d.d (1H, H^7 or H^4, ^3J 10.0, ^4J 8.0 Hz), 12.7 br.s (1H, NH). Found, %: C 55.19; H 3.02; N 10.80. $C_{18}H_{12}F_3N_3O_2S$. Calculated, %: C 55.24; H 3.09; N 10.74.

2,3,4,5-Tetrafluoro(thiazol-2-yl)benzamide (VIIIa). To 0.5 g (5 mmol) of 2-aminothiazole **VII** in 10 ml of dry toluene was added 1.7 g (8 mmol) of tetrafluorobenzoyl chloride (**Ia**), the reaction mixture was heated at reflux for 2 h and filtered while hot. The precipitate of amide **VIIIa** separated on cooling was filtered off and recrystallized from ethanol. Yield 1.0 g (73%), mp 128–130°C. ^{1}H NMR spectrum, δ, ppm: 7.35 d (1H, H^5, ^3J 3.7 Hz), 7.58 d (1H, H^4, ^3J 3.7 Hz), 7.85 m (1H, $H^{6'}$), 12.9 br.s (1H, NH). 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.

Pentafluoro(thiazol-2-yl)benzamide (VIIIb) was similarly obtained. Yield 75%, mp 186–188°C. ^{1}H NMR spectrum, δ, ppm: 7.40 d (1H, H^5, ^3J 3.7 Hz), 7.59 d (1H, H^4, ^3J 3.7 Hz), 13.3 br.s (1H, NH). Found, %: C 40.78; H...N 9.57. $C_{10}H_3F_5N_2OS$. Calculated, %: C 40.83; H 1.03; N 9.52.

6,7,8-Trifluorothiazolo[3,2-*a*]quinazolin-4-one (IXa). To 1.0 g (3.6 mmol) of amide **VIIIa** was added 2.5 g of diphenyl ether, and the mixture was boiled for 2 h. On cooling the precipitate of thiazoloquinazolinone **IXa** was filtered off, washed with 2-propanol, and recrystallized from DMSO. Yield 0.64 g (69%), mp 246–248°C. ^{1}H NMR spectrum, δ, ppm: 7.42 d (H^{52}, ^3J 4.8 Hz), 7.99 d.d.d. (H^5, ^3J 10.1, ^4J 8.1, ^5J 2.3 Hz), 8.20 d (H^{42}, ^3J 4.8 Hz). Mass spectrum, *m/z* (I_{rel}, %): 256 (100) $[M]^+$, 228 (67), 170 (10), 157 (11), 130 (18), 58 (11). Found, %: C 46.95; H...N 10.87. $C_{10}H_3F_3N_2OS$. Calculated, %: C 46.88; H 1.18; N 10.93.

5,6,7,8-Tetrafluorothiazolo[3,2-*a*]quinazolin-4-one (IXb) was analogously prepared. Yield 64%, mp 248–250°C. ^{1}H NMR spectrum, δ, ppm: 7.45 d (H^{52}, ^3J 4.8 Hz), 8.21 d (H^{42}, ^3J 4.8 Hz). Mass spectrum, *m/z* (I_{rel}, %): 274 (100) $[M]^+$, 246 (80), 175 (10), 148 (28), 58 (13). Found, %: C 43.85; H…N 10.17. $C_{10}H_2F_4N_2OS$. Calculated, %: C 43.80; H 0.74; N 10.22.

6,8-Difluoro-7-(morpholin-4-yl)thiazol[3,2-*a*]-quinazolin-4-one (Xb). To 0.6 g (2.3 mmol) of compound **IXa** in 5.5 ml of DMF was added 0.76 ml (7.7 mmol) of morpholine. The reaction mixture was boiled for 5 h and then evaporated to a half of its volume. The separated

precipitate of derivative **Xb** was filtered off, washed with ethanol, and recrystallized from DMSO. Yield 0.6 g (81%), mp 280–282°C. ^{1}H NMR spectrum, δ, ppm: 3.33 m [4H, N(CH_2)$_2$], 3.74 m [4H, O(CH_2)$_2$], 7.36 d (H^{52}, ^3J 4.9 Hz), 7.68 m (H^5), 8.20 d (H^{42}, ^3J 4.9 Hz). Mass spectrum, *m/z* (I_{rel}, %): 323 (100) [*M*]$^+$, 265 (66), 237 (45), 118 (22). Found, %: C 51.93; H 3.38; N 13.07. $C_{14}H_{11}F_2N_3O_2S$. Calculated, %: C 52.01; H 3.43; N 13.00.

Compounds **Xa** and **Xc** were obtained in the similar way.

6,8-Difluoro-7-(pyrrolidin-1-yl)thiazol[3,2-*a*]-quinazolin-4-one (Xa). Yield 73%, mp 254–256°C. ^{1}H NMR spectrum, δ, ppm: 1.90 m [4H, (CH_2)$_2$], 3.67 m [4H, N(CH_2)$_2$], 7.32 d (H^{52}, ^3J 4.9 Hz), 7.56 d.d (H^5, ^3J 13.8, ^5J 1.8 Hz), 8.14 d (H^{42}, ^3J 4.9 Hz). Mass spectrum, *m/z* (I_{rel}, %): 307 (100) [*M*]$^+$, 306 (81), 265 (13), 223 (16), 221 (11). Found, %: C 54.77; H 3.72; N 13.61. $C_{14}H_{11}F_2N_3OS$. Calculated, %: C 54.72; H 3.67; N 13.67.

6,8-Difluoro-7-(4-ethoxycarbonylpiperazin-1-yl)thiazolo[3,2-*a*]quinazolin-4-one (Xc). Yield 78%, mp 230–232°C. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3), 3.30 m [4H, N(CH_2)$_2$], 3.52 m [4H, N(CH_2)$_2$], 4.08 q (2H, OCH_2), 7.36 d (H^{52}, ^3J 5.0 Hz), 7.69 d.d (H^5, ^3J 11.6, ^5J 1.5 Hz), 8.19 d (H^{42}, ^3J 5.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 394 (100) [*M*]$^+$, 379 (20), 293 (13), 292 (48), 266 (31), 265 (20), 252 (12), 238 (18), 56 (67). Found, %: C 51.82; H 4.13; N 14.17. $C_{17}H_{16}F_2N_4O_3S$. Calculated, %: C 51.77; H 4.09; N 14.21.

Mixture of 6,8-difluoro-7-(pyrrolidin-1-yl)-thiazolo[3,2-*a*]quinazolin-4-one (Xa) and *N*-(thiazol-2-yl)-2,3,5-trifluoro-4-(pyrrolidin-1-yl)benzamide (XI). To 0.5 g (1.6 mmol) of amide **VIIIa** in 5 ml of DMF was added 0.5 ml (6.4 mmol) of pyrrolidine. The reaction mixture was boiled for 5 h, on cooling the precipitate was filtered off and recrystallized from DMSO. ^{1}H NMR spectrum, δ, ppm: 1.87 m [4H, (CH_2)$_2$ (**XI**)], 1.91 m [4H, (CH_2)$_2$ (**Xa**)], 3.62 m [4H, N(CH_2)$_2$ (**XI**)], 3.67 m [4H, N(CH_2)$_2$ (**Xa**)], 7.27 d [1H, H^5, ^3J 3.6 Hz (**XI**)], 7.31 d [1H, H^2, ^3J 5.0 Hz (**Xa**)], 7.42 d.d.d [1H, $H^{6'}$, ^3J 14.6, ^4J 6.7, ^5J 2.2 Hz (**XI**)], 7.53 d [1H, H^4, ^3J 3.6 Hz (**XI**)], 7.55 d.d [1H, H^6, ^3J 13.5, ^5J 3.6 Hz (**Xa**)], 8.14 d [1H, H^1, ^3J 5.0 Hz (**Xa**)], 12.9 br.s [1H, NH (**XI**)]. The ratio of compounds **Xa** and **XI** was 5:4.

***N*-(1,3-Dihydrobenzimidazol-2-ylidene)-2,3,4,5-tetrafluorobenzamide (XIIIa).** *a.* To a dispersion of 0.5 g (3.8 mmol) of 2-aminobenzimidazol (**XII**) in 12 ml of anhydrous toluene was added a solution of 0.81 g (4 mmol) of tetrafluorobenzoyl chloride (**Ia**) in 2 ml of toluene. The reaction mixture was heated at reflux for 2 h; on cooling the separated precipitate of the acylation product **XIIIa** was filtered off and recrystallized from ethanol. Yield 1.0 g (85%), mp > 250°C. ^{1}H NMR spectrum, δ, ppm: 7.15 m (2H, H^5, H^6), 7.41 m (2H, H^4, H^7), 7.75 m (1H, $H^{6'}$), 12.4 br.s (2H, NH). Mass spectrum, *m/z* (I_{rel}, %): 309 (43%) [*M*]$^+$, 290 (29), 289 (28), 281 (19), 262 (17), 177 (100), 160 (20), 149 (35), 132 (15), 105 (24), 99 (13), 90 (10). Found, %: C 54.43; H 2.34; N 13.52. $C_{14}H_7F_4N_3O$. Calculated, %: C 54.38; H 2.28; N 13.59.

b. To a dispersion of 0.5 g (3.8 mmol) of 2-aminobenzimidazola (**XII**) in 12 ml of anhydrous dichloromethane was added a solution of 0.81 g (4 mmol) of tetrafluorobenzoyl chloride (**Ia**) in 2 ml of toluene and 1.2 ml (8 mmol) of triethylamine. The reaction mixture was left standing at room temperature for 24 h. The separated precipitate of the acylation product **XIIIa** was filtered off, washed with water, and recrystallized from DMSO. Yield 0.94 g (80%).

1'*H*-6,7,8-Trifluorobenzimidazo[3,2-*a*]quinazolin-4-one (XIVa). To 0.25 g (0.81 mmol) of compound **XIIIa** was added 1.5 ml of diphenyl ether, and the mixture was boiled for 2 h. On cooling the separated precipitate of compound **XIVa** was filtered off, washed with 2-propanol, and recrystallized from DMSO. Yield 0.17 g (72%), mp > 250°C. ^{1}H NMR spectrum, δ, ppm: 7.23–7.37 m (2H, H^{52}, H^{62}), 7.55 m (1H, H^{72}), 7.97 m (1H, H^{42}), 8.02 d.d.d (1H, H^5, ^3J 10.1, ^4J 8.3, ^5J 2.4), 12.9 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 289 (100%) [*M*]$^+$, 288 (12), 261 (26), 123 (12). Found, %: C 58.19; H 2.14; N 14.48. $C_{14}H_6F_3N_3O$. Calculated, %: C 58.14; H 2.09; N 14.53.

1'*H*-5,6,7,8-Tetrafluorobenzimidazo[3,2-*a*]-quinazolin-4-one (XIVb). To a dispersion of 0.5 g (3.8 mmol) of 2-aminobenzimidazole **XII** in 12 ml of anhydrous dichloromethane was added a solution of 0.88 g (4 mmol) of pentafluorobenzoyl chloride (**Ib**) in 2 ml of toluene and 1.2 ml (8 mmol) of triethylamine. The reaction mixture was left standing at room temperature for 24 h. The separated precipitate of compound **XIVb** was filtered off, washed with water, and recrystallized from DMSO. Yield 0.91 g (78%), mp > 250°C. ^{1}H NMR spectrum, δ, ppm: 7.31 m (1H, benzimidazole), 7.40 m (2H, benzimidazole), 8.38 m (1H, benzimidazole), 13.0 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %):

307 (100) $[M]^+$, 279 (14), 260 (11). Found, %: C 54.77; H 1.69; N 13.62. $C_{14}H_5F_4N_3O$. Calculated, %: C 54.72; H 1.63; N 13.68.

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