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Dedicated to Full Member of the Russian Academy of Sciences O. N. Chupakhin on his 75th anniversary

Fluorine-Containing Heterocycles: XVIII.* Monofluoro Derivatives of Quinazolines and 1,3-Benzothiazin-4-ones

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Abstract—5- and 7-Fluoro-substituted quinazolines and 1,3-benzothiazin-4-ones were synthesized starting from 2-amino-6-fluorobenzonitrile and mono- and difluoro-substituted benzoic acid derivatives. The reactivities of di- and tetrafluoro-substituted benzoyl chlorides and benzoyl isothiocyanates in cyclocondensations leading to fluorinated quinazolines and 1,3-benzothiazines were compared.

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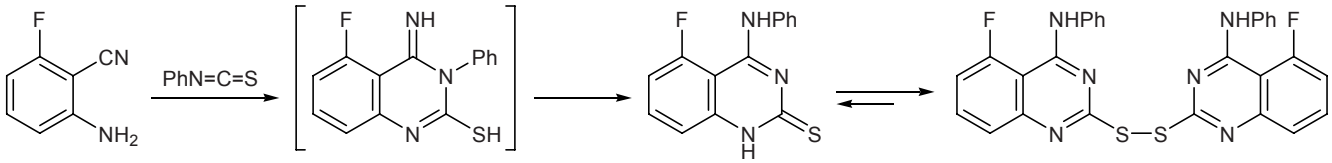
2-Substituted quinazolin-4-ones were classed with the base structural fragment of new drugs for the treatment of strokes, traumatic brain damages, and Parkinson's disease, which were reported at the XVIIth International Symposium on Medicinal Chemistry [2]. Compounds promising from the viewpoint of medicinal chemistry were found among quinazolinones and their derivatives containing a fluorine atom in the benzene ring. In particular, 5- and 7-fluoroquinazolin-4-ones exhibit antitumor activity [3, 4]. 4-Alkylsulfanyl- and 4-alkylaminoquinazolines having a fluorine atom in the 6-position were found to possess fungicidal and other kinds of biological activity [5, 6]. 5- and 7-Fluoro-1,3-benzothiazin-4-ones also attract interest [7] as sulfur analogs of monofluoro-substituted quinazolin-4-ones, but these compounds were poorly studied. On the other hand, we previously synthesized 6,7,8-trifluoro-1,3-benzothiazin-4-ones from polyfluorobenzoyl isothiocyanates and CH-active benzimidazoles or pyridines, and some of the products were found to exhibit moderate to high tuberculostatic activity [8]. Synthesis of their analogs having only one fluorine atom in the benzene ring seems to be promising from the viewpoint of reducing the toxicity of potential tuberculostatics.

We previously showed that 2-amino-6-fluorobenzonitrile (**I**) is a convenient starting compound for the synthesis of 2-substituted 5-fluoroquinazolin-4(1*H*)-ones [9]. The reaction of compound **I** with phenyl isothiocyanate was studied (Scheme 1). The product obtained by heating the reactants for 3 h at 100°C was characterized by ^{1}H NMR and mass spectra. The ^{1}H NMR spectrum contained signals from aromatic protons, a doublet from NH proton in the arylamino

Scheme 1.



I **IIa** **IIb**

* For communication XVII, see [1].

group (δ 9.05 ppm, ^4J = 14.9 Hz), and a one-proton signal at δ 12.7 ppm, which may be assigned to the thioamide NH proton. In the electron-impact mass spectrum of the product, the base peak was that with *m*/*z* 270; also, a strong fragment ion peak resulting from elimination of SCN from the former was present (*m*/*z* 213). These findings led us to assign the structure of 5-fluoro-4-phenylaminoquinazoline-2(1*H*)-thione (**IIa**) to the isolated compound [9]. However, more recent X-ray diffraction data showed that this compound in crystal has the structure of disulfide **IIb** (Fig. 1). Molecule **IIb** consists of two quinazoline fragments linked through a disulfide bridge. One quinazoline fragment is planar (deviations of its atoms from the mean-square plane do not exceed 0.035 Å), whereas the phenylamino group in the second quinazoline fragment declines from the quinazoline plane (the dihedral angle between the mean-square planes of the corresponding rings is 30.3°). The observed difference is related to paired π–π interaction involving the quinazoline ring in one part of the molecule (the distance between the interacting planes [*x*, *y*, *z*] and [1 – *x*, 1 – *y*, –*z*] is 3.5 Å), which does not occur in the second part. In all other respects, the quinazoline fragments are characterized by similar structures (the corresponding bond lengths and bond angles are almost equal, and they approach standard values). The C^2–C^3 and C^{16}–C^{17} bonds are appreciably extended [1.446(2) Å] due to electron-withdrawing effect of nitrogen atoms in the quinazoline ring and negative inductive effect of the nitrogen atom in the phenylamino group. The structure of molecule **IIb** is shown in Fig. 1, and a fragment of crystal packing is shown in Fig. 2.

The IR spectrum of disulfide **IIb** contained an absorption band at 440 cm^{-1}, which may be assigned to vibrations of the disulfide group [10]. Compound **IIb** displayed in the chemical ionization mass spectrum the molecular ion peak with *m*/*z* 541 and a peak from ion with *m*/*z* 271, resulting from cleavage of the disulfide S–S bond.

Likewise, the structure of 5-fluoro-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**IVa**) was assigned to the product obtained by us previously by reaction of 2-amino-6-fluorobenzoic acid with *N*-phenylthiourea [9] (Scheme 2). The ^{1}H NMR spectrum of this compound, apart from signals belonging to aromatic protons, contained a signal at δ 13.0 ppm, which may be attributed to NH proton in the thiolactam fragment. However, the IR and mass spectral data led us to presume disulfide structure **IVb**. In the IR spectrum of **IVb** we observed an absorption band at

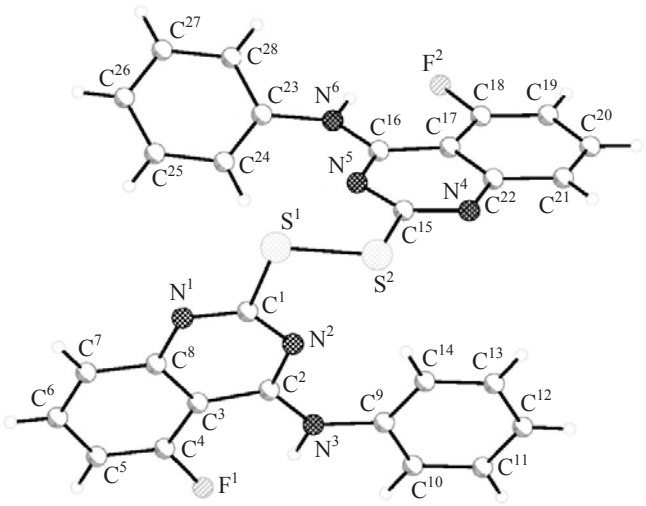


Fig. 1. Structure of the molecule of 2,2′-dithiobis(5-fluoro-4-phenylaminoquinazoline) (**IIb**) according to the X-ray diffraction data.

445 cm^{-1}, which is likely to arise from vibrations of the disulfide group (as in the IR spectrum of **IIb**). Compound **IVb** displayed the molecular ion peak (*m*/*z* 543) in the chemical ionization mass spectrum, and the main fragmentation pathway was cleavage of the S–S bond (*m*/*z* 271).

Summarizing the ^{1}H NMR, IR, X-ray diffraction, and mass spectral data for compounds **II** and **IV**, we can conclude that the disulfide structure in solution is

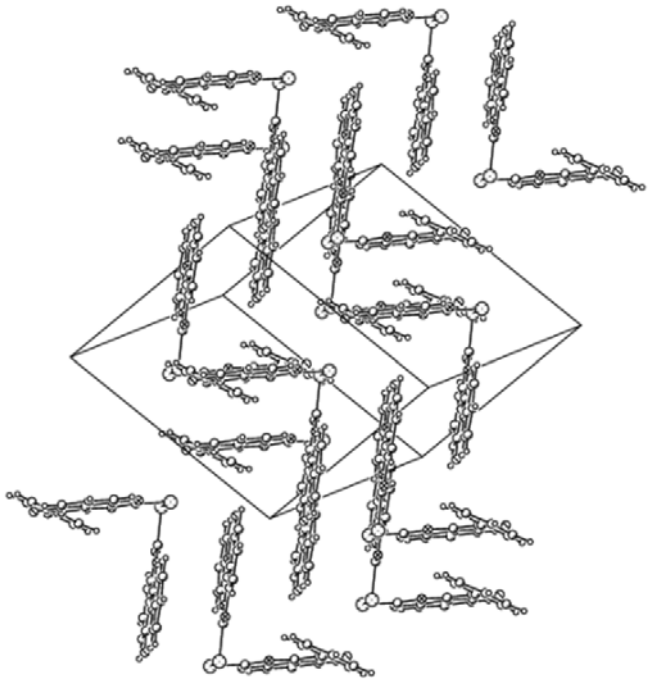
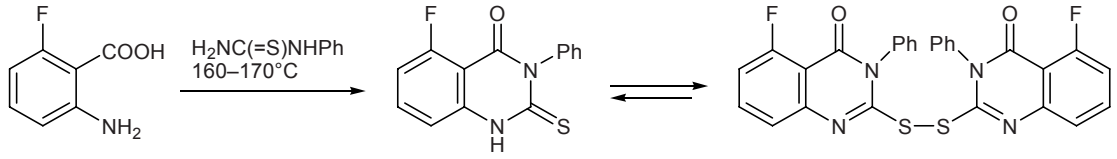


Fig. 2. A fragment of crystal packing of 2,2′-dithiobis-(5-fluoro-4-phenylaminoquinazoline) (**IIb**).

Scheme 2.



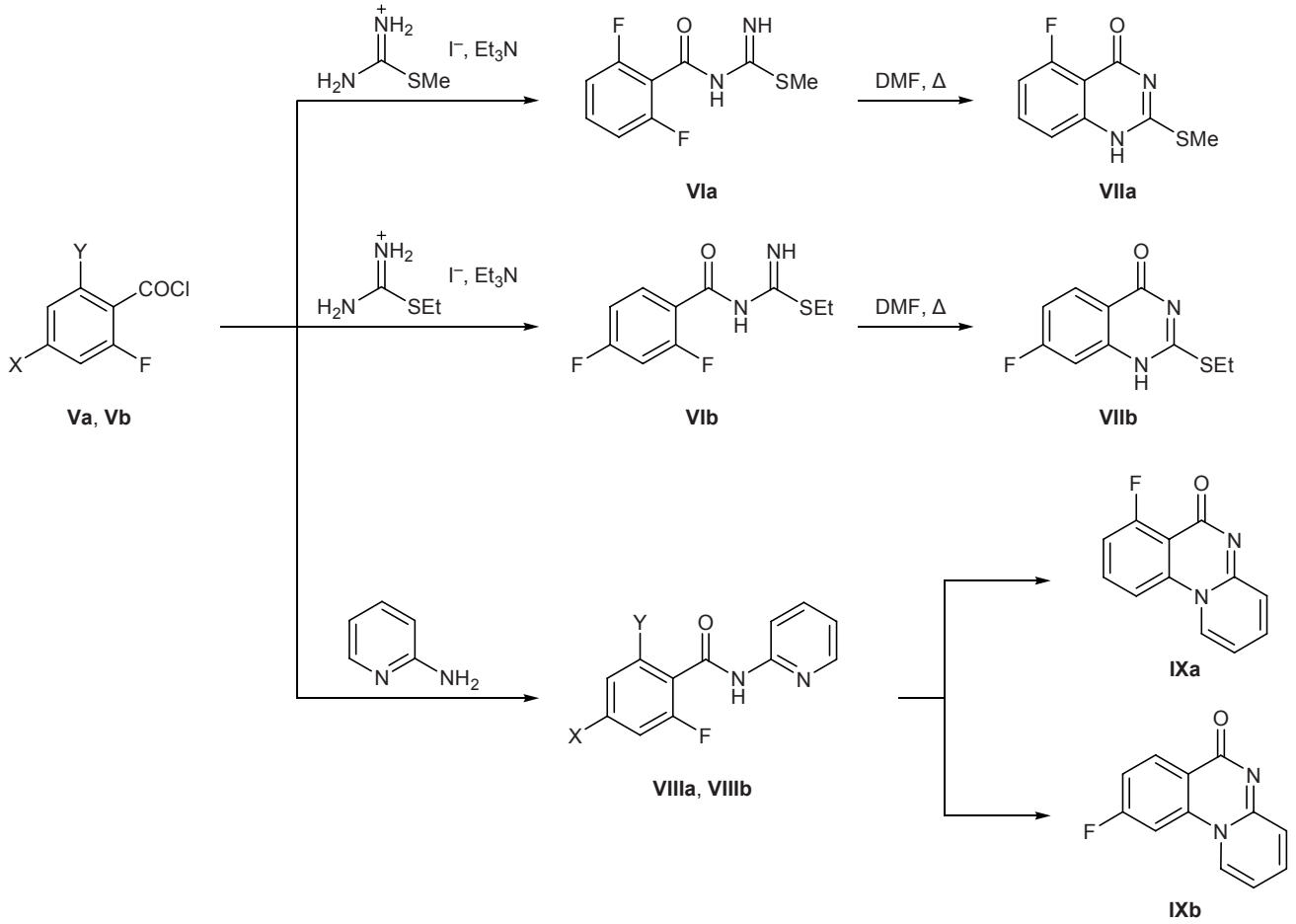
III **IVa** **IVb**

fairly labile; in proton-donor solvent (or in the presence of traces of water) it is converted into thiol form which exists in equilibrium with the thione tautomer.

The presence of an alkylsulfanyl group in position *2* of quinazolinones makes the formation of disulfide structure impossible; Moreover, 2-alkylsulfanyl derivatives can be readily modified at the 2-position via nucleophilic substitution reactions. We have synthesized 5-fluoro-2-methylsulfanyl- and 2-ethylsulfanyl-7-fluoroquinazolin-4(1*H*)-ones **VIIa** and **VIIb** according to the procedure described previously [9], which was based on cyclocondensation of tetrafluorobenzoyl chloride with *S*-alkylisothioureas as N,N-binucleophiles (Scheme 3). By carrying out the reactions of benzoyl chlorides **Va** and **Vb** with *S*-alkylisothiuronium iodides at room temperature in methylene chloride in the presence of triethylamine we succeeded in isolating *S*-alkyl-*N*-aroylisothioureas **VIa** and **VIb** in good yield. Subsequent heating of thioureas **VI** in boiling anhydrous DMF for 4 h gave compounds **VIIa** and **VIIb** (Scheme 3).

Compounds **VII** displayed in the ^{1}H NMR spectra signals from aromatic protons, a broadened one-proton singlet from the NH group, and signals from protons in

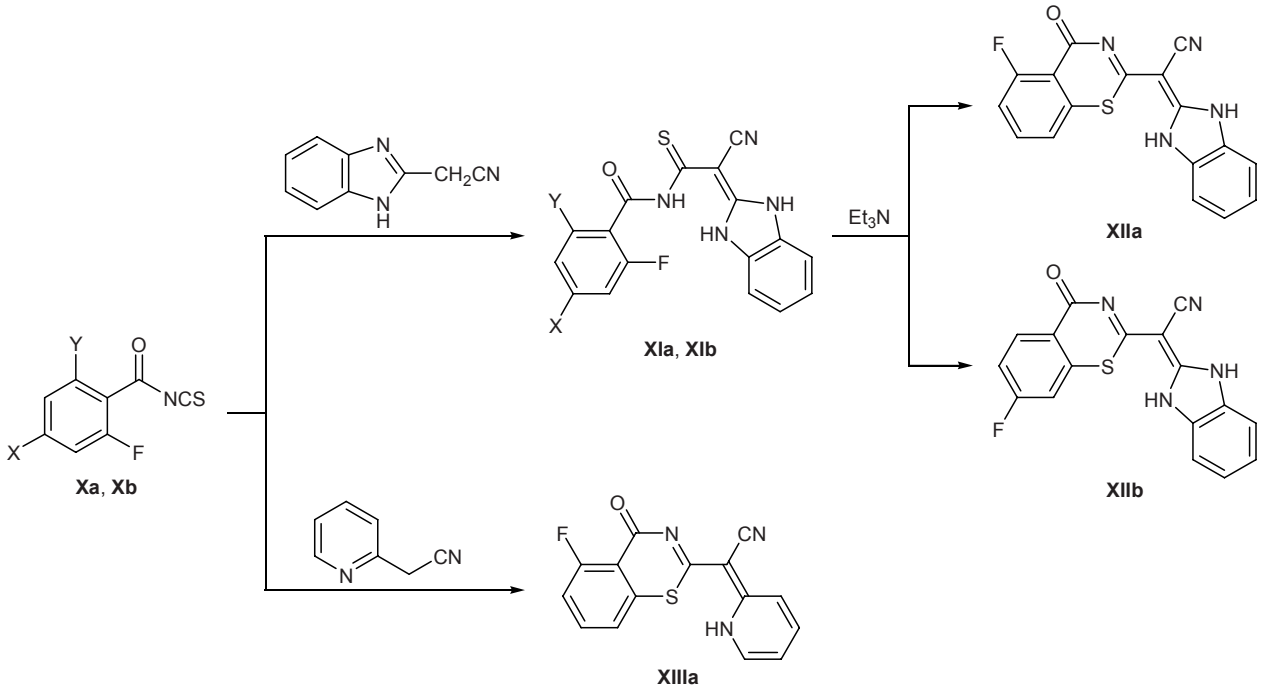
Scheme 3.



Va, **Vb** **VIa** **VIb** **VIIa** **VIIb** **VIIIa**, **VIIIb** **IXa** **IXb**

V, **VIII**, Y = F, X = H (**a**); Y = H, X = F (**b**).

Scheme 4.



the alkyl group. In the mass spectrum of **VIIb**, the base peak was that with *m*/*z* 137 $[M - EtS - CN]^+$, while the molecular ion peak (*m*/*z* 224) had an intensity of 82%. In addition, the $[M - EtS - CN - CO]^+$ ion peak was present in support of the 2-ethylsulfanylquinazolin-4-one structure. The most abundant ion in the mass spectrum of **VIIa** was $[M - H]^+$, *m*/*z* 209.

The yield in the cyclization **VIb** → **VIIb** was considerably lower than in the formation of 5-fluoro analog **VIIa** and 2-ethylsulfanyl-6,7,8-trifluoroquinazolin-4(1*H*)-one [11].

Difluoro-substituted benzoyl chlorides were also used as starting materials in the synthesis of monofluoropyrido[1,2-*a*]quinazolinones. By heating pyridin-2-amine with benzoyl chlorides **Va** and **Vb** over a period of 2 h we obtained the corresponding acylation products only at the exocyclic nitrogen atom (compounds **VIIIa** and **VIIIb**), whereas in the reaction with tetrafluorobenzoyl chloride both nitrogen atoms in 2-aminopyridine (endo- and exocyclic) were acylated with formation of bis-aroyl derivatives [12]. The structure of compounds **VIII** was confirmed by the ^{1}H NMR data (see Experimental). Benzamides **VIIIa** and **VIIIb** underwent intramolecular ring closure to tricyclic derivatives **IXa** and **IXb** on heating in boiling toluene in the presence of triethylamine. Their ^{1}H NMR and mass spectra were consistent with the structure of 6*H*-pyrido[1,2-*a*]quinazolin-6-ones (**IX**).

2,4- and 2,6-Difluorobenzoyl chlorides **Va** and **Vb** are also convenient starting compounds for the synthesis of monofluoro-substituted 1,3-benzothiazin-4-ones that are thia analogs of quinazolin-4-ones. For this purpose, benzoyl chlorides **Va** and **Vb** were converted into the corresponding isothiocyanates **Xa** and **Xb**, and the latter were brought into reactions with C-nucleophiles, 2-cyanomethylpyridine and 2-cyanomethylbenzimidazole (Scheme 4). The addition of 2-cyanomethylbenzimidazole at the N=C bond of isothiocyanates **Xa** and **Xb** occurred in acetonitrile at room temperature. The cyclization of addition products **XIa** and **XIb** to 1,3-benzothiazin-4-ones **XIIa** and **XIIb** was effected by heating in boiling toluene in the presence of triethylamine. According to published data [7], a 1:1 mixture of the addition product and 1,3-benzothiazin-4-one was formed in the reaction of tetrafluorobenzoyl isothiocyanate with 2-cyanomethylbenzimidazole even at room temperature.

The reaction of another C-nucleophile, 2-cyanomethylpyridine, with 2,6-difluorobenzoyl isothiocyanate (**Xa**) was as facile as with tetra- and pentafluorobenzoyl isothiocyanates [8], and it led to the formation of 2-substituted 5-fluoro-1,3-benzothiazin-4-one (**XIIIa**) at room temperature.

To conclude, we have synthesized new monofluoro-substituted quinazoline and 1,3-benzothiazin-4-one derivatives which attract interest as potential biologic-

Table 1. Coordinates of atoms (in fractions of unit cell axes, × 10^4) and their thermal parameters U_{eq} in the molecule of 2,2′-dithiobis(5-fluoro-4-phenylaminoquinazoline) (**IIb**)

Atom	*x*	*y*	*z*	$U_{eq}\times10^3$	Atom	*x*	*y*	*z*	$U_{eq}\times10^3$
S^1	778(1)	2359(1)	2956(1)	69(1)	C^{23}	3966(2)	3527(2)	4769(2)	67(1)
S^2	2191(1)	889(1)	2590(1)	68(1)	C^4	1352(3)	7231(2)	–571(2)	77(1)
N^5	3833(2)	1769(2)	3586(1)	55(1)	C^9	4477(2)	3698(2)	–648(2)	65(1)
F^2	7893(1)	1461(1)	4634(1)	91(1)	C^{19}	8767(2)	–301(2)	3961(2)	81(1)
N^2	2143(2)	3695(2)	1084(1)	57(1)	C^{21}	7264(3)	–1061(2)	3101(2)	78(1)
N^6	5097(2)	2603(2)	4474(2)	68(1)	C^{20}	8562(3)	–1157(2)	3442(2)	85(1)
N^4	4822(2)	–55(2)	2931(2)	66(1)	C^{10}	5457(3)	4017(3)	–1547(2)	87(1)
N^1	50(2)	4786(2)	1878(2)	68(1)	C^{24}	2809(2)	4135(2)	4135(2)	73(1)
C^{17}	6299(2)	780(2)	3804(2)	56(1)	C^7	–782(3)	7077(3)	1084(2)	84(1)
F^1	2401(2)	7337(1)	–1414(1)	102(1)	C^{28}	4102(3)	3838(3)	5737(2)	86(1)
C^{15}	3806(2)	878(2)	3104(2)	57(1)	C^5	400(3)	8337(2)	–546(2)	91(1)
C^{22}	6112(2)	–96(2)	3278(2)	61(1)	C^{25}	1771(3)	5056(3)	4457(2)	89(1)
C^1	1026(2)	3778(1)	1826(2)	57(1)	C^{14}	4614(3)	2425(3)	31(2)	89(1)
N^3	3396(2)	4743(2)	–505(2)	70(1)	C^{27}	3051(4)	4761(3)	6044(3)	106(1)
C^{16}	5053(2)	1734(2)	3952(2)	55(1)	C^{12}	6664(3)	1792(3)	–1091(3)	94(1)
C^2	2296(2)	4781(2)	270(2)	57(1)	C^{13}	5712(3)	1485(3)	–190(3)	100(1)
C^{18}	7660(2)	627(2)	4128(2)	67(1)	C^{26}	1886(3)	5363(3)	5408(3)	105(1)
C^3	1316(2)	6000(2)	215(2)	62(1)	C^6	–672(3)	8244(3)	296(3)	98(1)
C^8	201(2)	5937(2)	1064(2)	66(1)	C^{11}	6546(3)	3055(3)	–1761(2)	100(1)

Table 2. Bond lengths (*d*) in the molecule of 2,2′-dithiobis(5-fluoro-4-phenylaminoquinazoline) (**IIb**)

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
S^1–C^1	1.769(2)	C^{17}–C^{22}	1.406(3)	C^9–C^{14}	1.369(3)	C^5–C^6	1.376(4)
S^1–S^2	2.0101(8)	C^{17}–C^{16}	1.446(3)	C^9–C^{10}	1.380(3)	C^5–H^{5A}	0.9300
S^2–C^{15}	1.778(2)	F^1–C^4	1.360(3)	C^{19}–C^{20}	1.386(3)	C^{25}–C^{26}	1.358(4)
N^5–C^{16}	1.321(2)	C^{22}–C^{21}	1.407(3)	C^{19}–H^{19A}	0.9300	C^{25}–H^{25A}	0.9300
N^5–C^{15}	1.333(2)	N^3–C^2	1.348(3)	C^{21}–C^{20}	1.361(3)	C^{14}–C^{13}	1.377(3)
F^2–C^{18}	1.364(3)	N^3–C^9	1.414(3)	C^{21}–H^{21A}	0.9300	C^{14}–H^{14A}	0.9300
N^2–C^2	1.316(2)	N^3–H^3	0.869(19)	C^{20}–H^{20A}	0.9300	C^{27}–C^{26}	1.367(4)
N^2–C^1	1.338(2)	C^2–C^3	1.446(3)	C^{10}–C^{11}	1.385(3)	C^{27}–H^{27A}	0.9300
N^6–C^{16}	1.351(3)	C^{18}–C^{19}	1.352(3)	C^{10}–H^{10A}	0.9300	C^{12}–C^{13}	1.361(4)
N^6–C^{23}	1.418(3)	C^3–C^4	1.396(3)	C^{24}–C^{25}	1.381(3)	C^{12}–C^{11}	1.359(4)
N^6–H^4	0.814(19)	C^3–C^8	1.410(3)	C^{24}–H^{24A}	0.9300	C^{12}–H^{12A}	0.9300
N^4–C^{15}	1.307(2)	C^8–C^7	1.400(3)	C^7–C^6	1.358(4)	C^{13}–H^{13A}	0.9300
N^4–C^{22}	1.375(3)	C^{23}–C^{24}	1.360(3)	C^7–H^{7A}	0.9300	C^{26}–H^{26A}	0.9300
N^1–C^1	1.300(2)	C^{23}–C^{28}	1.386(3)	C^{28}–C^{27}	1.3810(3)	C^6–H^{6A}	0.9300
N^1–C^8	1.366(3)	C^4–C^5	1.360(3)	C^{28}–H^{28A}	0.9300	C^{11}–H^{11A}	0.9300
C^{17}–C^{18}	1.397(3)						

Table 3. Bond angles (ω) in the molecule of 2,2′-dithiobis(5-fluoro-4-phenylaminoquinazoline) (**IIb**)

Angle	ω, deg	Angle	ω, deg	Angle	ω, deg	Angle	ω, deg
$C^1S^1S^2$	105.16(7)	$N^5C^{16}N^6$	118.15(19)	$C^{18}C^{19}C^{20}$	119.1(2)	$C^{26}C^{25}C^{24}$	120.7(3)
$C^{15}S^2S^1$	105.25(7)	$N^5C^{16}C^{17}$	120.64(18)	$C^{18}C^{19}H^{19A}$	120.4	$C^{26}C^{25}H^{25A}$	119.7
$C^{16}N^5C^{15}$	117.08(17)	$N^6C^{16}C^{17}$	121.21(19)	$C^{20}C^{19}H^{19A}$	120.4	$C^{24}C^{25}H^{25A}$	119.7
$C^2N^2C^1$	116.66(18)	$N^2C^2N^3$	118.8(2)	$C^{20}C^{21}C^{22}$	120.3(2)	$C^9C^{14}C^{13}$	120.1(2)
$C^{16}N^6C^{23}$	128.5(2)	$N^2C^2C^3$	120.8(2)	$C^{20}C^{21}H^{21A}$	119.8	$C^9C^{14}H^{14A}$	120.0
$C^{16}N^6H^6$	113.2(16)	$N^3C^2C^3$	120.4(2)	$C^{22}C^{21}H^{21A}$	119.8	$C^{13}C^{14}H^{14A}$	120.0
$C^{23}N^6H^6$	117.5(15)	$F^2C^{18}C^{19}$	117.9(2)	$C^{21}C^{20}C^{19}$	120.5(2)	$C^{26}C^{27}C^{28}$	120.9(3)
$C^{15}N^4C^{22}$	114.56(17)	$F^2C^{18}C^{17}$	118.5(2)	$C^{21}C^{20}H^{20A}$	119.8	$C^{26}C^{27}H^{27A}$	119.6
$C^1N^1C^8$	115.01(19)	$C^{19}C^{18}C^{17}$	123.6(2)	$C^{19}C^{20}H^{20A}$	119.8	$C^{28}C^{27}H^{27A}$	119.6
$C^{18}C^{17}C^{22}$	116.49(19)	$C^4C^3C^8$	116.3(2)	$C^9C^{10}C^{11}$	120.1(3)	$C^{13}C^{12}C^{11}$	119.1(3)
$C^{18}C^{17}C^{16}$	127.6(2)	$C^4C^3C^2$	127.7(2)	$C^9C^{10}H^{10A}$	120.0	$C^{13}C^{12}H^{12A}$	120.4
$C^{22}C^{17}C^{16}$	115.96(18)	$C^8C^3C^2$	116.0(2)	$C^{11}C^{10}H^{10A}$	120.0	$C^{11}C^{12}H^{12A}$	120.4
$N^4C^{15}N^5$	129.62(19)	$N^1C^8C^7$	118.6(2)	$C^{23}C^{24}C^{25}$	120.2(2)	$C^{12}C^{13}C^{14}$	121.2(3)
$N^4C^{15}S^2$	111.54(15)	$N^1C^8C^3$	121.73(19)	$C^{23}C^{24}H^{24A}$	119.9	$C^{12}C^{13}H^{13A}$	119.4
$N^5C^{15}S^2$	118.84(15)	$C^7C^8C^3$	119.6(2)	$C^{25}C^{24}H^{24A}$	119.9	$C^{14}C^{13}H^{13A}$	119.4
$N^4C^{22}C^{17}$	122.11(18)	$C^{24}C^{23}C^{28}$	119.7(2)	$C^6C^7C^8$	120.8(3)	$C^{25}C^{26}C^{27}$	119.4(3)
$N^4C^{22}C^{21}$	117.8(2)	$C^{24}C^{23}N^6$	123.5(2)	$C^6C^7H^{7A}$	119.6	$C^{25}C^{26}H^{26A}$	120.3
$C^{17}C^{22}C^{21}$	120.0(2)	$C^{28}C^{23}N^6$	116.8(2)	$C^8C^7H^{7A}$	119.6	$C^{27}C^{26}H^{26A}$	120.3
$N^1C^1N^2$	129.7(2)	$F^1C^4C^5$	117.7(3)	$C^{27}C^{28}C^{23}$	119.2(3)	$C^7C^6C^5$	120.9(3)
$N^1C^1S^1$	111.32(16)	$F^1C^4C^3$	118.3(2)	$C^{27}C^{28}H^{28A}$	120.4	$C^7C^6H^{6A}$	119.5
$N^2C^1S^1$	118.92(16)	$C^5C^4C^3$	123.9(3)	$C^{23}C^{28}H^{28A}$	120.4	$C^5C^6H^{6A}$	119.5
$C^2N^3C^9$	131.5(2)	$C^{14}C^9C^{10}$	118.9(2)	$C^6C^5C^4$	118.4(3)	$C^{12}C^{11}C^{10}$	120.6(3)
$C^2N^3H^3$	114.1(12)	$C^{14}C^9N^3$	125.1(2)	$C^6C^5H^{5A}$	120.8	$C^{12}C^{11}H^{11A}$	119.7
$C^9N^3H^3$	114.4(12)	$C^{10}C^9N^3$	115.9(2)	$C^4C^5H^{5A}$	120.8	$C^{10}C^{11}H^{11A}$	119.7

ally active substances. 2,6-Difluorobenzoyl derivatives were shown to be more reactive than their 2,4-substituted analogs in the cyclocondensation process. A simple one-step procedure for the synthesis of fluorine-containing bis(quinazolinyl) disulfide was described. Some of the synthesized compounds were tested for tuberculostatic activity at the Research Institute of Phthisiopulmonology, Ministry of Health Protection and Social Development of the Russian Federation. Compounds **IVb** and **VIIb** showed relatively high activity against *Micobacterium tuberculosis* $H_{37}R_V$ (minimal inhibitory concentration 0.36 μg/ml).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker DRX-400 spectrometers at 250.14 and 400.13 MHz, respectively. The ^{19}F NMR spectra were measured on a Bruker DRX-500 instrument at 376.45 MHz. The chemical shifts were determined relative to tetramethylsilane (^{1}H) or hexafluorobenzene (^{19}F); DMSO-d_6 was used as solvent. The mass spectra were obtained 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), as well as on a Shimadzu LCMS-2010 instrument (positive and negative ion detection, atmospheric pressure chemical ionization; selected ion monitoring, profile scan mode).

The X-ray diffraction data for a single crystal of compound **IIb** were acquired at 293 K on an Xcalibur 3 diffractometer (CCD detector; MoK_α irradiation, λ 0.71073 Å). Colorless crystals, 0.5×0.6×0.9 mm, triclinic crystal system, space group *P*0 (pseudo-*P*-1); unit cell parameters: a = 9.8095(11), b = 11.2052(9), c = 12.359(2) Å; α = 70.047(12), β = 82.411(11), γ = 75.528(9)°. The structure was solved by the direct method in isotropic approximation and was refined in anisotropic approximation using SHELXL-97 software package [13]. The coordinates of atoms and their ther-

mal parameters are collected in Table 1, and the bond lengths and bond angles are listed in Tables 2 and 3, respectively.

2,2′-Dithiobis(5-fluoro-4-phenylaminoquinazoline) (IIb). A mixture of 0.5 g (3.6 mmol) of 2-amino-6-fluorobenzonitrile (**I**) and 1 ml (7.2 mmol) of phenyl isothiocyanate was heated for 3.5 h at 100°C. The mixture was cooled, and the precipitate was filtered off and recrystallized from DMSO. Yield 0.93 g (95%). IR spectrum, ν, cm^{-1}: 440 (S–S), 1100 (C–F), 1500–1640 (C=C, C=N), 3420 br (NH). ^{1}H NMR spectrum, δ, ppm: 7.02 d.d (1H, 7-H, ^3J = 7.9, 12.5 Hz), 7.17 m (1H, Ph), 7.28 d (1H, 8-H, ^3J = 8.6 Hz), 7.39 m (2H, Ph), 7.61 d.d.d (6-H, ^4J = 2.1, ^3J = 7.2, 11.4 Hz), 7.82 m (2H, Ph), 9.01 d (1H, NH, J_{HF} = 15.3 Hz), 12.7 br.s (1H, NH). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 272 (20) $[M/2 + 2H]^+$, 270 (100) $[M/2]^+$, 213 (56) $[M/2 – SCN]^+$, 93 (34) $[C_6H_5NH_2]^+$, 77 (56) $[C_6H_5]^+$. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 542 (31) $[M + H]^+$, 541 (73) $[M]^+$, 271 (43) $[M/2 + H]^+$, 256 (100) $[M/2 – 14]^+$. Found, %: C 61.55; H 3.39; N 10.23. $C_{28}H_{18}F_2N_6S_2$. Calculated, %: C 62.21; H 3.36; N 10.29. *M* 540.61.

2,2′-Dithiobis[5-fluoro-3-phenylquinazolin-4(3*H*)-one] (IVb). A mixture of 0.5 g (3.2 mmol) of benzoic acid **III** and 0.49 g (3.2 mmol) of *N*-phenylthiourea was heated for 1 h at 160–170°C. The melt was cooled, 10 ml of water was added, and the precipitate was filtered off and recrystallized from ethanol. Yield 70%, mp 250–252°C. IR spectrum, ν, cm^{-1}: 445 (S–S), 1180 (C–F), 1540–1680 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 6.99 t (1H, 7-H, ^3J = 8.4 Hz), 7.19 d (2H, Ph, ^3J = 6.7 Hz), 7.28 d (1H, 8-H, ^3J = 8.2 Hz), 7.37–7.52 m (3H, Ph), 7.69 m (1H, 6-H), 13.0 br.s (1H, NH). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 271 (84) $[M/2]^+$, 271 (100) $[M/2 – H]^+$, 137 (43) $[M/2 – Ph – NCS]^+$, 110 (56) $[M/2 – Ph – NCS – CO]^+$, 77 (49) $[C_6H_5]^+$. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 543 (31) $[M]^+$, 544 (13) $[M + H]^+$, 272 (18) $[M/2 + H]^+$, 271 (33) $[M/2]^+$. Found, %: C 61.55; H 3.39; N 11.97. $C_{28}H_{16}F_2N_4O_2S_2$. Calculated, %: C 61.98; H 2.97; N 10.32. *M* 542.58.

***N*-(2,6-Difluorobenzoyl)-*S*-methylisothiourea (VIa).** Triethylamine, 2.7 ml (19.4 mmol), and a solution of 19.6 ml (9.7 mmol) of 2,6-difluorobenzoyl chloride (**Va**) in 6 ml of toluene were added in succession under stirring to a solution of 2.3 g (9.7 mmol) of *S*-ethylthiourea in 20 ml of anhydrous methylene chloride. The mixture was kept for 24 h at room temperature and evaporated, and the residue was washed with water and recrystallized from ethanol. Yield 84%, mp 64–66°C. ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 6.98 m (2H, H_{arom}), 7.44 m (1H, H_{arom}), 9.54 br.s (2H, NH). Found, %: C 46.99; H 3.44; N 12.30. $C_9H_8F_2N_2OS$. Calculated, %: C 46.95; H 3.50; N 12.17.

***N*-(2,4-Difluorobenzoyl)-*S*-ethylisothiourea (VIb)** was synthesized in a similar way. Yield 81%, mp 144–146°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3), 3.11 q (2H, SCH_2), 7.13 m (2H, H_{arom}), 8.07 m (1H, H_{arom}), 9.52 br.s (2H, NH). Found, %: C 48.89; H 4.13; N 11.39. $C_{10}H_{10}F_2N_2OS$. Calculated, %: C 49.16; H 4.13; N 11.47.

5-Fluoro-2-methylsulfanylquinazolin-4(1*H*)-one (VIIa). A solution of 0.7 g (2.9 mmol) of isothiourea **VIa** in 6 ml of anhydrous DMF was heated for 4 h under reflux. The mixture was evaporated, and the residue was recrystallized from ethanol. Yield 67%, mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 7.01 d.d (7-H, ^3J = 8.1, 10.2 Hz), 7.29 d (8-H, ^3J = 8.1 Hz), 7.63 d.d.d (1H, 6-H, ^4J = 2.7, ^3J = 6.6, 10.8 Hz), 12.44 br.s (1H, NH). Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 210 (16) $[M]^+$, 209 (100) $[M – H]^+$. Found, %: C 51.45; H 3.39; N 13.33. $C_9H_7FN_2OS$. Calculated, %: C 51.42; H 3.36; N 13.32. *M* 210.23.

2-Ethylsulfanyl-7-fluoroquinazolin-4(1*H*)-one (VIIb) was synthesized in a similar way. Yield 35%, mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 1.40 t (3H, CH_3), 3.19 q (2H, SCH_2), 7.13 m (2H, 5-H, 8-H), 8.07 m (1H, 6-H), 12.37 br.s (1H, NH). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 224 (82) $[M]^+$, 196 (37) $[M – CO]^+$, 137 (100) $[M – EtS – CN]^+$, 108 (96). Found, %: C 53.25; H 4.09; N 12.93. $C_{10}H_9FN_2OS$. Calculated, %: C 53.55; H 4.05; N 12.49. *M* 224.25.

2,6-Difluoro-*N*-(pyridin-2-yl)benzamide (VIIIa). 2,6-Difluorobenzoyl chloride, 1.87 g (10.6 mmol), was added to a solution of 0.5 g (5.3 mmol) of 2-aminopyridine in 15 ml of anhydrous toluene. The mixture was heated for 1.5 h under reflux and cooled, and the precipitate was filtered off and recrystallized from ethanol. Yield 1.06 g (85%), mp 228–230°C. ^{1}H NMR spectrum, δ, ppm: 7.52 d.d (1H, 5-H, *J* = 8.1, 6.8 Hz), 7.6–7.8 m (2H, 3′-H, 5′-H), 8.11 m (1H, 4′-H), 8.28 m (1H), 8.57 m (1H), 9.55 d (1H, 6-H, *J* = 6.8 Hz), 10.8 br.s (1H, NH). Found, %: C 61.48; H 3.39; N 12.01. $C_{12}H_8F_2N_2O$. Calculated, %: C 61.54; H 3.44; N 11.96.

2,4-Difluoro-*N*-(pyridin-2-yl)benzamide (VIIIb) was synthesized in a similar way. Yield 60%, mp 276–278°C. ^{1}H NMR spectrum, δ, ppm: 7.61 d.d (1H, 5-H, *J* = 7.1, 6.8 Hz), 7.77 m (1H, 3′-H), 7.91 d (1H, 3-H, *J* = 8.4 Hz), 8.37 d.d (1H, 4-H, *J* = 8.4, 7.1 Hz), 8.46 m

(1H, 5′-H), 8.81 m (1H, 6′-H), 9.62 d (1H, 6-H, J = 6.8 Hz), 10.9 br.s (1H, NH). Found, %: C 61.46; H 3.37; N 12.02. $C_{12}H_8F_2N_2O$. Calculated, %: C 61.54; H 3.44; N 11.96.

7-Fluoro-6*H*-pyrido[1,2-*a*]quinazolin-6-one (IXa). Triethylamine, 0.2 g (2.0 mmol), was added to a suspension of 0.23 g (1.0 mmol) of amide **VIIIa** in 10 ml of toluene, the mixture was heated for 3 h under reflux, cooled, and evaporated, and the residue was washed with water and recrystallized from ethanol. Yield 0.17 g (78%), mp 258–260°C. ^{1}H NMR spectrum, δ, ppm: 6.99 d.d.d (1H, 2-H, ^3J = 7.5, 6.6, ^4J = 1.2 Hz), 7.21 d.d (1H, 4-H, ^3J = 9.1, ^4J = 1.2 Hz), 7.42 m (1H, FC_6H_3), 7.74 d.d.d (1H, 3-H, ^3J = 8.9, 6.6, ^4J = 1.2 Hz), 7.90 m (1H, FC_6H_3), 8.27 m (1H, FC_6H_3), 8.99 d (1H, 1-H, ^3J = 7.5 Hz). Mass spectrum (APCI), m/z (I_{rel}, %): 256 (100) [M + CH_3CN]$^+$, 215 (53) [M + H]$^+$. Found, %: C 67.33; H 3.36; N 13.02. $C_{12}H_7FN_2O$. Calculated, %: C 67.29; H 3.30; N 13.08. M 214.20.

9-Fluoro-6*H*-pyrido[1,2-*a*]quinazolin-6-one (IXb) was synthesized in a similar way. Yield 57%, mp >300°C. ^{1}H NMR spectrum, δ, ppm: 7.04 d.d.d (1H, 2-H, ^3J = 7.0, 6.3, ^4J = 1.5 Hz), 7.23 d (1H, 4-H, ^3J = 9.1 Hz), 7.56 m (1H, FC_6H_3), 7.78 d.d.d (1H, 3-H, ^3J = 9.1, 6.3, ^4J = 1.4 Hz), 8.32 m (1H, FC_6H_3), 8.42 m (1H, FC_6H_3), 8.99 d (1H, 1-H, ^3J = 7.0 Hz). Mass spectrum (ACPI), m/z (I_{rel}, %): 256 (100) [M + MeCN]$^+$, 215 (52) [M + H]$^+$. Found, %: C 67.30; H 3.38; N 13.04. $C_{12}H_7FN_2O$. Calculated, %: C 67.29; H 3.30; N 13.08. M 214.20.

***N*-[2-Cyano-2-(2,3-dihydro-1*H*-benzimidazol-2-ylidene)ethanethioyl]-2,6-difluorobenzamide (XIa).** A solution of 0.4 g (5 mmol) of ammonium thiocyanate in 5 ml of anhydrous acetonitrile was added to a solution of 0.6 ml (5 mmol) of 2,6-difluorobenzoyl chloride in 3 ml of anhydrous acetonitrile. The mixture was heated for 5 min at 40°C, the precipitate of NH_4Cl was filtered off, and a suspension of 0.8 g (5 mmol) of 2-cyanomethylbenzimidazole in 5 ml of acetonitrile was added to the filtrate containing isothiocyanate **Xa**. The mixture was kept for 1 h at room temperature, and the precipitate was filtered off and recrystallized from ethanol. Yield 1.6 g (92%), mp 160–162°C. ^{1}H NMR spectrum, δ, ppm: 7.04 m (2H, $C_6H_3F_2$), 7.32 m (2H, C_6H_4), 7.48 m (1H, $C_6H_3F_2$), 7.68 m (2H, C_6H_4), 10.82 br.s (1H, NH), 13.74 br.s (2H, NH). Found, %: C 57.30; H 2.88; N 15.77. $C_{17}H_{10}F_2N_4OS$. Calculated, %: C 57.30; H 2.83; N 15.72.

***N*-[2-Cyano-2-(2,3-dihydro-1*H*-benzimidazol-2-ylidene)ethanethioyl]-2,4-difluorobenzamide (XIb)** was synthesized in a similar way from 2,4-difluorobenzoyl chloride and 2-cyanomethylbenzimidazole. Yield 90%, mp 175–177°C. ^{1}H NMR spectrum, δ, ppm: 7.17 m (2H, $C_6H_3F_2$), 7.34 m (2H, C_6H_4), 7.68 m (2H, C_6H_4), 7.81 m (1H, $C_6H_3F_2$), 10.28 br.s (1H, NH), 13.74 br.s (2H, NH). Found, %: C 57.33; H 2.84; N 15.75. $C_{17}H_{10}F_2N_4OS$. Calculated, %: C 57.30; H 2.83; N 15.72.

(2,3-Dihydro-1*H*-benzimidazol-2-ylidene)-(5-fluoro-4-oxo-4*H*-1,3-benzothiazin-2-yl)acetonitrile (XIIa). Triethylamine, 0.5 ml (3.4 mmol), was added to a solution of 0.6 g (1.7 mmol) of compound **XIa** in 10 ml of anhydrous toluene, and the mixture was heated for 3 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, and recrystallized from DMSO. Yield 0.5 g (82%), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 7.19–7.28 m (3H, 7-H, C_6H_4), 7.43 d (1H, 8-H, ^3J = 8.1 Hz), 7.57–7.7.1 m (3H, 6-H, C_6H_4), 13.42 br.s (2H, NH). Mass spectrum (ACPI), m/z (I_{rel}, %): 335 (100) [M – H]$^+$, 336 (43) [M]$^+$. Found, %: C 61.00; H 2.68; N 16.64. $C_{17}H_9FN_4OS$. Calculated, %: C 60.71; H 2.70; N 16.66. M 336.34.

(2,3-Dihydro-1*H*-benzimidazol-2-ylidene)-(7-fluoro-4-oxo-4*H*-1,3-benzothiazin-2-yl)acetonitrile (XIIb) was synthesized in a similar way. Yield 85%, mp >300°C. ^{1}H NMR spectrum, δ, ppm: 7.20–7.29 m (3H, 5-H or 8-H, C_6H_4), 7.51–7.59 m (3H, 8-H or 5-H, C_6H_4), 8.30 m (1H, 6-H), 13.53 br.s (2H, NH). Mass spectrum (ACPI), m/z (I_{rel}, %): 336 (32) [M]$^+$, 335 (100) [M – H]$^+$. Found, %: C 60.83; H 2.718; N 16.70. $C_{17}H_9FN_4OS$. Calculated, %: C 60.71; H 2.70; N 16.66. M 336.34.

(5-Fluoro-4-oxo-4*H*-1,3-benzothiazin-2-yl)[pyridin-2(1*H*)-ylidene]acetonitrile (XIII). A solution of 5 mmol of isothiocyanate **Xa** in 12 ml of anhydrous acetonitrile was added to 0.84 g (7 mmol) of (pyridin-2-yl)acetonitrile in 10 ml of acetonitrile. The mixture was kept for 24 h at room temperature and evaporated, and the residue was washed with ethanol and recrystallized from DMSO. Yield 0.7 g (82%), mp 255–257°C. ^{1}H NMR spectrum, δ, ppm: 7.07 m (2H, 7-H, pyridine), 7.46 m (2H, 8-H, pyridine), 7.75 m (1H, 6-H), 8.24 m (1H, pyridine), 8.55 m (1H, pyridine), 10.87 br.s (1H, NH). Mass spectrum (ACPI), m/z (I_{rel}, %): 297 (19) [M]$^+$, 296 (100) [M – H]$^+$. Found, %: C 60.59; H 2.73; N 14.18. $C_{15}H_8FN_3OS$. Calculated, %: C 60.60; H 2.71; N 14.13. M 297.31.

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