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Synthetic approaches to 2-aryl/hetaryl- and 2-(hetaryl)ylidene derivatives of fluorinated 1,3-benzothiazin-4-ones

A series of 2-hetaryl- and 2-(hetaryl)ylidene substituted 5-fluoro-8-nitro-1,3-benzothiazin-4-ones was synthesized by interaction of 2,6-difluoro-3-nitrobenzoylisothiocyanate with C-nucleophiles. Cyclocondensation of polyfluorobenzoylchlorides with aryl and hetaryl thioamides represents new approach to 1,3-benzothiazin-4-ones. Some compounds proved to be promising for further development of tuberculostatic agents.

Keywords: 1,3-benzothiazin-4-ones; 2-fluorobenzoylchloride; 2-fluorobenzoyl-isothiocyanate; indole; pyrrole; cyanomethylbenzimidazole; benzoylmethylbenzimidazole; thioamide; cyclocondensation; tuberculostatics.

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Introduction

Many synthetic benzothiazines are biologically actives, which play an important role in treatment of various diseases. Some 2-amino substituted 1,3-benzothiazin-4-ones (2-amino-1,3-benzothiazinones) represent a promising new class of antitubercular agents [1]. Other 1,3-benzothiazin-4-one derivatives, mostly 2-aryl and 2-(pyridin-2-yl) ones, are attractive due to their ability to suppress an oxidative stress-induced cardiomyocyte apoptosis [2]. Synthetic approaches to 2-amino-1,3-benzothiazin-4-ones are sufficiently developed, whereas not many ones are available for incorporation of C–C bond into position 2 [3]. The synthetic methods are limited to the following:

- interaction of 2-mercaptobenzoic acids with aryl/hetaryl nitriles [2];
- rearrangement of N-arylthiomethylaroylamides catalyzed by phosphorus oxychloride, followed by oxidation of 4*H*-1,3-benzothiazines with potassium permanganate [4];
- addition of C-nucleophiles to 2-fluorobenzoylisothiocyanates and subsequent intramolecular condensation [5].

The last approach opens wide opportunities for modification of position 2 of 1,3-benzothiazin-4-ones. Previously we

studied the interaction of polyfluorobenzoylisothiocyanates with CH-reactive benzimidazoles [5], 2,6-difluorobenzoylisothiocyanate with the same benzimidazoles and 2-cyanomethylpyridine [6], *o*-fluorobenzoylisothiocyanates with N-methylpyrrole and N-methylindole [7]. We presented only one example of 2-indolyl-5-fluoro-8-nitro-1,3-benzothiazin-4-one in recent paper [8].

In this article, we wish to report new data on 2-substituted 5-fluoro-8-nitro-1,3-benzothiazinones and introduce efficient synthetic approach to 2-aryl/hetaryl derivatives of 1,3-benzothiazin-4-ones based on cyclocondensation of polyfluorobenzoyl chlorides with thioamides.

Experimental

^{1}H and ^{19}F NMR (nuclear magnetic resonance) spectra were recorded in dimethylsulfoxide-d_6 (DMSO-d_6) on the spectrometer "Bruker-Avance-400" (400 MHz), using tetramethylsilane as internal reference for ^{1}H NMR and $CFCl_3$ for ^{19}F NMR. Mass spectra were recorded on a SHIMADZU GCMS-QP2010 Ultra instrument with electron impact ionization (EI) of the sample. Microanalyses (C, H, N) were performed using the Perkin — Elmer 2400 elemental analyzer. Melting points were measured on the Stuart melting point apparatus SMP10 (AC/DC input 230 V AC, Merck supplier).

2,6-Difluorobenzoic acid **1**, 2,3,4,5-tetrafluorobenzoyl chloride **10a** and pentafluorobenzoyl chloride **10b** were purchased from Merck (CAS numbers 385-00-2, 94695-48-4, 2251-50-5). 3-Nitro-2,6-difluorobenzoic acid **2** was synthesized according to the literature [9]. Procedure for toluene solution of 2,6-difluoro-3-nitrobenzoylchloride **3** was reported [8]. 2-Benzoylmethylbenzimidazole was prepared from 2-methylbenzimidazole [5], 2-cyanomethyl-benzimidazole was synthesized by condensation of ethyl cyanoacetate with *o*-phenylenediamine [10]. Thioamides **11** were prepared by the addition of hydrogen sulfide to the corresponding nitriles [11].

5-Fluoro-8-nitro-2-(1-methylpyrrol-2-yl) — 1,3-benzothiazin-4-one (5). The solution of ammonium isothiocyanate (0.4758 g, 6.26 mmol) in acetonitrile (10 mL) was added to toluene solution of 2,6-difluoro-3-nitrobenzoylchloride **3** (0.88 mL, 6.26 mmol). Reaction mixture was stirred at 40 °C for 5 min, the precipitate of NH_4Cl was filtered off and 1-methylpyrrole (0.761 g, 9.39 mmol) was added to a solution of 2,6-difluoro-3-nitrobenzoylisothiocyanate **3.** The mixture was stirred at room temperature for 3 h, the precipitate of benzothiazinone **5** was filtered off and washed with hot ethanol (10 mL). Yield 1.72 g (90%), mp 194–196 °C. ^{1}H NMR, δ (ppm), *J* (Hz): 4.09 s (3H, CH_3), 6.30 dd (1H, $H^{4'}$, $^3J_{HH}$ 4.1, $^4J_{HH}$ 2.3), 7.29 dd (1H, $H^{3'}$, $^3J_{HH}$ 4.2, $^4J_{HH}$ 1.3), 7.37 m (1H, $H^{5'}$), 7.62 dd (1H, H^6, $^3J_{HH}$ 9.2, $^3J_{FH}$ 9.4), 8.70 dd (1H, H^7, $^3J_{HH}$ 9.2, $^4J_{FH}$ 4.5). ^{19}F NMR, δ (ppm), *J* (Hz): — 99.05 dd (1F, $^3J_{FH}$ 9.5, $^4J_{FH}$ 4.0). MS (EI), *m/z* (I_{rel} (%)): 305 $[M]^+$ (14), 106 (100), 105 (15). Found, %: C 51.17; H 2.60; N 13.74. $C_{13}H_8FN_3O_3S$. Calculated, %: C 51.15; H 2.64; N 13.76.

Compounds **6–9** were synthesized by the same method.

5-Fluoro-8-nitro-2-(5-methoxy-1-methylindol-3-yl) — 1,3-benzothiazin-4-one (6). Yield 80%, mp 274–276 °C. ^{1}H NMR, δ (ppm), *J* (Hz): 3.83 s (3H, NCH_3), 3.93 s (3H, OCH_3), 7.01 d (1H, $H^{6'}$, $^3J_{HH}$

8.8), 7.54 d (1H, $H^{7'}$, $^3J_{HH}$ 8.8), 7.65 dd (1H, H^6, $^3J_{HH}$ 9.3, $^3J_{FH}$ 9.5), 7.97 s (1H, $H^{4'}$), 8.66 s (1H, $H^{2'}$), 8.70 dd (1H, H^7, $^3J_{HH}$ 9.3, $^4J_{FH}$ 4.3). $^{19}F\{^1H\}$ NMR, δ (ppm): — 99.27 s. MS (EI), *m/z* (I_{rel} (%)): 385 $[M]^+$ (31), 187 (12), 186 (100), 171 (41), 143 (28). Found, %: C 56.13; H 3.15; N 10.87. $C_{18}H_{12}FN_3O_4S$. Calculated, %: C 56.10; H 3.14; N 10.90.

5-Fluoro-8-nitro-2-(2-methylindol-3-yl) — 1,3-benzothiazin-4-one (7). Yield 91%, mp 207–209 °C. ^1H NMR, δ (ppm), *J* (Hz): 2.87 s (3H, CH_3), 7.25 m (2H, C_6H_4), 7.45 m (1H, C_6H_4), 7.66 dd (1H, H^6, $^3J_{HH}$ 9.3, $^3J_{FH}$ 9.6), 8.34 m (1H, C_6H_4), 8.71 dd (1H, H^7, $^3J_{HH}$ 9.3, $^4J_{FH}$ 4.6), 12.5 br. s (1H, NH). $^{19}F\{^1H\}$ NMR, δ (ppm): — 98.42 s. MS (EI), *m/z* (I_{rel} (%)): 355 $[M]^+$ (21), 157 (12), 156 (100), 155 (50), 81 (10). Found, %: C 57.43; H 2.82; N 11.85. $C_{17}H_{10}FN_3O_3S$. Calculated, %: C 57.46; H 2.84; N 11.83.

1-(1,3-Dihydrobenzimidazol-2-yliden) — 1-(5-fluoro-8-nitro-4-oxo-4*H*-1,3-benzothiazin-2-yl) — acetonitrile (8). Yield 75%, mp 319–321 °C. ^1H NMR, δ (ppm), *J* (Hz): 7.30 m (2H, C_6H_4), 7.50 dd (1H, H^6, $^3J_{HH}$ 9.2, $^3J_{FH}$ 9.8), 7.64 m (2H, C_6H_4), 8.62 dd (1H, H^7, $^3J_{HH}$ 9.2, $^4J_{FH}$ 4.4), 13.31 br. s (2H, NH). $^{19}F\{^1H\}$ NMR, δ (ppm): — 97.49 s. MS (EI), *m/z* (I_{rel} (%)): 381 $[M]^+$ (39), 183 (13), 182 (100), 155 (12), 103 (23), 81 (12). Found, %: C 53.50; H 2.15; N 18.36. $C_{17}H_8FN_5O_3S$. Calculated, %: C 53.54; H 2.11; N 18.37.

2-(1,3-Dihydrobenzimidazol-2-yliden) — 2-(5-fluoro-8-nitro-4-oxo-4*H*-1,3-benzothiazin-2-yl) — acetophenone (9). Yield 89%, mp 265–267 °C. ^1H NMR, δ (ppm), *J* (Hz): 7.36 m (5H, C_6H_5), 7.53 m (4H, C_6H_4), 7.60 dd (1H, H^6, $^3J_{HH}$ 9.2, $^3J_{FH}$ 9.5), 8.56 dd (1H, H^7, $^3J_{HH}$ 9.2, $^4J_{FH}$ 4.5), 13.36 br. s (2H, NH). ^{19}F $\{^1H\}$ NMR, δ (ppm): — 98.39 s. MS (EI), *m/z* (I_{rel} (%)): 460 $[M]^+$ (24), 432 (13), 431 (41), 355 (25), 261 (46), 260 (100), 206 (16), 156 (16), 105 (45), 77 (71), 51 (10). Found, %: C 60.03; H 2.83; N 12.20. $C_{23}H_{13}FN_4O_4S$. Calculated, %: C 60.00; H 2.85; N 12.17.

6,7,8-Trifluoro-2-phenyl-1,3-benzothiazin-4-one (12a). Tetrafluorobenzoylchloride **10a** (0.85 g, 4 mmol) was added to thiobenzamide **11a** (0.397 g, 2.9 mmol) in dry toluene (8 mL), reaction mixture was refluxed for 3 h and then cooled. The precipitate of benzothiazinone **12a** was filtered off and recrystallized from DMSO. Yield 0.646 g (76%), mp 160–162 ^{0}C. ^1H NMR, δ (ppm), *J* (Hz): 7.62 m (2H, Ph), 7.73 m (1H, Ph), 8.15 ddd (1H, H^5, ^3J 10.3, ^4J 7.4, ^5J 2.2), 8.19 m (2H, Ph). ^{19}F NMR, δ (ppm), *J* (Hz): 151.84 ddd (1F, F^7, ^3J 22.5, ^3J 21.5, ^4J 7.4), 135.10 ddd (1F, F^8, ^3J 21.5, ^4J 6.2, ^5J 2.2), 132.50 ddd (1F, F^6, ^3J 22.5, ^3J 10.3, ^4J 6.2). MS (EI), *m/z* (I_{rel} (%)): 293 $[M]^+$ (11), 190 (100), 162 (30). Found, %: C 57.51, H 1.88, N 4.62. $C_{14}H_6F_3NOS$. Calculated, %: C 57.34, H 2.06, N 4.78.

Compounds **12b-h** were synthesized by the same method.

6,7,8-Trifluoro-2-(*p*-chlorophenyl) — 1,3-benzothiazin-4-one (12b). Yield 59%, mp 204–206 ^{0}C. ^1H NMR, δ (ppm), *J* (Hz): 7.73 d (2H, $H^{3',5'}$, ^3J 8.8), 8.23 d (2H, $H^{2',6'}$, ^3J 8.8), 8.24 ddd (1H, H^5, ^3J 10.6, ^4J 7.5, ^5J 2.1). ^{19}F NMR, δ (ppm), *J* (Hz): 151.68 ddd (1F, F^7, ^3J 22.5, ^3J 21.2, ^4J 7.5), 135.02 ddd (1F, F^8, ^3J 21.5, ^4J 6.3, ^5J 2.1), 132.29 ddd (1F, F^6, ^3J 22.5, ^3J 10.6, ^4J 6.3). MS (EI), *m/z* (I_{rel} (%)): 327 $[M]^+$ (4), 190 (100), 162 (27). Found, %: C 51.42, H 1.66, N 4.13. $C_{14}H_5F_3NOSCl$. Calculated, %: C 51.31, H 1.54, N 4.27.

6,7,8-Trifluoro-2-(*p*-tolyl) — 1,3-benzothiazin-4-one (12c). Yield 71%, mp 184–186 ^{0}C. ^1H NMR, δ (ppm), *J* (Hz): 2.46 s (3H, CH_3), 7.43 d (2H, $H^{3',5'}$, ^3J 8.0), 8.09 d (2H, $H^{2',6'}$, ^3J 8.0), 8.14 ddd (1H, H^5, ^3J 10.0, ^4J 7.5, ^5J 2.3). Found, %: C 58.75, H 2.70, N 4.41. $C_{15}H_8F_3NOS$. Calculated, %: C 58.63, H 2.62, N 4.56.

6,7,8-Trifluoro-2-(pyridyl-2) — 1,3-benzothiazin-4-one (12d). Yield 76%, mp 166–168 ^{0}C. ^{1}H NMR, δ (ppm), *J* (Hz): 7.75 dd (1H, H$^{5'}$, ^3J 8.0, ^3J 4.0), 8.10 td (1H, H$^{4'}$, ^3J 8.0, ^4J 1.8), 8.13 ddd (1H, H^5, ^3J 10.4, ^4J 7.4, ^5J 2.2), 8.38 d (1H, H$^{3'}$, ^3J 8.0), 8.79 dd (1H, H$^{6'}$, ^3J 4.0, ^4J 1.8). ^{19}F NMR, δ (ppm), *J* (Hz): 151.95 ddd (1F, F^7, ^3J 22.5, ^3J 21.1, ^4J 7.4), 135.64 ddd (1F, F^8, ^3J 21.1, ^4J 6.2, ^5J 2.2), 132.70 ddd (1F, F^6, ^3J 22.5, ^3J 10.4, ^4J 6.2). Found, %: C 52.95, H 1.63, N 9.67. $C_{13}H_5F_3N_2OS$. Calculated, %: C 53.06, H 1.71, N 9.52.

5,6,7,8-Tetrafluoro-2-phenyl-1,3-benzothiazin-4-one (12e). Yield 80%, mp 165–167 ^{0}C. ^{1}H NMR, δ (ppm), *J* (Hz): 7.63 m (2H, Ph), 7.76 m (1H, Ph), 8.17 m (2H, Ph). MS (EI), *m/z* (I_{rel} (%)): 311 $[M]^+$ (7), 208 (100), 180 (24), 111 (5). Found, %: C 53.83, H 1.81, N 4.67. $C_{14}H_5F_4NOS$. Calculated, %: C 54.02, H 1.62, N 4.50.

5,6,7,8-Tetrafluoro-2-(*p*-chlorophenyl) — 1,3-benzothiazin-4-one (12f). Yield 62%, mp 186–188 ^{0}C. ^{1}H NMR, δ (ppm), *J* (Hz): 7.66 d (2H, H$^{3',5'}$, ^3J 8.8), 8.20 d (2H, H$^{2',6'}$, ^3J 8.8). Found, %: C 48.83, N 3.97. $C_{14}H_4F_4NOSCl$. Calculated, %: C 48.64, H 1.17, N 4.05.

5,6,7,8-Tetrafluoro-2-(*p*-tolyl) — 1,3-benzothiazin-4-one (12g). Yield 74%, mp 191–193 ^{0}C. ^{1}H NMR, δ (ppm), *J* (Hz): 2.46 s (3H, CH_3), 7.43 d (2H, H$^{3',5'}$, ^3J 8.4), 8.08 d (2H, H$^{2',6'}$, ^3J 8.4). Found, %: C 55.46, H 2.24, N 4.19. $C_{15}H_7F_4NOS$. Calculated, %: C 55.39, H 2.17, N 4.31.

5,6,7,8-Tetrafluoro-2-(pyridyl-2) — 1,3-benzothiazin-4-one (12h). Yield 77%, mp 182–184 ^{0}C. ^{1}H NMR, δ (ppm), *J* (Hz): 7.76 ddd (1H, H$^{5'}$, ^3J 8.0, ^3J 4.8, ^4J 0.8), 8.10 td (1H, H$^{4'}$, ^3J 8.0, ^4J 1.8), 8.36 dd (1H, H$^{3'}$, ^3J 8.0, ^4J 0.8), 8.79 dd (1H, H$^{6'}$, ^3J 4.8, ^4J 1.8). Found, %: C 49.92, N 9.09. $C_{13}H_4F_4N_2OS$. Calculated, %: C 50.01, H 1.29, N 8.97.

Results and discussion

We developed an efficient synthetic approach to 2-hetaryl/(hetaryl)ylidene-substituted fluorinated 1,3-benzothiazinones, for this purpose we studied the interaction of the range of C-nucleophiles (indoles, N-methylpyrrole, 2-cyanomethyl- and 2-benzoylmethyl- benzimidazoles) with 2,6-difluoro-3-nitrobenzoylisothiocyanate **4** in acetonitrile at room temperature (Figure 1). According to ^{1}H and ^{19}F NMR spectra, the reaction leads to the formation of 1,3-benzothiazin-4-ones **5–9**, the intermediate addition products were not isolated, and fluorine atom at C^5 was not subjected to substitution with nucleophilic reagent. It is worth noting that the intramolecular cyclization proceeded at milder reaction conditions than in the case of 2,6-difluoro- and 2,3,4,5-tetrafluorobenzoyl derivatives (refluxing in acetonitrile or dimethylformamide in the presence of trimethylamine [7]).

The signals of H^6 and H^7 in ^{1}H NMR spectra of benzothiazinones **5–9** exhibit more complicated multiplicity than in the case of 2,5-diaminobenzothiazinones [8], which indicates that the fluorine atom remains in position 5. To prove that the alternative product of cyclization, 5-fluoro-6-nitro isomer, was not formed ^{19}F NMR spectra without suppression of F-H spin-spin interaction were registered. In such spectra of compounds **5–9** double doublet signals with $^3J_{FH}$ = 9.5–10.1 Hz and $^4J_{FH}$ = 3.9–4.0 Hz are present, so the formation of 5-fluoro-8-nitroisomers was confirmed. The peaks of molecular ions in the mass spectra of benzothiazinones **5–9** have a relative intensity of 14–39%.

Thus, we demonstrated the difference in behavior of C-nucleophiles and N-nucleophiles under the reaction with 2,6-difluoro-3-nitrobenzoylisothiocyanate **4**: application of C-nucleophiles allows to obtain derivatives of 5-fluoro-8-nitrobenzothiazinone, whereas the reaction with cycloalkylimines fails to avoid the nucleophilic substitution of fluorine at position 5. The proposed strategy opens wide opportunities for varying the substituent at position 2 of 8-nitrobenzothiazin-4-ones.

We presented novel one-stage synthetic approach to 2-substituted fluorine-containing 1,3-benzothiazin-4-ones based on cyclocondensation of polyfluorobenzoyl chlorides with thioamides as S,N-dinucleophiles. New 6,7,8-trifluoro- and 5,6,7,8-tetrafluoro-derivatives of 1,3-benzothiazin-4-ones **12a-h** were obtained by the reaction of polyfluorobenzoylchlorides **10a,b** and thioamides **11a-d** in boiling toluene for 3 h in 59–80% yields (Figure 2), notably that intermediate N-aroylation products were not isolated. Signals of NH groups are absent in ^{1}H NMR spectra of compounds **12a-h**, spectra of 6,7,8-trifluorobenzothiazinones **12a-d** exhibited ddd signal of fluoroarene residue H^{5} proton at 8.13–8.24 ppm. The number of signals in ^{19}F NMR spectra is in accordance with the structure of benzothiazinones **12**. The peaks of molecular ions in the mass

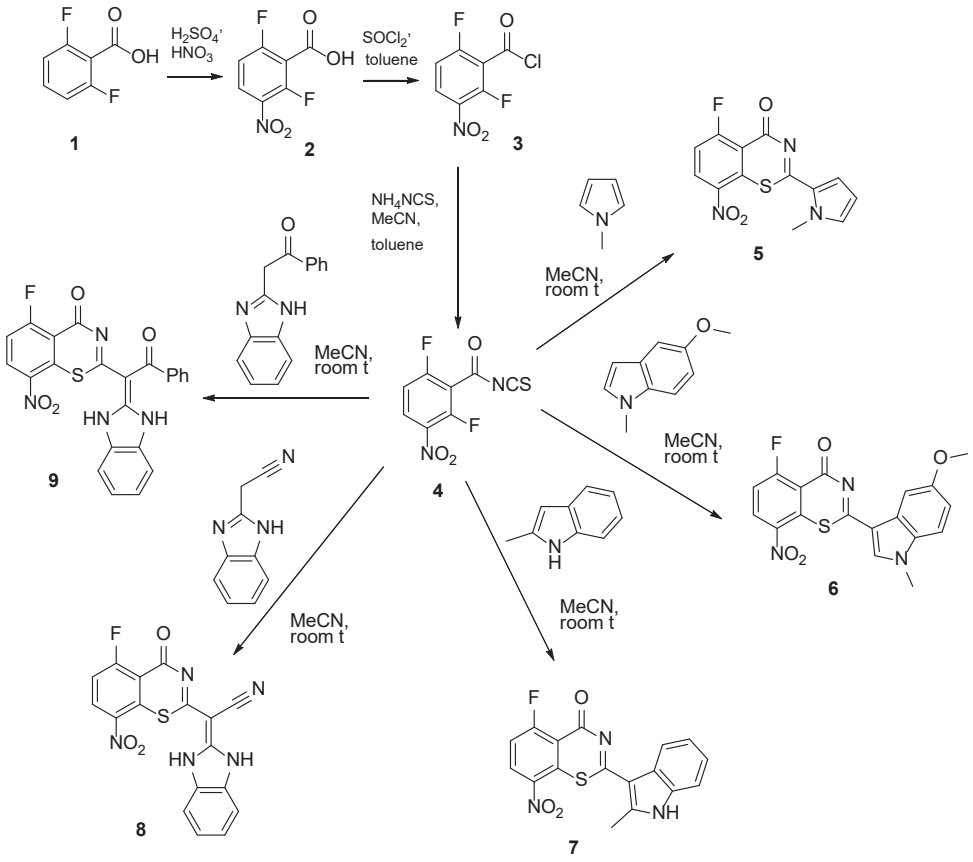


Fig. 1. Synthesis of 5-fluoro-8-nitro-1,3-benzothiazin-4-ones **5–9**

spectra of benzothiazinones **12** have low relative intensity of 4–11%. The ions *m*/*z* 190 or *m*/*z* 208 with 100% intensity were observed for benzothiazinones **12,** moreover, peaks *m*/*z* 162 or *m*/*z* 180 correspond to ions $[M\text{-}RCN\text{-}CO]^+$. The most abundant peak was reported to be characteristic for elimination of RCN fragment from molecular ions of 2-R-6,7,8-trifluoro-1,3-benzothiazin-4-ones [5–7].

The presented approach allows to obtain a variety of 2-aryl/hetaryl-substituted 1,3-benzothiazinones and successfully complements the previously described cyclocondensation of polyfluorobenzoylchlorides with benzimidazol-2-thiones as cyclic S,N-dinucleophiles leading to [*b*]-annelated fluorobenzothiazinones [12]. Unfortunately, we failed to obtain 5-fluoro- and 5-fluoro-8-nitro analogs using the method shown in Figure 2.

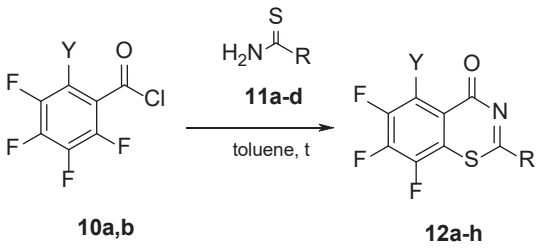
Tuberculostatic activity of polyfluorinated benzothiazinnes **12** was studied at two laboratories, namely Ural Research Institute for Phthisiopulmonology (URIP) and University of Illinois, Chicago Institute for Tuberculosis Research (INR); the data are presented in Table 1.

Table 1

Data on tuberculostatic activity of fluorinated 2-aryl/pyridyl-1,3-benzothiazin-4-ones 12 against *Mycobacterium tuberculosis* $H_{37}R_v$*

Comp	MIC values (URIP data), μg/mL	% Inhibition at 128 μg/mL (ITR data)		MIC values, μg/mL (ITR data)		IC_{50}, μg/mL (ITR data)
		MABA	LORA	MABA	LORA	
12b	12.5	28	66	-	-	—
12c	12.5	95	100	58.0	52.3	>128
12d	0.3	—	—	>128	>128	—
12f	3.12	0	100	—	**3.7**	53.5
12g	nd	74	99	—	26.3	—
12h	12.5	0	100	—	55.8	65.9

* MIC–Minimal inhibitory concentration; IC_{50} — the half maximal inhibitory concentration; URIP — Ural Research Institute for Phthisiopulmonology; INR — Chicago Institute for Tuberculosis Research; MABA — microplate Alamar Blue assay; LORA — low-oxygen recovery assay.



10a,b **12a-h**

10: Y = H (**a**), F (**b**); **11**: R = Ph (**a**), 4-Cl-C_6H_4 (**b**), 4-Me-C_6H_4 (**c**), 2-Py (**d**); **12**: Y = H, R = Ph (**a**), 4-Cl-C_6H_4 (**b**), 4-Me-C_6H_4 (**c**), 2-Py (**d**); Y = F, R = Ph (**e**), 4-Cl-C_6H_4 (**f**), 4-Me-C_6H_4 (**g**), 2-Py (**h**).

Fig. 2. Synthesis of polyfluorinated 2-aryl/pyridyl-1,3-benzothiazin-4-ones **12a-h**

According to trials conducted in URIP, benzothiazinone **12d** exhibited the highest activity (MIC 0.3 μg/mL, isoniazide as reference compound with MIC 0.15 μg/mL). Data obtained in ITR revealed **12f** as the most promising derivative towards the dormant multi-resistant strain of micobacteria $H_{37}R_V$–CA-luxAB (MIC 3.7 μg/mL, rifampicinum as reference compound with MIC 8.26 μg/mL).

Conclusions

To sum up, we developed efficient synthetic approaches to fluorine-containing 1,3-benzothiazin-4-ones bearing aryl, hetaryl and (hetaryl)ylidene residues at position 2 and demonstrate that some of them are promising for design of new antitubercular agents.

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