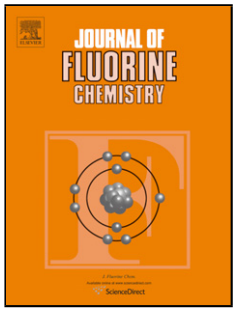


Title: SYNTHESIS AND ANTITUBERCULAR EVALUATION OF FLUORINATED 2-CYCLOALKYLIMINO SUBSTITUTED 1,3-BENZOTHIAZIN-4-ONES

Authors: Emiliya V. Nosova, Olga A. Batanova, Galina N. Lipunova, Svetlana K. Kotovskaya, Pavel A. Slepukhin, Marionella A. Kravchenko, Valery N. Charushin

PII: S0022-1139(19)30004-1
DOI: https://doi.org/10.1016/j.jfluchem.2019.02.009
Reference: FLUOR 9292

To appear in: *FLUOR*

Received date: 4 January 2019
Revised date: 20 February 2019
Accepted date: 22 February 2019

Please cite this article as: Nosova EV, Batanova OA, Lipunova GN, Kotovskaya SK, Slepukhin PA, Kravchenko MA, Charushin VN, SYNTHESIS AND ANTITUBERCULAR EVALUATION OF FLUORINATED 2-CYCLOALKYLIMINO SUBSTITUTED 1,3-BENZOTHIAZIN-4-ONES, *Journal of Fluorine Chemistry* (2019), https://doi.org/10.1016/j.jfluchem.2019.02.009

SYNTHESIS AND ANTITUBERCULAR EVALUATION OF FLUORINATED 2-CYCLOALKYLIMINO SUBSTITUTED 1,3-BENZOTHIAZIN-4-ONES

Emiliya V. Nosova,*[a,b] Olga A. Batanova,[a] Galina N. Lipunova,[b] Svetlana K. Kotovskaya,[a,b] Pavel A. Slepukhin,[a,b] Marionella A. Kravchenko[c] and Valery N. Charushin[a,b]

[a]*Department of Organic and Biomolecular Chemistry, Ural Federal University, 19 Mira st., Ekaterinburg 620002, Russia. E-mail: emily74@rambler.ru*
[b]*Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences 22 S. Kovalevskaya st. /20 Akademicheskaya st., Ekaterinburg 620137, Russia*
[c]*Ural Research Institute for Phthisiopulmonology, 50 XXII Parts'ezda St., Ekaterinburg 620039, Russia*
**The corresponding author*

Highlights

- Interaction of *o*-fluorobenzoyl isothiocyanates with cycloalkylimines was studied
- Synthesis of novel 5-fluoro- and 6,7,8-trifluoro-1,3-benzothiazin-4-ones was developed
- X-ray data for 6,7,8-trifluoro-2-(thiomorpholin-4-yl)-1,3-benzothiazin-4-one were obtained
- Fluorinated benzothiazinones exhibit a good level of antimycobacterial activity

Abstract

Novel fluorinated 2-substituted 1,3-benzothiazin-4-ones were obtained through the addition of N-nucleophiles to *ortho*-fluorobenzoylisothiocyanates, followed by cyclization of fluorobenzoyl-thioureas. Synthetic approaches to original 2-cycloalkylimino- and 2-carbonylpiperazino-substituted benzothiazinones, bearing different number of fluorine atoms in the benzene ring have been found. 2-Ethoxycarbonylpiperazino-5-fluoro-1,3-benzothiazin-4-one proved to exhibit a high tuberculostatic activity *in vitro* (MIC 0.7 microgram/mL), thus indicating that a search of biologically active compounds in this family of heterocycles appears to be a reasonable approach.

Keywords: fluorinated benzothiazinones, *o*-fluorobenzoylisothiocyanates, 4-ethoxycarbonyl-piperazine, tuberculosis, multi-drug-resistant tuberculosis, *in vitro* activity.

1. Introduction

Tuberculosis (TB) is one of the most urgent problems for modern world community, and it is recognized by World Health Organization (WHO) as a disease, which demands a number of active measures to prevent distribution of this danger over the world. Among main problems associated with treatment of TB the following ones have to be mentioned: a restricted arsenal of efficient anti-tuberculosis drugs; a fast appearance of stable forms of TB mycobacteria in the course of treatment; and, as a result, a wide spread of patients with multi-drug resistant (MDR-TB) and extensively drug-resistant *M. tuberculosis* (XDR-TB) strains [1, 2].

Benzothiazinone derivatives are of particular interest due to their recently discovered ability to be active against TB mycobacteria by blocking decaprenylphosphoryl-*beta*-D-ribose-2-epimerase (DprE1), the enzyme catalyzing transformation of decaprenylphosphoryl substituted ribose into its epimere, the corresponding arabinose, and this conversion proved to be the key step in biosynthesis of arabinane, as a building block for TB mycobacteria cell wall [3]. Indeed, benzothiazinones BTZ043 and PBTZ169, bearing the trifluoromethyl group in position 6 and the nitro group at C-8 proved to be the most promising in this respect (Figure 1) [4, 5]. It is quite understandable that 6-trifluoromethyl-8-nitro-1,3-benzothiazin-4-ones, bearing not only piperidine or piperazine fragments, but a variety of cycloalkylimino substituents, have been intensively studied during the last decade [6-11].

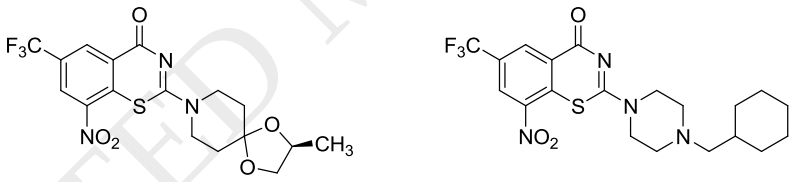


Figure 1. Structures of the known DprE1 inhibitors.

In general, several approaches are considered to be suitable to obtain 2-amino-1,3-benzothiazin-4-ones: a) cyclocondensation of 2-mercaptobenzoic acid with the appropriate cyanamides [12]; b) the reaction of 2-chlorobenzcarboxamide with sodium salt of dithiocarbamate [13, 14]; c) addition of primary or secondary amines to 2-halo substituted benzoylisothiocyanates with subsequent intramolecular cyclizations [6, 15, 16]. In this respect benzoylisothiocyanates, bearing an additional fluorine atom in the *ortho*-position of the benzene ring seem to be the most suitable intermediates for the synthesis of fluorinated 2-cycloalkylimino-1,3-benzothiazin-4-ones [17].

It has been shown that the reaction of tetrafluorobenzoylisothiocyanates with amino-azines provides a convenient approach to 2-heterylamino-6,7,8-trifluoro-1,3-benzothiazin-4-ones [17]; and a number of compounds from the obtained family of fluorine-containing benzo-thiazinones have demonstrated a high antitubercular activity [18].

The aim of this communication is to describe the synthesis of 2-cycloalkylimino-1,3-benzothiazin-4-ones, bearing one or several fluorine atoms in the benzene ring, and to study their antimicrobial activity, including that relative to multi-drug resistant strains of *M. tuberculosis*, to expand synthetic opportunities for the development of anti-tuberculosis agents.

2. Results and discussion

Fluorinated benzoyl isothiocyanates **2a-d** have been found to react smoothly with some cycloalkylimines **3** in acetonitrile at room temperature (reaction time 3 h) to give the corresponding addition products **4a**–**p** in 76–89% yields (Scheme 1). Fluorobenzoyl substituted derivatives **4** were characterized by ^{1}H, ^{13}C and ^{19}F NMR data.

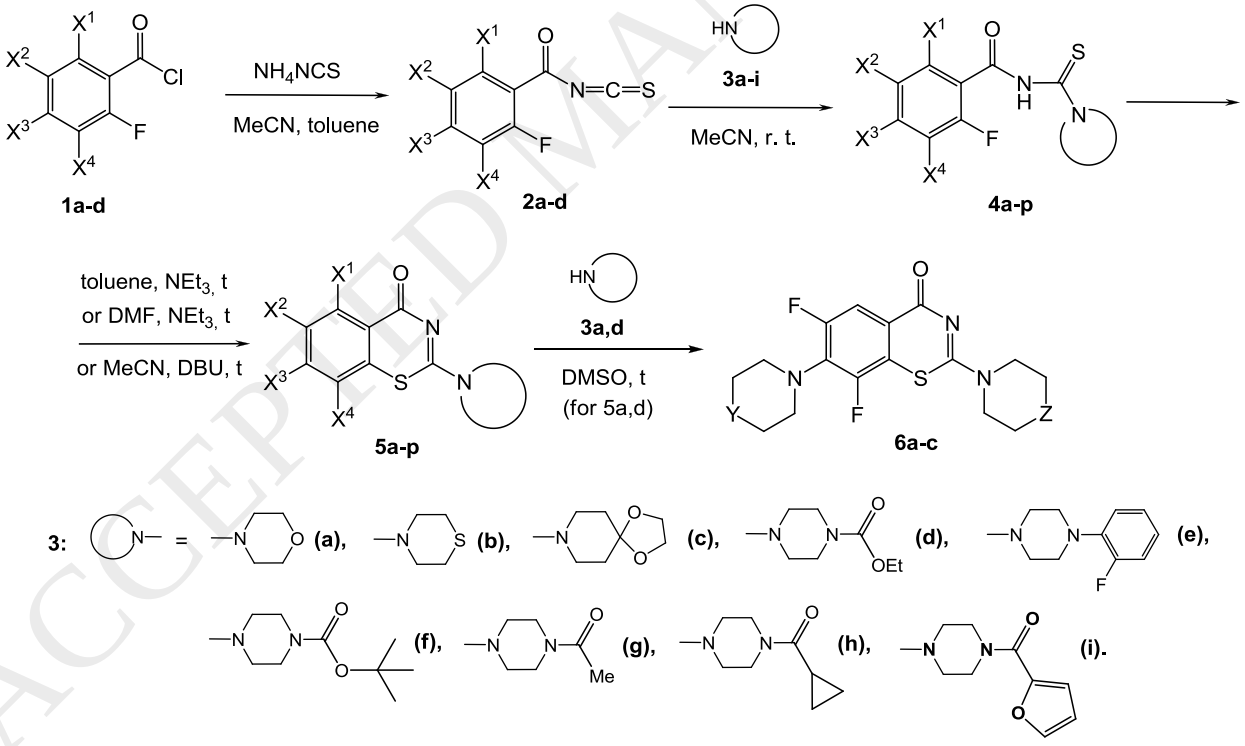
The ^{1}H NMR spectra of compounds **4a**–**p** confirm the presence in their molecules of cycloalkylamino fragments and NH groups (broadened signals at δ 10.7–11.4 ppm), while proton multiplet at δ 7.55–7.61 ppm in the spectra of compounds **4a-f** is a typical one for the tetrafluorobenzoyl moiety. The ^{1}H NMR spectra of 2,6-difluorobenzoyl compounds **4g-n** contain a two-proton signal of H-3 and H-5 at 7.03–7.11 ppm and one-proton triplet of triplets of H-4 at 7.47–7.52 ppm. Multiplets of three benzene ring protons in the range of 7.11–7.78 ppm were observed in the ^{1}H NMR spectra of 2,4-difluoro and 2,3-difluoro derivatives **4o,p**.

The ^{19}F NMR spectra of compounds **4a-f** proved to exhibit four signals of C_6HF_4 fragment: at -137.68– (-137.84) ppm, -138.73– (-138.83) ppm, -151.61– (-151.78) ppm and -155.29– (-155.37) ppm. In the ^{19}F NMR spectra of symmetrical 2,6-difluorobenzoyl derivatives **4g-n** a singlet at -112.74 – (-113.06) ppm was observed. 2,4-Difluorobenzoyl compound **4o** was characterized by two doublets, originating from these fluorine atoms at -107.58 and -104.49 ppm with ^{4}J= 11 Hz, whereas two doublets in the ^{19}F NMR spectra of 2,3-difluoro analogue **4p** were shifted upfield (-139.26 and -133.35 ppm with ^{3}J 18.5 = Hz).

Tetrafluorobenzoyl substituted thioureas **4a-f** have been shown to undergo intramolecular cyclization into 1,3-benzothiazin-4-ones **5a-f** (yields 59–84%); this conversion takes place smoothly on heating for 3−6 hours in boiling toluene in the presence of triethylamine (Scheme 1). Attempts to perform cyclization of difluorobenzoyl compounds **4g-p** into the corresponding 1,3-benzothiazin-4-ones **5g-p** under the same conditions (reflux in toluene, the presence of triethylamine), have failed. However, heating of compounds **4g-p** in DMF in the presence of triethylamine (reaction time 6-8 hours) proved to be an effective procedure for the synthesis of 5-

fluoro-1,3-benzothiazin-4-ones **5g-p** (Scheme 1). Compounds **5g-j,l-p** were obtained in 78-85% yields, whereas the yield of 4-(*t*-butoxycarbonyl)piperazin-1-yl derivative **(5k)** was only 45%. It has been found that **4k** undergoes cyclization into benzothiazinone **5k** in refluxing acetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 81% yield.

The structure of 1,3-benzothiazin-4-ones **5a**–**p** has been confirmed by ^{1}H, ^{13}C, ^{19}F NMR and mass spectra. The ^{1}H NMR spectra of **5a**–**f** have exhibited signals from protons of cycloalkylimino fragments (similar to the ^{1}H NMR spectra of the starting thioureas), and the multiplicity of H-5 signal has changed to a double doublet of doublets (δ 7.99–8.01 ppm), while NH signal has disappeared expectedly. In the ^{19}F NMR spectra of compounds **5a**–**f** multiplet signals from three fluorine atoms were observed, while spectra of 4-(2-fluorophenyl)piperazinyl derivative **5e** exhibited one more signal from the C_6H_4F fragment. The molecular ion peaks in mass spectra of 2-cycloalkylamino-1,3-benzothiazin-4-ones **5a**–**f** have relative intensities of 2–32%. The ion *m*/*z* 190 with 100% intensity was observed for benzothiazinone **5a,** whereas the most abundant peak was observed in case of 2-heterylamino-6,7,8-trifluoro-1,3-benzothiazin-4-ones due to elimination of HetNHCN fragment from its molecular ion [11].



1, 2: X^1 = H, X^2 = X^3 = X^4 = F (**a**); X^1 = F, X^2 = X^3 = X^4 = H (**b**);
X^3 = F, X^1 = X^2 = X^4 = H (**c**); X^4 = F, X^1 = X^2 = X^3 = H (**d**);
4, 5: X^1 = H, X^2 = X^3 = X^4 = F, cycloalkylimino = morpholin-4-yl **(a)**, thiomorpholin-4-yl **(b)**, 1,4-dioxa-8-azaspiro[4.5]decane-8-yl **(c),** 4-ethoxycarbonylpiperazin-1-yl **(d)**, 4-(2-fluorophenyl)piperazin-1-yl **(e),** 4-(*t*-butoxycarbonyl)piperazin-1-yl **(f)**;
X^1 = F, X^2 = X^3 = X^4 = H, cycloalkylimino = morpholin-4-yl **(g)**, thiomorpholin-4-yl **(h)**, 4-ethoxycarbonylpiperazin-1-yl **(i)**, 4-(2-fluorophenyl)piperazin-1-yl **(j)**, 4-(*t*-butoxycarbonyl)piperazin-1-yl **(k)**, 4-acetylpiperazin-1-yl **(l)**,

4-cyclopropylcarbonylpiperazin-1-yl **(m)**, 4-(2-furoyl)piperazin-1-yl **(n)**,
X^3 = F, X^1 = X^2 = X^4 = H, cycloalkylimino = 4-ethoxycarbonylpiperazin-1-yl **(o)**;
X^4 = F, X^1 = X^2 = X^3 = H, cycloalkylimino = 4-ethoxycarbonylpiperazin-1-yl **(p)**.
6: Z = N-COOEt, Y = O (**a**); Z = Y = O (**b**); Z = Y = N-COOEt (**c**).

Scheme 1

According to the XRD data, compound **5b** is crystallized in the centrosymmetric space group of the monoclinic system (Figure 2). The benzothiazine part of the molecule is planar. The bond distances for double and single bonds of the thiazinone moiety are well distinguished (the distances N(2)-C(3) = 1.370(3) Å, N(2)-C(1) = 1.303(3) Å). The thiomorpholino fragment has a "chair" conformation with (pseudo)axial position of the substituent at N(1) atom. The N(1) atom has a planar trigonal configuration and strong conjugation with the thiazine ring (the bond distances N(1)-C(1) = 1.338(3) Å, N(1)-C(2) = N(1)-C(12) = 1.465(4) Å). The crystal packing is presented by stacks with shortened intermolecular contacts (with interatomic distances more when 3.35 Å). Also, the F…F contacts are observed between stacks with distances F(2)…F(2) [1-x, 1-y, 3-z] 2.711 Å. The shortened F…H and O…H contacts with participation of CH_2-groups of the thiomorpholino moiety are induced probably by other interatomic contacts.

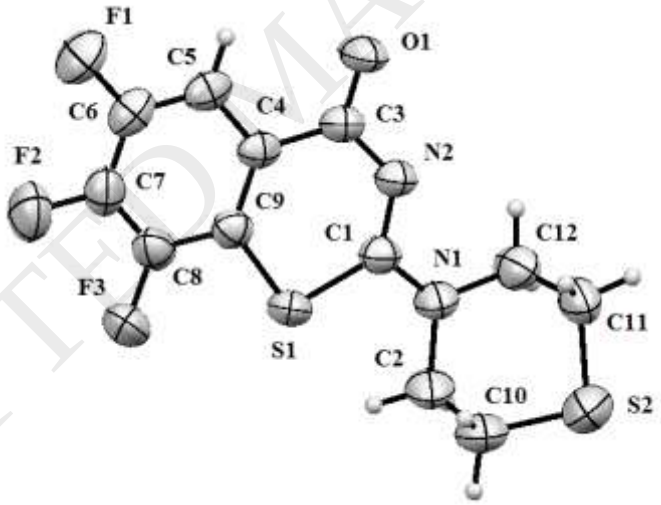


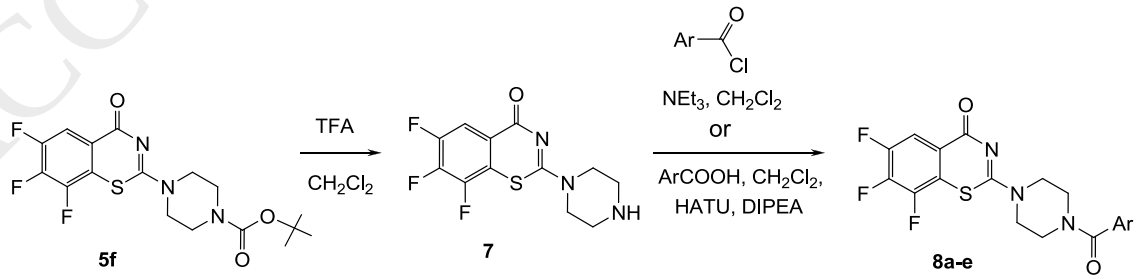
Figure 2. The molecule of benzothiazinone **5b** according to the XRD data in the thermal ellipsoids of the 50% probability level.

The ^{1}H NMR spectra of 5-fluorobenzothiazinones **5g-n** exhibit three groups of signals for the benzene ring protons: H-6 signals are observed in the region of 7.18−7.30 ppm, H-8 at 7.32−7.47 ppm, and triple doublets of H-7 at 7.58−7.65 ppm. In the ^{19}F NMR {^{1}H} spectra of compounds **5g-n** singlets at -107.86−(-108.95) ppm belong to fluorine atoms of the benzene ring. In the ^{19}F NMR spectra of 7-fluoro-1,3-benzothiazin-4-one **5o** the signal of 7-fluoro atom is observed at -106.44 ppm, whereas in case of its 8-fluoro analogue **5p** it resonates at -115.94 ppm.

The mass spectra of mono-fluorinated 2-cycloalkylimino-1,3-benzothiazin-4-ones **5g-p** contain peaks of molecular ions with intensities 3–23%, and the most abundant for benzothiazinones **5g-i,l,o,p** peak *m/z* 154, corresponding to the fragment $[M\text{-}R_2NCN]^+$.

Nucleophilic substitution of F(7) atom by morpholine **3a** or 1-ethoxycarbonylpiperazine **3d** in benzothiazinones **5a,d**, proceeding in refluxing DMSO, afforded 6,8-difluoro-1,3-benzothiazin-4-ones **6a-c**, bearing cycloalkylimino substituents in positions 2 and 7 (Scheme 1). The ^{1}H NMR spectra of 6,8-difluorobenzothiazinones **6a**–**c** exhibit proton resonances of cycloalkylimino fragment, as well as H-5 signals at 7.73–7.74 ppm. In the ^{19}F NMR spectra of compounds **6** signals of two fluorine atoms were observed at -120.4–(-120.9) ppm and -124.0–(-124.5) ppm. The mass spectra of fluorinated 1,3-benzothiazin-4-ones **6** contain peaks of molecular ions with intensities 32–44%, while for compounds **6a,b** the most abundant was the peak *m/z* 257, corresponding to the fragment $[M\text{-}R_2NCN]^+$. It is worth noting that compounds **6b,c** proved to be identical to products obtained from the reaction of 2-(2-pyridylamino)-6,7,8-trifluoro-1,3-benzothiazin-4-one due to replacement of 7-fluoro and the amino group in position 2 [17].

Modification of the piperazine fragment in compound **5f** was performed through deprotection of Boc and subsequent aroylation (Scheme 2) under the same reaction conditions, as described for 4-carbonyl piperazine substituted 6-trifluoromethyl-8-nitro-1,3-benzothiazin-4-ones [7]. Deprotection of Boc, proceeding in trifluoroacetic acid, afforded the intermediate **7** in 70% yield. To get target compounds **8**, benzothiazinone **7** was condensed with the corresponding carboxylic acids or acyl chlorides, respectively. Compound **7** proved to react with carboxylic acids catalyzed by combination of HATU and DIPEA at room temperature, or could directly be condensed with aroyl chlorides for 4 hours at 55 °C, thus giving benzothiazinones **8a-e**. The structures of compounds **8a-e** were determined by ^{1}H NMR, ^{19}F NMR and MS. In the ^{19}F NMR spectra of benzothiazinones **8a-e** the signals of F-6 were observed at -134.40−(-134.61) ppm, F-8 in the range of -136.17−(-136.24) ppm, and double doublets of F-7 were exhibited at -153.38−(-153.49) ppm.



8: Ar = 4-*t*BuC$_6$H$_4$ (**a**), Ph (**b**), 2,6-diFC$_6$H$_3$ (**c**), 4-EtC$_6$H$_4$ (**d**), 3-FC$_6$H$_4$ (**e**).

Scheme 2

Fluorinated benzothiazinones **5, 6, 8** were screened to estimate the level of their activity against *Mycobacterium tuberculosis* $H_{37}R_v$ strain, and the influence of two factors (a number and positions of fluorine atoms in the benzene ring, as well as the nature of the substituent at the position 2) on their activity was considered. 5-Fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one **(5i)** exhibited the highest activity (MIC 0.7 μg/mL) [19], transfer from **5i** to 7-fluoro (**5o,** MIC 12.5 μg/mL), 8-fluoro (**5p,** MIC 12.5 μg/mL), 6,8-difluoro (**6a-c,** MIC 12.5 μg/mL) or 6,7,8-trifluoro (**5d,** MIC 12.5 μg/mL) derivatives led to a decrease of activity. Replacement of ethoxycarbonylpiperazinyl fragment (**5i,** MIC 0.7 μg/mL) with thiomorpholino (**5h,** MIC 3.1 μg/mL**)**, morpholino (**5g,** MIC 12.5 μg/mL**)**, 4-(2-fluorophenyl)piperazino (**5j,** MIC 12.5 μg/mL**)**, 4-acylpiperazino (**5l,m,** MIC 12.5 μg/mL**)** or 4-(2-furoyl)piperazino (**5n,** MIC 12.5 μg/mL**)** also led to a decrease of activity. In the series of 6,7,8-trifluoro-1,3-benzothiazin-4-ones **5a-f, 8** only 2-thiomorpholinyl compound **5b** proved to exhibit MIC 6.2 μg/mL, the rest of derivatives demonstrated a lower activity (**5a,c-f, 8**, MIC 12.5 μg/mL).

It is worth noting that compound **5i** exhibits the highest activity (MIC 0.7 μg/mL) not only against *M. tuberculosis* $H_{37}R_v$, but also against *M. avium*, *M. terrae* and MDR strains (Table). It is important that, unlike the known anti-tuberculosis drug Isoniazide, benzothiazinone **5i** was active against MDR strains, while its acute toxicity in mice LD_{50} was found to be 600 mg/kg.

Table

In vitro antimycobacterial activity of 5-fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one **5i** and its acute *in vivo* toxicity in mice

Com-Pound	Antimycobacterial activity against different strains of *M. tuberculosis* (MIC in μg/mL)				LD_{50} in mice (mg/kg)
	$H_{37}R_V$	*M. avium*	*M. terrae*	MDR-TB [a]	
5i	0.7	0.7	0.7	0.7	600
LEV	0.5 [b]	n.d.	n.d.	n.d.	1500-2000 [b]
INH	0.1	0.1	0.1	–	149[c] 151[d]

n.d. – not determined; INH – Izoniazid; LEV – Levofloxacin;

[a] MDR-TB – Rifampin and Izoniazid resistant *Mycobacterium tuberculosis* strain having Beijing genotype with a combination of mutations *Ser 531-Leu 315* and *Ser-Thr* in *rpoB* and *katC* genes, respectively.

[b] LD_{50} oral administration in mice and rats [20].

[c] LD_{50} i.v. administration in mice [20].

[d] LD_{50} i.p. administration in mice [20].

3. Conclusion

In summary, an efficient synthetic approach to fluorine-containing 2-cycloalkylimino substituted 1,3-benzothiazin-4-ones has been developed. It is based on addition of N-nucleophiles to *o*-fluorobenzoyl substituted isothiocyanates and subsequent intramolecular cyclizations of intermediates. As a result, novel 1,3-benzothiazin-4-ones, with varying number and positions of fluorine atoms in the benzene ring have been obtained.

In the series of novel fluorinated benzothiazinones a number of compounds have been discovered which exhibit a good level of antimycobacterial activity. These compounds can possibly be modified further to reach a better potency than the reference drugs. The results obtained show that some fluorobenzothiazinones can be regarded as promising anti-*M. tuberculosis* agents. Further studies are necessary to be done to get more detailed data concerning structure–activity relationships (QSAR).

4. Experimental

4.1. General

Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification.

The ^{1}H NMR (400.13 MHz) and ^{19}F NMR (376.45 MHz) spectra were obtained on a Bruker Avance II DMX400 spectrometer using DMSO-d_6 as the solvent. The ^{1}H NMR experiments were carried out using trimethylsilane as the internal standard and the ^{19}F NMR spectra were recorded with $CFCl_3$ (C_6F_6 was used as secondary reference, δ_F –162.9 ppm). ^{13}C (125.7 MHz) NMR spectra were recorded on the AVANCE-500 spectrometer in DMSO-d_6 solution.

Mass spectra were recorded on a SHIMADZU GCMS-QP2010 Ultra instrument with electron ionization (EI) of the sample. Microanalyses (C, H, N) were performed using a Perkin–Elmer 2400 elemental analyzer. Melting points were measured on the instrument Boetius. Microanalyses (C, H, N) were performed using the Perkin–Elmer 2400 elemental analyzer.

The structure of compound **5b** was determined on an Xcalibur E X-ray diffractometer. The single crystal (colorless prism, 0.25×0.20×0.15) of compound **5b** ($C_{12}H_9F_3N_2OS_2$) was used for X-ray analysis. Analysis was performed at 295(2) K on an automated "Xcalibur 3" diffractometer on standard procedure (graphite monochromated MoKα irradiation (λ= 71.073 pm), ω-scans with 1° step, CCD detector). An empirical absorption correction was applied (μ = 0.437 mm^{-1}). Crystal is monoclinic, space group $P2_1/n$ with a = 6.7672(12), b = 18.952(2), c = 10.4881(14) Å, β = 102.592(16)°, V = 1312.8(3) Å^3, Z = 4. On the angles 2.26 < θ < 27.10° 5056 reflections were measured, among them 2849 unique reflections (R_{int} = 0.0297), 1952 reflections with $I>2\sigma(I)$. Completeness to θ = 26.00 is 98.30%. The structure was solved by direct method and refined by

full-matrix least squares at F^2 using the SHELXTL program package.[1] All non-hydrogen atoms were refined anisotropically, the positions of the hydrogen atoms were calculated as a riding model in isotropic approximation. Goodness to fit at F^2 1.061; final R values [$I>2\sigma(I)$]: R_1 = 0.0586, wR_2 = 0.1550; R value (all reflections): R_1 = 0.0837, wR_2 = 0.1835. Largest difference peak and hole were 0.498 and -0.309 ēÅ^{-3}.

CCDC 1875321 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.

Commercially purchased 2,3,4,5-tetrafluorobenzoylchloride **1a**, 2,6-difluoro-benzoylchloride **1b**, 2,4-difluorobenzoylchloride **1c** and 2,3-difluorobenzoylchloride **1d** were used for the preparation of intermediates **2a-d**.

4.2. Procedure for the Synthesis of o-fluorosubstituted N-(cycloalkylimino-4-carbothioyl)benzamides (4a-p)

General Procedure

To *o*-fluorobenzoylchloride **1** (4.5 mmol) a solution of ammonium thiocyanate (0.35 g, 4.5 mmol) in acetonitlile (13 mL) was added. Reaction mixture was stirred at 40 °C for 5 min, the precipitate of NH_4Cl was filtered off, and cycloalkylimine **3** (4.5 mmol) was added to a solution of *o*-fluorobenzoylisothiocyanate **2**. Mixture was stirred at room temperature for 3 h, the precipitate was filtered off and recrystallized from ethanol.

*2,3,4,5-Tetrafluoro-N-(morpholine-4-carbothioyl)benzamide **(4a)***

Yield 76%, mp 201−203 °C. ^{1}H NMR (DMSO-d_6): 3.72 (m, 6H, N(CH_2)$_2$, OCH_2), 4.14 (m, 2H, OCH_2), 7.60 (m, 1H, C_6HF_4), 11.1 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): -137.79 (m, 1F), -138.83 (m, 1F), -151.71 (m, 1F), -155.37 (m, 1F). ^{13}C NMR (DMSO-d_6): 42.92 (s, NCH_2), 50.64 (s, NCH_2), 63.31 (s, OCH_2), 65.48 (s, OCH_2), 112.11 (d, C-6, $^2J_{CF}$ = 19.9 Hz), 129.84 (m, C-1), 139.81 (dt, C-3, $^1J_{CF}$ = 249.8, $^2J_{CF}$ = 15.0 Hz), 141.36 (dt, C-4, $^1J_{CF}$ = 253.6, $^2J_{CF}$ = 13.4 Hz), 145.12 (dd, C-2, $^1J_{CF}$ = 246.6, $^2J_{CF}$ = 13.4 Hz), 146.03 (dd, C-2, $^1J_{CF}$ = 246.6, $^2J_{CF}$ = 11.8 Hz), 159.21 (s, CO), 178.48 (s, CS). MS, *m/z* (rel. int.): 322 (19) [M]$^+$, 177 (31), 149 (19), 99 (13), 86 (100), 58 (12), 56 (11). Calcd for $C_{12}H_{10}F_4N_2O_2S$: C 44.72; H 3.13; N 8.69. Found: C 44.61; H 3.07; N 8.78.

*2,3,4,5-Tetrafluoro-N-(thiomorpholine-4-carbothioyl)benzamide **(4b)***

Yield 81%, mp 154−156 °C. ^{1}H NMR (DMSO-d_6): 2.78 (m, 4H, S(CH_2)$_2$), 3.92 (m, 2H, NCH_2), 4.39 (m, 2H, NCH_2), 7.57 (m, 1H, C_6HF_4), 11.1 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): -137.68

(m, 1F), -138.73 (m, 1F), -151.67 (m, 1F), -155.33 (m, 1F). Calcd for $C_{12}H_{10}F_4N_2OS_2$: C 42.60; H 2.98; N 8.28. Found: C 42.49; H 2.87; N 8.36.

2,3,4,5-Tetrafluoro-N-(1,4-dioxa-8-azaspiro[4.5]decane-8-carbothioyl)benzamide ***(4c)***

Yield 79%, mp 156−158 °C. ^{1}H NMR (DMSO-d_6): 1.83 (m, 4H, $(CH_2)_2$), 3.96 (m, 6H, $N(CH_2)_2$, OCH_2), 4.20 (m, 2H, OCH_2), 7.56 (m, 1H, C_6HF_4), 10.9 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): -137.72 (m, 1F), -138.78 (m, 1F), -151.78 (m, 1F), -155.37 (m, 1F). Calcd for $C_{15}H_{14}F_4N_2O_3S$: C 47.62; H 3.73; N 7.40. Found: C 42.51; H 3.64; N 7.48.

2,3,4,5-Tetrafluoro-N-(4-ethoxycarbonylpiperazine-1-carbothioyl)benzamide ***(4d)***

Yield 82%, mp 153−155 °C. ^{1}H NMR (DMSO-d_6): 1.26 (t, 3H, CH_3), 3.57 (m, 4H, $N(CH_2)_2$), 3.70 (m, 2H, NCH_2), 4.10 (m, 4H, OCH_2, NCH_2), 7.61 (m, 1H, C_6HF_4), 11.2 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): -137.84 (m, 1F), -138.82 (m, 1F), -151.69 (m, 1F), -155.37 (m, 1F). Calcd for $C_{15}H_{15}F_4N_3O_3S$: C 45.80; H 3.84; N 10.68. Found: C 45.70; H 3.83; N 10.74.

2,3,4,5-Tetrafluoro-N-[(4-(2-fluorophenyl)piperazine-1-carbothioyl]benzamide ***(4e)***

Yield 77%, mp 99−101 °C. ^{1}H NMR (DMSO-d_6): 3.21 (m, 4H, $N(CH_2)_2$), 3.83 (m, 2H, NCH_2), 4.30 (m, 2H, NCH_2), 7.00 (m, 1H, C_6H_4F), 7.09 (m, 3H, C_6H_4F), 7.61 (m, 1H, C_6HF_4), 10.8 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -122.71 (s, 1F), -137.72 (m, 1F), -138.79 (m, 1F), -151.69 (m, 1F), -155.34 (m, 1F). Calcd for $C_{18}H_{14}F_5N_3OS$: C 52.05; H 3.40; N 10.12. Found: C 51.94; H 3.33; N 10.19.

2,3,4,5-Tetrafluoro-N-(4-t-butoxycarbonylpiperazine-1-carbothioyl)benzamide ***(4f)***

Yield 82%, mp 144−146 °C. ^{1}H NMR (DMSO-d_6): 1.45 (s, 9H, $C(CH_3)_3$), 3.54 (m, 4H, $N(CH_2)_2$), 3.68 (m, 2H, $N(CH_2)$), 4.10 (m, 2H, $N(CH_2)$), 7.55 (m, 1H, C_6HF_4), 11.1 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -137.56 (s, 1F); -138.73 (м, 1F); -151.61 (m, 1F); -155.29 (m, 1F). Calcd for $C_{17}H_{19}F_4N_3O_3S$: C 48.45; H 4.54; N 9.97. Found: C 48.50; H 4.56; N 9.90.

2,6-Difluoro-N-(morpholine-4-carbothioyl)benzamide ***(4g)***

Yield 84%, mp 177−179 °C. ^{1}H NMR (DMSO-d_6): 3.74 (m, 6H, $N(CH_2)_2$, OCH_2), 4.13 (m, 2H, OCH_2), 7.08 (ddd, 2H, H-3, H-5, J = 10.8, J = 8.0, J = 2.6 Hz), 7.50 (tt, 1H, H-4, J = 8.4, J = 6.6 Hz), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -113.06 (s). ^{13}C NMR (DMSO-d_6): 50.26 (s, NCH_2), 50.16 (s, NCH_2), 65.53 (s, $O(CH_2)_2$), 111.93 (dd, C-3, C-5, $^2J_{CF}$ = 23.3, $^4J_{CF}$ = 6.2 Hz), 114.04 (t, C-1, $^2J_{CF}$ = 21.8 Hz), 132.57 (t, C-4, $^3J_{CF}$ = 9.5 Hz), 157.70 (s, C(O)Ar), 158.83 (dd, C-

2, C-6, $^{1}J_{CF}$ = 249.5, $^{3}J_{CF}$ = 7.9 Hz), 178.94 (C=S). Calcd for $C_{12}H_{12}F_2N_2O_2S$: C 50.34; H 4.22; N 9.78. Found: C 50.27; H 4.16; N 9.84.

2,6-Difluoro-N-(thiomorpholine-4-carbothioyl)benzamide ***(4h)***

Yield 82%, mp 115−117 °C. ^{1}H NMR (DMSO-d_6): 2.79 (m, 4H, $S(CH_2)_2$), 3.96 (m, 2H, NCH_2), 4.38 (m, 2H, NCH_2), 7.08 (ddd, 2H, H-3, H-5, *J* = 10.9, *J* = 8.0. *J* = 2.6 Hz), 7.49 (tt, 1H, H-4, *J* = 8.4, *J* = 6.5 Hz), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -112.98 (s). ^{13}C NMR (DMSO-d_6): 26.37 (s, SCH_2), 26.75 (s, SCH_2), 52.69 (s, $N(CH_2)_2$), 111.94 (dd, C-3, C-5, $^{2}J_{CF}$ = 24.6, $^{4}J_{CF}$ = 4.1 Hz), 114.07 (t, C-1, $^{2}J_{CF}$ = 21.8 Hz), 132.56 (t, C-4, $^{3}J_{CF}$ = 9.5 Hz), 157.59 (s, C(O)Ar), 158.82 (dd, C-2, C-6, $^{1}J_{CF}$ = 249.5, $^{3}J_{CF}$ = 8.1 Hz), 178.40 (C=S). Calcd for $C_{12}H_{12}F_2N_2OS_2$: C 47.67; H 4.00; N 9.26. Found: C 47.59; H 3.94; N 9.31.

2,6-Difluoro-N-(4-ethoxycarbonylpiperazine-1-carbothioyl)benzamide ***(4i)***

Yield 83%, mp 154−156 °C. ^{1}H NMR (DMSO-d_6): 1.26 (t, 3H, CH_3), 3.57 (m, 4H, $N(CH_2)_2$), 3.72 (m, 2H, NCH_2), 4.10 (m, 4H, OCH_2, NCH_2), 7.11 (ddd, 2H, H-3, H-5, *J* = 10.8, *J* = 7.9. *J* = 2.5), 7.50 (tt, 1H, H-4, *J* = 8.4, *J* = 6.5 Hz), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -113.01 (s). ^{13}C NMR (DMSO-d_6): 14.50 (s, CH_3), 42.34 (s, $N(CH_2)_2$), 49.61 (s, $N(CH_2)_2$), 61.01 (s, OCH_2), 111.93 (dd, C-3, C-5, $^{2}J_{CF}$ = 26.3, $^{4}J_{CF}$ = 5.0 Hz), 114.03 (t, C-1, $^{2}J_{CF}$ = 21.2 Hz), 132.59 (t, C-4, $^{3}J_{CF}$ = 9.7 Hz), 154.53 (s, COO), 157.86 (s, C(O)Ar), 158.85 (dd, C-2, C-6, $^{1}J_{CF}$ = 250.7, $^{3}J_{CF}$ = 8.5 Hz), 178.38 (C=S). Calcd for $C_{15}H_{17}F_2N_3O_3S$: C 50.41; H 4.79; N 11.76. Found: C 50.35; H 4.71; N 11.83.

2,6-Difluoro-N-[(4-(2-fluorophenyl)piperazine-1-carbothioyl]benzamide ***(4j)***

Yield 77%, mp 155−157 °C. ^{1}H NMR (DMSO-d_6): 3.22 (m, 4H, $N(CH_2)_2$), 3.85 (m, 2H, NCH_2), 4.31 (m, 2H, NCH_2), 6.98 (m, 1H, C_6H_4F), 7.07 (m, 5H, C_6H_4F, H-3, H-5), 7.52 (m, 1H, H-4), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -112.96 (s, 2F), -122.60 (s, 1F). Calcd for $C_{18}H_{16}F_3N_3OS$: C 56.98; H 4.25; N 11.08. Found: C 56.86; H 4.14; N 11.17.

*2,6-Difluoro-**N**-(4-t-butoxycarbonylpiperazine -1-carbothioyl)benzamide* ***(4k)***

Yield 76%, mp 130−132 °C. ^{1}H NMR (DMSO-d_6): 1.45 (s, 9H, $C(CH_3)_3$), 3.54 (m, 4H, $N(CH_2)_2$), 3.70 (m, 2H, $N(CH_2)$), 4.10 (m, 2H, $N(CH_2)$), 7.06 (t, 2H, H-3, H-5, ^{3}J = 8.0 Hz), 7.51 (m 1H, H-4), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -112.93 s. Calcd for $C_{17}H_{21}F_2N_3O_3S$: C 52.98; H 5.49; N 10.90. Found: C 52.90; H 5.45; N 10.85.

2,6-Difluoro-N-(4-acetylpiperazin-1-carbothioyl)benzamide ***(4l)***

Yield 89%, mp 189−191 °C. ^{1}H NMR (DMSO-d_6): 2.05 (s, 3H, CH_3), 3.71–4.09 (m, 8H, 2N(CH_2)$_2$), 7.03 (ddd, 2H, H-3, H-5, $^{3}J_{HF}$ = 13.5, ^{3}J = 8.6, $^{5}J_{HF}$ = 1.6 Hz), 7.47 (tt, 1H, H-4, ^{3}J = 12.8, $^{4}J_{HF}$ = 4.8 Hz), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -112.79 s. ^{13}C NMR (DMSO-d_6): 21.19 (s, CH_3), 44.24 (s, NCH_2), 44.65 (s, NCH_2), 49.67 (s, NCH_2), 50.08 (s, NCH_2), 112.02 (dd, C-3, C-5, $^{2}J_{CF}$ = 23.8, $^{4}J_{CF}$ = 4.6 Hz), 114.03 (t, C-1, $^{2}J_{CF}$ = 21.8 Hz), 132.60 (t, C-4, $^{3}J_{CF}$ = 10.6 Hz), 157.80 (s, C(O)Me), 158.82 (dd, C-2, C-6, $^{1}J_{CF}$ = 253.4, $^{3}J_{CF}$ = 8.7 Hz), 168.64 (s, C(O)Ar), 178.23 (C=S). Calcd for $C_{14}H_{15}F_2N_3O_2S$: C 51.37; H 4.62; N 12.84. Found: C 51.44; H 4.68; N 12.79.

2,6-Difluoro-N-(4-cyclopropylcarbonylpiperazin-1-carbothioyl)benzamide ***(4m)***

Yield 88%, mp 148−150 °C. ^{1}H NMR (DMSO-d_6): 0.82 (m, 4H, 2CH_2), 1.91 (dd, 1H, CH, ^{3}J 10.2, ^{3}J = 5.5 Hz), 3.79 (m, 8H, 2N(CH_2)$_2$), 7.07 (dt, 2H, H-3, H-5, $^{3}J_{HF}$ = 6.1, ^{3}J = 8.2 Hz), 7.47 (m, 1H, H-4), 10.7 (s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -112.92 s. Calcd for $C_{16}H_{17}F_2N_3O_2S$: C 54.38; H 4.85; N 11.89. Found: C 54.45; H 4.91; N 11.83.

2,6-Difluoro-N-[4-(2-furoyl)carbonylpiperazin-1-carbothioyl]benzamide ***(4n)***

Yield 81%, mp 192−194 °C. ^{1}H NMR (DMSO-d_6): 3.89–4.19 (m, 8H, 2N(CH_2)$_2$), 6.56 (dd, 1H, H$^{4'}$, ^{3}J 3.4, ^{3}J 1.7 Гц), 7.04 (m, 3H, H-3, H-5, H-3'), 7.50 (tt, 1H, H-4, ^{3}J = 12.9, $^{4}J_{HF}$ = 8.6 Hz), 7.68 (d, 1H, H-5', ^{3}J = 5.0 Hz), 11.4 (s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6), δ, м.д.: -112.74 s. Calcd for $C_{17}H_{15}F_2N_3O_3S$: C 53.82; H 3.99; N 11.08. Found: C 53.90; H 4.05; N 11.02.

2,4-Difluoro-N-(4-ethoxycarbonylpiperazine-1-carbothioyl)benzamide ***(4o)***

Yield 85%, mp 162−164 °C. ^{1}H NMR (DMSO-d_6): 1.26 (t, 3H, CH_3), 3.57 (m, 4H, N(CH_2)$_2$), 3.66 (m, 2H, NCH_2), 4.08 (m, 4H, OCH_2, NCH_2), 7.11 (m, 2H, $C_6H_3F_2$), 7.72 (m, 1H, $C_6H_3F_2$), 10.9 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -107.58 (d, 1F, $^{4}J_{FF}$ = 11 Hz), -104.49 (d, 1F, $^{4}J_{FF}$ = 11 Hz). ^{13}C NMR (DMSO-d_6): 14.50 (s, CH_3), 42.32 (s, N(CH_2)$_2$), 49.59 (s, N(CH_2)$_2$), 60.99 (s, OCH_2), 104.64 (t, C-3, $^{2}J_{CF}$ =26.2 Hz), 111.80 (dd, C-5, $^{2}J_{CF}$ =29.4, $^{4}J_{CF}$ =4.6 Hz), 119.71 (dd, C-1, $^{2}J_{CF}$ =14.5, $^{4}J_{CF}$ =3.4 Hz), 132.15 (m, C-6), 154.54 (s, COO), 160.19 (dd, C-2, $^{1}J_{CF}$ =255.8, $^{4}J_{CF}$ =14.3 Hz), 161.16 (s, C(O)Ar), 164.02 (dd, C-4, $^{1}J_{CF}$ =252.8, $^{4}J_{CF}$ =12.0 Hz), 179.19 (C=S). Calcd for $C_{15}H_{17}F_2N_3O_3S$: C 50.41; H 4.79; N 11.76. Found: C 50.32; H 4.68; N 11.84.

2,3-Difluoro-N-(4-ethoxycarbonylpiperazine-1-carbothioyl)benzamide ***(4p)***

Yield 83%, mp 135−137 °C. ^{1}H NMR (DMSO-d_6): 1.21 (t, 3H, CH_3), 3.32 (m, 2H, N(CH_2)), 3.86 (m, 2H, N(CH_2)), 4.13 (q, 2H, CH_2), 7.26 (m, 1H, H-5), 7.47 м (m, 1H, H-4), 7.78 (m, 1H, H-6), 11.3 (br. s, 1H, NH). ^{19}F NMR {^{1}H} (DMSO-d_6): -139.26 (d, 1F, $^{3}J_{FF}$ = 18.5 Hz), -133.35 (d, 1F,

$^3J_{FF}$ = 18.5 Hz). Calcd for $C_{15}H_{17}F_2N_3O_3S$: C 50.41; H 4.79; N 11.76. Found: C 50.36; H 4.73; N 11.82.

4.3. Procedure for the Synthesis of fluorinated 2-cycloalkylimino-1,3-benzothiazin-4-ones (5a-p)

General Procedure for the synthesis of 6,7,8-trifluoro-2-cycloalkylimino-1,3-benzothiazin-4-ones ***(5a-f)***

To a suspension of 2,3,4,5-tetrafluoro-N-(cycloalkylimino-4-carbothioyl)benzamide **(4a-f)** (4.5 mmol) in toluene (20 mL) triethylamine (1.25 mL, 9 mmol) was added. Reaction mixture was refluxed during 3–7 h (control by TLC), and then cooled. The precipitate was filtered off, washed with water (20 mL) and recrystallized from ethanol.

6,7,8-Trifluoro-2-(morpholin-4-yl)-1,3-benzothiazin-4-one ***(5a)***

Yield 59%, mp 208−210 °C. ^{1}H NMR (DMSO-d_6): 3.75 (m, 4H, N(CH_2)$_2$), 3.88 (m, 4H, O(CH_2)$_2$), 8.00 (ddd, 1H, H-5, ^3J = 10.5, ^4J = 7.5, ^5J = 2.2 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.66 (dd, 1F, F-6, J = 21.4, J = 4.8 Hz), -136.31 (dd, 1F, F-8, J = 20.6, J = 4.8 Hz), -153.56 (dd, 1F, F-7, J = 20.8, J = 21.3 Hz). ^{13}C NMR (DMSO-d_6): 50.26 (s, NCH_2), 50.16 (s, NCH_2), 65.53 (s, O(CH_2)$_2$), 111.13 (d, C-5, $^2J_{CF}$ = 22.8 Hz), 113.11 (d, C-4a, $^3J_{CF}$ = 18.9 Hz), 118.33 (m, C-8a), 141.49 (dt, C-7, $^1J_{CF}$ = 257.8, $^2J_{CF}$ = 18.2 Hz), 145.44 (dd, C-8, $^1J_{CF}$ = 249.4, $^2J_{CF}$ = 14.6 Hz), 149.54 (dd, C-6, $^1J_{CF}$ = 247.6, $^2J_{CF}$ = 13.0 Hz), 159.27 (s, C-2), 164.48 (s, C(O)). MS, *m/z* (rel. int.): 302 (16) $[M]^+$, 259 (13), 245 (17), 191 (11), 190 (100), 162 (43), 144 (11), 93 (12), 55 (11). Calcd for $C_{12}H_9F_3N_2O_2S$: C 47.68; H 3.00; N 9.27. Found: C 47.81; H 3.07; N 9.19.

6,7,8-Trifluoro-2-(thiomorpholin-4-yl)-1,3-benzothiazin-4-one ***(5b)***

Yield 84%, mp 210−212 °C. ^{1}H NMR (DMSO-d_6): 2.78 (m, 4H, S(CH_2)$_2$), 4.18 (m, 2H, (NCH_2)$_2$), 7.99 (ddd, 1H, H-5, ^3J = 9.9, ^4J = 7.5, ^5J = 2.1). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.57 (dd, 1F, F-6, J = 21.6, J = 4.8 Hz), -136.28 (dd, 1F, F-8, J = 20.0, J = 4.8 Hz), -153.50 (t, 1F, F-7, J = 20.8 Hz). ^{13}C NMR (DMSO-d_6): 26.44 (s, S(CH_2)$_2$), 49.14 (s, N(CH_2)$_2$), 110.48 (d, C-5, $^2J_{CF}$ = 23.2 Hz), 113.09 (d, C-4a, $^3J_{CF}$ = 19.7 Hz), 118.37 (m, C-8a), 141.51 (dt, C-7, $^1J_{CF}$ = 258.5, $^2J_{CF}$ = 19.2 Hz), 145.44 (dd, C-8, $^1J_{CF}$ = 248.9, $^2J_{CF}$ = 15.0 Hz), 149.50 (dd, C-6, $^1J_{CF}$ = 248.9, $^2J_{CF}$ = 13.2 Hz), 159.32 (s, C-2), 164.58 (s, C(O)). MS, *m/z* (rel. int.): 318 (20) $[M]^+$, 245 (42), 218 (13), 191 (12), 190 (58), 162 (38), 144 (10), 127 (14), 93 (11), 69 (100), 68 (11), 55 (14), 46 (19), 45 (11), 42 (15). Calcd for $C_{12}H_9F_3N_2OS_2$: C 45.28; H 2.85; N 8.80. Found: C 45.20; H 2.77; N 8.89.

6,7,8-Trifluoro-2-(1,4-dioxa-8-azaspiro[4.5]decane-8-yl)-1,3-benzothiazin-4-one ***(5c)***

Yield 73%, mp 203−205 °C. ^{1}H NMR (DMSO-d_6): 1.79 (m, 4H, $(CH_2)_2$), 3.94 (m, 8H, $N(CH_2)_2$, $O(CH_2)_2$), 7.99 (ddd, 1H, H-5, ^{3}J = 9.9, ^{4}J = 7.5, ^{5}J = 2.1 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.78 (dd, 1F, F-6, J = 21.7, J = 4.7 Hz), -136.39 (dd, 1F, F-8, J = 20.4, J = 4.8 Hz), -153.67 (t, 1F, F-7, J = 21.0 Hz). ^{13}C NMR (DMSO-d_6): 33.88 (s, CH_2), 34.33 (s, CH_2), 48.27 (s, $N(CH_2)_2$), 63.95 (s, OCH_2CH_2O), 105.63 (s, C-4'), 111.44 (d, C-5, $^{2}J_{CF}$ = 22.3 Hz), 113.14 (d, C-4a, $^{3}J_{CF}$ = 24.8 Hz), 118.17 (m, C-8a), 141.46 (dt, C-7, $^{1}J_{CF}$ = 251.7, $^{2}J_{CF}$ = 12.4 Hz), 145.37 (dd, C-8, $^{1}J_{CF}$ = 244.6, $^{2}J_{CF}$ = 13.6 Hz), 149.45 (dd, C-6, $^{1}J_{CF}$ = 247.8, $^{2}J_{CF}$ = 12.4 Hz), 154.46 (s, C-2), 164.51 (s, C(O)). MS, *m/z* (rel. int.): 358 (32) $[M]^+$, 289 (71), 258 (21), 245 (31), 191 (25), 190 (82), 162 (36), 100 (15), 99 (100), 87 (14), 86 (35), 56 (11), 55 (37), 43 (11), 42 (24). Calcd for $C_{15}H_{13}F_3N_2O_3S$: C 50.28; H 3.66; N 7.82. Found: C 50.19; H 3.57; N 7.93.

6,7,8-Trifluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one ***(5d)***

Yield 74%, mp 173−175 °C. ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H, CH_3), 3.58 (m, 4H, $N(CH_2)_2$), 3.91 (m, 4H, $N(CH_2)_2$), 4.12 (q, 2H, OCH_2), 8.00 (ddd, 1H, H-5, ^{3}J = 9.6, ^{4}J = 7.5, ^{5}J = 1.5 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.62 (dd, 1F, F-6, J = 21.7, J = 4.7 Hz), -136.28 (dd, 1F, F-8, J = 20.3, J = 4.6 Hz), -153.52 (dd, 1F, F-7, J = 21.2, J = 20.9). ^{13}C NMR (DMSO-d_6): 14.51 (s, CH_3), 42.47 (s, $N(CH_2)_2$), 45.49 (s, $N(CH_2)_2$), 61.07 (s, OCH_2), 111.44 (d, C-5, $^{2}J_{CF}$ = 22.3 Hz), 113.10 (d, C-4a, $^{3}J_{CF}$ = 25.1 Hz), 118.15 (m, C-8a), 141.44 (dt, C-7, $^{1}J_{CF}$ = 252.6, $^{2}J_{CF}$ = 12.6 Hz), 145.36 (dd, C-8, $^{1}J_{CF}$ = 244.2, $^{2}J_{CF}$ = 13.9 Hz), 149.48 (dd, C-6, $^{1}J_{CF}$ = 248.4, $^{2}J_{CF}$ = 12.6 Hz), 154.48 (s, C-2), 159.76 (s, COO), 164.48 (s, C(O)). MS, *m/z* (rel. int.): 373 (9) $[M]^+$, 258 (42), 245 (15), 190 (45), 162 (21), 157 (10), 128 (72), 69 (42), 56 (100), 55 (20), 42 (31). Calcd for $C_{15}H_{14}F_3N_3O_3S$: C 48.26; H 3.78; N 11.25. Found: C 48.19; H 3.69; N 11.33.

6,7,8-Trifluoro-2-[(4-(2-fluorophenyl)piperazin-1-yl]-1,3-benzothiazin-4-one ***(5e)***

Yield 77%, mp 191−193 °C. ^{1}H NMR (DMSO-d_6): 3.21 (m, 4H, $N(CH_2)_2$), 4.06 (m, 4H, $N(CH_2)_2$), 6.98-7.12 (m, 4H, C_6H_4F), 8.01 (ddd, 1H, H-5, ^{3}J = 9.6, ^{4}J = 7.5, ^{5}J = 1.6 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -122.67 (s, 1F), -134.61 (dd, 1F, F-6, J = 21.6, J = 4.7 Hz), -136.28 (dd, 1F, F-8, J = 20.3, J = 4.7 Hz), -153.55 (t, 1F, F-7, J = 21.0 Hz). ^{13}C NMR (DMSO-d_6): 45.49 (s, $N(CH_2)_2$), 49.37 (s, $N(CH_2)_2$), 111.29 (d, C-5, $^{2}J_{CF}$ = 21.8 Hz), 113.12 (d, C-4a, $^{3}J_{CF}$ = 23.8 Hz), 116.28 (d, C-3', $^{2}J_{CF}$ = 22.6 Hz), 118.15 (m, C-8a), 119.64 (d, C-6', $^{3}J_{CF}$ = 2.4 Hz), 123.02 (d, C-1', $^{2}J_{CF}$ = 8.7 Hz), 124.87 (d, C-5', $^{4}J_{CF}$ = 4.9 Hz), 139.04 (d, C-4', $^{3}J_{CF}$ = 7.3 Hz),
141.42 (dt, C-7, $^{1}J_{CF}$ = 251.4, $^{2}J_{CF}$ = 12.6 Hz), 145.36 (dd, C-8, $^{1}J_{CF}$ = 245.2, $^{2}J_{CF}$ = 13.7 Hz), 149.45 (dd, C-6, $^{1}J_{CF}$ = 248.4, $^{2}J_{CF}$ = 12.6 Hz), 154.48 (s, C-2), 154.91 (d, C-2', $^{1}J_{CF}$ = 244.7 Hz), 164.48 (s, C(O)). MS, *m/z* (rel. int.): 395 (2) $[M]^+$, 151 (10), 150 (100), 138 (33), 137 (24), 123

(34), 122 (69), 95 (11). Calcd for $C_{18}H_{13}F_4N_3OS$: C 54.68; H 3.31; N 10.63. Found: C 54.59; H 3.20; N 10.71.

6,7,8-Trifluoro-2-(4-t-butoxycarbonylpiperazine)-1,3-benzothiazin-4-one ***(5f)***

Yield 79 %, mp 193−195 °C. ^{1}H NMR (DMSO-d_6): 1.46 (m, 9H, $C(CH_3)_3$), 3.54 (m, 4H, $N(CH_2)_2$), 3.90 (m, 4H, $N(CH_2)_2$), 8.00 (m, 1H, H-5). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.40 (d, 1F, F-6, $^3J_{FF}$ = 21.3 Hz), -136.25 (d, 1F, F-8, $^3J_{FF}$ = 19.9 Hz); -153.47 (dd, 1F, F-7, $^3J_{FF}$ = 21.3, $^3J_{FF}$ = 19.9 Hz). ^{13}C NMR (DMSO-d_6): 27.51 (s, $(CH_3)_3$), 42.52 (s, $N(CH_2)_2$), 45.64 (s, $N(CH_2)_2$), 71.48 (s, $OCMe_3$), 111.42 (d, C-5, $^2J_{CF}$ = 22.1 Hz), 113.12 (d, C-4a, $^3J_{CF}$ = 25.5 Hz), 118.17 (m, C-8a), 141.43 (dt, C-7, $^1J_{CF}$ = 249.8, $^2J_{CF}$ = 13.1 Hz), 145.36 (dd, C-8, $^1J_{CF}$ = 248.6, $^2J_{CF}$ = 13.5 Hz), 150.04 (dd, C-6, $^1J_{CF}$ = 249.7, $^2J_{CF}$ = 12.8 Hz), 154.51 (s, C-2), 159.74 (s, COO), 164.39 (s, C(O)). MS, *m/z* (rel. int.): 401 (2) $[M]^+$, 190 (13), 69 (36), 57 (100), 56 (25), 42 (11), 41 (21). Calcd for $C_{17}H_{18}F_3N_3O_3S$: C 50.87; H 4.52; N 10.47. Found: C 50.82; H 4.56; N 10.39.

General Procedure for the synthesis of monofluorinated 2-cycloalkylimino-1,3-benzothiazin-4-ones ***(5g-p)***

Method A. To a solution of difluoro-N-(cycloalkylimino-4-carbothioyl)benzamide **(4g-p)** (1.16 mmol) in DMF (3 mL) triethylamine (0.33 mL, 2.32 mmol) was added. Reaction mixture was refluxed during 6 h, and then cooled. The precipitate was filtered off, washed with water (20 mL) and recrystallized from ethanol.

Method B. To a solution of difluoro derivative **(4k)** (0.347 g, 0.9 mmol) in MeCN (15 mL) DBU (0.3 mL, 1.99 mmol) was added. Reaction mixture was refluxed during 3 h, and then cooled. The precipitate was filtered off, suspended in water (20 mL), and pH was adjusted to 5 by addition of acetic acid. Colorless product **5k** was filtered off and recrystallized from ethanol.

5-Fluoro-2-(morpholin-4-yl)-1,3-benzothiazin-4-one ***(5g)***

Yield 81%, mp 193−195 °C. ^{1}H NMR (DMSO-d_6): 3.71 (m, 4H, $N(CH_2)_2$), 3.77 (m, 4H, $O(CH_2)_2$), 7.30 (ddd, 1H, H-6, ^3J = 11.2, ^3J = 8.2, ^4J = 0.9 Hz), 7.47 (dd, 1H, H-8, ^3J = 8.0, ^4J = 0.9 Hz), 7.65 (td, 1H, H-7, ^3J = 8.1, ^4J = 5.0 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.95 (s). ^{13}C NMR (DMSO-d_6): 50.22 (s, NCH_2), 51.34 (s, NCH_2), 65.58 (s, $O(CH_2)_2$), 112.42 (d, C-4a, $^2J_{CF}$ = 13.1 Hz), 116.34 (d, C-6, $^2J_{CF}$ = 24.6 Hz), 122.38 (d, C-8, $^4J_{CF}$ = 5.7 Hz), 133.62 (d, C-7, $^3J_{CF}$ = 7.9 Hz), 134.43 (s, C-8a), 154.53 (s, C-2), 161.78 (d, C-5, $^1J_{CF}$ = 259.4 Hz), 165.01 (d, C(O), $^3J_{CF}$ = 5.9 Hz). MS, *m/z* (rel. int.): 266 (11) $[M]^+$, 155 (11), 154 (100), 126 (21), 110 (16), 81 (16), 69 (30). Calcd for $C_{12}H_{11}FN_2O_2S$: C 54.13; H 4.16; N 10.52. Found: C 54.04; H 4.08; N 10.63.

5-Fluoro-2-(thiomorpholin-4-yl)-1,3-benzothiazin-4-one ***(5h)***

Yield 85%, mp 182−184 °C. ^{1}H NMR (DMSO-d_6): 2.79 (m, 4H, S(CH_2)$_2$), 4.12 (m, 2H, (NCH_2)$_2$), 7.20 (dd, 1H, H-6, ^{3}J = 10.6, ^{3}J = 8.7 Hz), 7.34 (d, 1H, H-8, ^{3}J = 8.0 Hz), 7.60 (td, 1H, H-7, ^{3}J = 8.1, ^{4}J = 5.0 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.21 (s). NMR (DMSO-d_6): 26.41 (s, S(CH_2)$_2$), 48.86 (s, N(CH_2)$_2$), 112.37 (d, C-4a, $^{2}J_{CF}$ = 12.8 Hz), 116.27 (d, C-6, $^{2}J_{CF}$ = 23.9 Hz), 122.30 (d, C-8, $^{4}J_{CF}$ = 5.2 Hz), 133.47 (d, C-7, $^{3}J_{CF}$ = 7.6 Hz), 134.35 (s, C-8a), 154.44 (s, C-2), 161.86 (d, C-5, $^{1}J_{CF}$ = 258.4 Hz), 165.03 (d, C(O), $^{3}J_{CF}$ = 5.5 Hz). MS, *m/z* (rel. int.): 282 (23) [M]$^{+}$, 209 (42), 182 (13), 180 (11), 155 (18), 154 (100), 152 (15), 127 (25), 126 (46), 110 (34), 108 (13), 94 (15), 69 (91), 46 (17), 45 (12), 42 (14). Calcd for $C_{12}H_{11}FN_2OS_2$: C 51.05; H 3.93; N 9.92. Found: C 50.97; H 3.85; N 10.01.

5-Fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one ***(5i)***

Yield 78%, mp 172−174 °C. ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H, CH_3), 3.56 (m, 4H, N(CH_2)$_2$), 3.84 (m, 4H, N(CH_2)$_2$), 4.11 (q, 2H, OCH_2), 7.20 (ddd, 1H, H-6, ^{3}J = 10.7, ^{3}J = 8.9, ^{4}J = 0.5 Hz), 7.36 (dd, 1H, H-8, ^{3}J = 8.0, ^{4}J = 0.5 Hz), 7.65 (td, 1H, H-7, ^{3}J = 8.1, ^{4}J = 5.0). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.25 (s). ^{13}C NMR (DMSO-d_6): 14.53 (s, CH_3), 42.56 (s, N(CH_2)$_2$), 45.18 (s, N(CH_2)$_2$), 61.04 (s, OCH_2), 112.39 (d, C-4a, $^{2}J_{CF}$ = 13.0 Hz), 116.29 (d, C-6, $^{2}J_{CF}$ = 24.2 Hz), 122.32 (d, C-8, $^{4}J_{CF}$ = 5.4 Hz), 133.58 (d, C-7, $^{3}J_{CF}$ = 7.8 Hz), 134.39 (s, C-8a), 154.49 (s, C-2), 160.20 (s, COO), 161.83 (d, C-5, $^{1}J_{CF}$ = 262.3 Hz), 165.00 (d, C(O), $^{3}J_{CF}$ = 5.9 Hz). MS, *m/z* (rel. int.): 337 (8) [M]$^{+}$, 269 (16), 222 (41), 209 (40), 182 (14), 157 (17), 155 (18), 154 (100), 128 (19), 126 (22), 110 (20), 69 (14), 56 (34), 55 (11), 42 (16). Calcd for $C_{15}H_{16}FN_3O_3S$: C 53.40; H 4.78; N 12.45. Found: C 53.35; H 4.71; N 12.53.

5-Fluoro-2-[(4-(2-fluorophenyl)piperazin-1-yl]-1,3-benzothiazin-4-one ***(5j)***

Yield 81%, mp 177−179 °C. ^{1}H NMR (DMSO-d_6): 3.19 (m, 4H, N(CH_2)$_2$), 3.99 (m, 4H, N(CH_2)$_2$), 6.97−7.12 (m, 4H, C_6H_4F), 7.20 (dd, 1H, H-6, ^{3}J = 10.6, ^{3}J = 8.8 Hz), 7.36 (d, 1H, H-8, ^{3}J = 8.0 Hz), 7.60 (td, 1H, H-7, ^{3}J = 8.0, ^{4}J = 5.1 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.27 (s, 1F), -122.66 (s, 1F). ^{13}C NMR (DMSO-d_6): 45.58 (s, N(CH_2)$_2$), 49.65 (s, N(CH_2)$_2$), 112.43 (d, C-4a, $^{2}J_{CF}$ = 9.2 Hz), 116.01 (d, C-6, $^{2}J_{CF}$ = 20.7 Hz), 116.28 (d, C-3', $^{2}J_{CF}$ = 22.6 Hz), 119.64 (d, C-6', $^{3}J_{CF}$ = 2.4 Hz), 122.35 (d, C-8, $^{4}J_{CF}$ = 5.5 Hz), 123.02 (d, C-1', $^{2}J_{CF}$ = 8.8 Hz), 124.87 (d, C-5', $^{4}J_{CF}$ = 4.9 Hz), 133.58 (d, C-7, $^{3}J_{CF}$ = 10.7 Hz), 134.43 (s, C-8a), 139.04 (d, C-4', $^{3}J_{CF}$ = 7.3 Hz), 154.92 (d, C-2', $^{1}J_{CF}$ = 245.9 Hz), 160.07 (s, C-2), 161.84 (d, C-5, $^{1}J_{CF}$ = 263.8 Hz), 165.13 (d, C(O), $^{3}J_{CF}$ = 6.3 Hz). MS, *m/z* (rel. int.): 359 (3) [M]$^{+}$, 222 (31), 154 (15), 150 (100), 123 (37), 122 (70). Calcd for $C_{18}H_{15}F_2N_3OS$: C 60.16; H 4.21; N 11.69. Found: C 60.04; H 4.11; N 11.83.

*5-Fluoro-2-(4-t-butoxycarbonylpiperazine)-1,3-benzothiazin-4-one (**5k**)*

Yield 45% (*method A*), 81% (*method B*), mp 158−160 °C. ^{1}H NMR (DMSO-d_6): 1.45 (s, 9H, $C(CH_3)_3$), 3.51 (m, 4H, $N(CH_2)_2$), 3.83 (m, 4H, $N(CH_2)_2$), 7.18 (dd, 1H, H-6, $^{3}J_{HF}$ = 10.6, ^{3}J = 8.9 Hz), 7.32 (d, 1H, H-8, ^{3}J = 8.0 Hz), 7.58 (td, 1H, H-7, ^{3}J = 8.0, $^{4}J_{HF}$ = 4.9 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.04 (s). ^{13}C NMR (DMSO-d_6): 27.54 (s, $(CH_3)_3$), 45.57 (s, $N(CH_2)_2$), 49.63 (s, $N(CH_2)_2$), 71.44 (s, $OCMe_3$), 112.42 (d, C-4a, $^{2}J_{CF}$ = 12.8 Hz), 116.26 (d, C-6, $^{2}J_{CF}$ = 23.7 Hz), 122.34 (d, C-8, $^{4}J_{CF}$ = 5.3 Hz), 133.55 (d, C-7, $^{3}J_{CF}$ = 7.6 Hz), 134.37 (s, C-8a), 154.46 (s, C-2), 160.24 (s, COO), 161.81 (d, C-5, $^{1}J_{CF}$ = 262.3 Hz), 165.02 (d, C(O), $^{3}J_{CF}$ = 5.9 Hz). MS, *m/z* (rel. int.): 365 (7) $[M]^+$, 292 (13), 222 (26), 210 (19), 209 (13), 197 (34), 155 (11), 154 (52), 126 (11), 110 (12), 69 (32), 57 (100), 56 (17), 41 (18). Calcd for $C_{17}H_{20}FN_3O_3S$: C 55.88; H 5.52; N 11.50. Found: C 55.81; H 5.48; N 11.53.

*5-Fluoro-2-(4-acetylpiperazin-1-yl)-1,3-benzothiazin-4-one **(5l)***

Yield 78 %, mp 206−208 °C. ^{1}H NMR (DMSO-d_6): 2.08 (s, 3H, CH_3), 3.63 (m, 4H, $N(CH_2)_2$), 3.84 (m, 4H, $N(CH_2)_2$), 7.19 (dd, 1H, H-6, $^{3}J_{HF}$ = 10.4, ^{3}J = 8.5 Hz), 7.33 (d, 1H, H-8, ^{3}J = 8.0 Hz), 7.58 (td, 1H, H-7, ^{3}J = 8.1, ^{4}J = 4.9 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.15 (s). ^{13}C NMR (DMSO-d_6): 21.19 (s, CH_3), 44.66 (s, $N(CH_2)_2$), 45.42 (s, $N(CH_2)_2$), 112.43 (d, C-4a, $^{2}J_{CF}$ = 10.1 Hz), 116.29 (d, C-6, $^{2}J_{CF}$ = 24.0 Hz), 122.34 (d, C-8, $^{4}J_{CF}$ = 5.4 Hz), 133.58 (d, C-7, $^{3}J_{CF}$ = 12.5 Hz), 134.42 (s, C-8a), 160.23 (s, C-2), 161.83 (d, C-5, $^{1}J_{CF}$ = 263.2 Hz), 165.02 (d, C(O), $^{3}J_{CF}$ = 4.8 Hz), 168.56 (s, C(O)Me). MS, *m/z* (rel. int.): 307 (5) $[M]^+$, 223 (10), 222 (27), 209 (25), 182 (13), 180 (11), 155 (21), 154 (100), 152 (12), 127 (24), 126 (31), 110 (28), 108 (10), 69 (23), 56 (32), 55 (12), 43 (47), 42(16). Calcd for $C_{14}H_{14}FN_3O_2S$: C 54.71, H 4.59, N 13.67. Found: C 54.78, H 4.63, N 13.61.

*5-Fluoro-2-(4-cyclopropylcarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one **(5m)***

Yield 85 %, mp 164−166 °C. ^{1}H NMR (DMSO-d_6): 0.76 (m, 4H, $2CH_2$), 1.94 (m, 1H, CH), 3.68 (m, 4H, $N(CH_2)_2$), 3.86 (m, 4H, $N(CH_2)_2$), 7.20 (ddd, 1H, H-6, $^{3}J_{HF}$ = 11.0, ^{3}J = 8.1, ^{4}J = 1.7 Hz), 7.33 (d, 1H, H-8, ^{3}J = 8.0 Hz), 7.58 (ddd, 1H, H-7, ^{3}J = 8.1, ^{4}J = 4.9, $^{5}J_{HF}$ = 2.2 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -108.12 (s). ^{13}C NMR (DMSO-d_6): 7.19 (s, $(CH_2)_2$), 10.31 (s, CH), 40.73 (s, NCH_2), 43.90 (s, NCH_2), 45.33 (s, $N(CH_2)_2$), 112.41 (d, C-4a, $^{2}J_{CF}$ = 9.8 Hz), 116.28 (d, C-6, $^{2}J_{CF}$ = 23.1 Hz), 122.32 (d, C-8, $^{4}J_{CF}$ = 5.9 Hz), 133.56 (d, C-7, $^{3}J_{CF}$ = 10.3 Hz), 134.42 (s, C-8a), 160.22 (s, C-2), 161.84 (d, C-5, $^{1}J_{CF}$ = 259.5 Hz), 169.99 (d, C(O), $^{3}J_{CF}$ = 4.8 Hz), 171.36 (s, C(O)Alk). MS, *m/z* (rel. int.): 333 (5) $[M]^+$, 265 (15), 223 (15), 222 (27), 209 (28), 182 (16), 180 (14), 155 (17), 154 (73), 153 (24), 152 (14), 126 (27), 124 (11), 110 (26), 108 (11), 69 (100), 56 (18), 55

(11), 42 (16), 41 (64), 39 (20). Calcd for $C_{16}H_{16}FN_3O_2S$: C 57.64, H 4.84, N 12.60. Found: C 57.71, H 4.90, N 12.55.

5-Fluoro-2-[4-(2-furoyl)carbonylpiperazin-1-yl]-1,3-benzothiazin-4-one ***(5n)***

Yield 81%, mp 202−204 °C. ^{1}H NMR (DMSO-d_6): 3.92 (m, 8H, 2N(CH_2)$_2$), 6.57 (dd, 1H, H-4', ^3J = 3.2, ^3J = 1.6 Hz), 7.04 (d, 1H, H-3', ^3J = 3.4 Hz), 7.18 (ddd, 1H, H-6, ^3J = 8.1, ^4J = 4.9, $^5J_{HF}$ 2.9 Hz), 7.32 (dd, 1H, H-8, ^3J = 8.1, $^4J_{HF}$ = 4.9 Hz), 7.58 (dd, 1H, H-7, $^3J_{HF}$ = 10.5, ^3J = 8.4 Hz), 7.71 м (m, 1H, H-5'). ^{19}F NMR {^{1}H} (DMSO-d_6), δ, м.д.: -107.86 (s). ^{13}C NMR (DMSO-d_6): 45.21 (s, N(CH_2)$_2$), 111.41 (s, C-4'), 112.43 (d, C-4a, $^2J_{CF}$ = 9.1 Hz), 116.10 (s, C-3'), 116.31 (d, C-6, $^2J_{CF}$ = 23.1 Hz), 122.35 (d, C-8, $^4J_{CF}$ = 4.4 Hz), 133.59 (d, C-7, $^3J_{CF}$ = 10.6 Hz), 134.41 (s, C-8a), 145.06 (s, C-5'), 146.65 (s, C-2'), 158.48 (s, C(O)-furoyl), 160.25 (s, C-2), 161.85 (d, C-5, $^1J_{CF}$ = 262.9 Hz), 165.01 (d, C(O), $^3J_{CF}$ = 4.8 Hz). MS, *m/z* (rel. int.): 359 (14) [M]$^+$, 291 (10), 209 (17), 182 (10), 180 (11), 163 (10), 155 (14), 154 (72), 126 (24), 110 (21), 95 (100), 94 (12), 81 (11), 69 (14), 56 (13), 39 (18). Calcd for $C_{17}H_{14}FN_3O_3S$: C 56.82, H 3.93, N 11.69. Found: C 56.88, H 4.00, N 11.63.

7-Fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one ***(5o)***

Yield 80%, mp 166−168 °C. ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H, CH_3), 3.57 (m, 4H, N(CH_2)$_2$), 3.86 (m, 4H, N(CH_2)$_2$), 4.11 (q, 2H, OCH_2), 7.28 (ddd, 1H, H-6, ^3J = 8.6, ^3J = 6.0, ^4J = 2.5 Hz), 7.48 (dd, 1H, H-8, ^3J = 8.8, ^4J = 2.5 Hz), 8.27 (dd, 1H, H-5, ^3J = 8.8, ^3J = 6.0). ^{19}F NMR {^{1}H} (DMSO-d_6): -106.44 (s). ^{13}C NMR (DMSO-d_6): 14.52 (s, CH_3), 42.52 (s, N(CH_2)$_2$), 45.14 (s, N(CH_2)$_2$), 61.04 (s, OCH_2), 112.67 (d, C-6, $^2J_{CF}$ = 26.4 Hz), 116.02 (d, C-8, $^2J_{CF}$ = 22.0 Hz), 118.98 (d, C-4a, $^4J_{CF}$ = 2.3 Hz), 132.40 (d, C-5, $^3J_{CF}$ = 7.4 Hz), 134.57 (d, C-8a, $^3J_{CF}$ = 9.9 Hz), 154.50 (s, COO), 161.33 (s, C-2), 163.58 (d, C-7, $^1J_{CF}$ = 253.4 Hz), 166.44 (s, C(O)). MS, *m/z* (rel. int.): 337 (15) [M]$^+$, 269 (27), 223 (14), 222 (58), 209 (47), 182 (17), 157 (15), 155 (22), 154 (100), 128 (32), 126 (37), 69 (19), 56 (43), 55 (11), 42 (17). Calcd for $C_{15}H_{16}FN_3O_3S$: C 53.40; H 4.78; N 12.45. Found: C 53.30; H 4.67; N 12.59.

8-Fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one ***(5p)***

Yield 84%, mp 173−175 °C. ^{1}H NMR (DMSO-d_6): 1.27 (m, 3H, CH_3), 3.58 (m, 4H, N(CH_2)$_2$), 3.92 (m, 4H, N(CH_2)$_2$), 4.13 (q, 2H, OCH_2), 7.50 (m, 2H, H-5, H-7), 8.08 (td, 1H, H-6, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 2.1 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -115.94 (s). ^{13}C NMR (DMSO-d_6): 14.53 (s, CH_3), 42.53 (s, N(CH_2)$_2$), 45.15 (s, N(CH_2)$_2$), 61.03 (s, OCH_2), 112.69 (d, C-7, $^2J_{CF}$ = 26.1 Hz), 116.68 (d, C-8a, $^2J_{CF}$ = 9.1 Hz), 121.75 (d, C-5, $^4J_{CF}$ = 4.4 Hz), 132.46 (d, C-6, $^3J_{CF}$ = 7.3 Hz), 134.41 (s, C-4a), 154.50 (s, COO), 161.33 (s, C-2), 162.69 (d, C-8, $^1J_{CF}$ = 252.1 Hz), 166.44 (s, C(O)). MS,

m/z (rel. int.): 337 $[M]^+$ (10), 269 (16), 223 (10), 222 (45), 209 (40), 182 (12), 180 (10), 154 (100), 128 (28), 126 (46), 108 (12), 69 (24), 56 (53), 55 (15), 42 (27). Calcd for $C_{15}H_{16}FN_3O_3S$: C 53.40; H 4.78; N 12.45. Found: C 53.34; H 4.71; N 12.53.

4.4. Procedure for the Synthesis of 2,7-bis(cycloalkylimino)-6,8-difluoro-1,3-benzothiazin-4-ones (6a-c)

General Procedure

To a solution of benzothiazinone **(5a,d)** (1.19 mmol) in DMSO (2 mL) cycloalkylimine (morpholine or 1-ethoxycarbonylpiperazine) (3.17 mmol) was added. Reaction mixture was refluxed during 8 h, and then cooled. The precipitate of compound **6** was filtered off and recrystallized from DMSO.

6,8-Difluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-7-(morpholin-4-yl)-1,3-benzothiazin-4-one ***(6a)***

Yield 73%, mp 255−257 °C. ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H, CH_3), 3.29 (m, 4H, $(CH_2)_2$), 3.56 (m, 4H, $(CH_2)_2$), 3.73 (m, 4H, $(CH_2)_2$), 3.88 (m, 4H, $(CH_2)_2$), 4.11 (q, 2H, OCH_2), 7.73 (dd, 1H, H-5, ^3J = 12.4, ^3J = 1.5 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -120.64 (d, 1F, $^4J_{FF}$ = 8.8 Hz), -124.40 (d, 1F, $^4J_{FF}$ = 8.8 Hz). ^{13}C NMR (DMSO-d_6): 14.49 (s, CH_3), 42.55 (s, $N(CH_2)_2$), 43.95 (s, $N(CH_2)_2$), 45.26 (s, $N(CH_2)_2$), 50.68 (s, $O(CH_2)_2$), 66.56 (s, OCH_2), 112.24 (d, C-5, $^2J_{CF}$ = 25.7 Hz), 115.92 (м, C-4a), 117.43 (m, C-8a), 130.99 (d, C-7, $^2J_{CF}$ = 12.8 Hz), 140.24 (d, C-8, $^1J_{CF}$ = 257.8 Hz), 148.53 (d, C-6, $^1J_{CF}$ = 257.8 Hz), 154.56 (s, COO), 160.29 (s, C-2), 165.34 (s, C(O)). MS, *m/z* (rel. int.): 440 (33) $[M]^+$, 372 (16), 326 (21), 325 (68), 313 (14), 312 (78), 283 (13), 258 (32), 257 (100), 256 (14), 200 (14), 199 (90), 171 (14), 170 (12), 141 (18), 139 (17), 128 (17), 57 (18), 56 (34), 42 (22). Calcd for $C_{19}H_{22}F_2N_4O_4S$: C 51.81; H 5.03; N 12.72. Found: C 51.70; H 4.92; N 12.84.

6,8-Difluoro-2,7-bis(morpholin-4-yl)-1,3-benzothiazin-4-one ***(6b)***

Yield 68%, mp 271−273 °C. ^{1}H NMR (DMSO-d_6): 3.29 (m, 4H, $N(CH_2)_2$), 3.74 (m, 8H, $N(CH_2)_2$, $O(CH_2)_2$), 3.86 (m, 4H, $O(CH_2)_2$), 7.73 (d, 1H, H-5, ^3J = 12 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -120.88 (d, 1F, $^4J_{FF}$ = 8.9 Hz), -124.47 (d, 1F, $^4J_{FF}$ = 8.9 Hz). ^{13}C NMR (DMSO-d_6): 42.55 (s, NCH_2), 43.95 (s, NCH_2), 66.56 (s, $O(CH_2)_2$), 112.26 (d, C-5, $^2J_{CF}$ = 25.8 Hz), 115.90 (м, C-4a), 117.46 (m, C-8a), 130.94 (d, C-7, $^2J_{CF}$ = 12.8 Hz), 140.26 (d, C-8, $^1J_{CF}$ = 257.5 Hz), 148.51 (d, C-6, $^1J_{CF}$ = 257.5 Hz), 160.26 (s, C-2), 165.32 (s, C(O)). MS, *m/z* (rel. int.): 369 (44) $[M]^+$, 258 (16), 257 (100), 199 (71), 171 (12), 170 (10), 139 (14), 57 (13), 42 (12). Calcd for $C_{16}H_{17}F_2N_3O_3S$: C 52.03; H 4.64; N 11.38. Found: C 51.94; H 4.58; N 11.44.

6,8-Difluoro-2,7-bis(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one ***(6c)***

Yield 79%, mp 245−247 °C. ^{1}H NMR (DMSO-d_6): 1.27 (t, 6H, 2CH_3), 3.27 (m, 4H, $(CH_2)_2$), 3.56 (m, 8H, 2$(CH_2)_2$), 3.89 (m, 4H, $(CH_2)_2$), 4.11 (m, 4H, 2OCH_2), 7.74 (dd, 1H, H-5, ^{3}J = 12.2, ^{3}J = 1.2 Hz). ^{19}F NMR {^{1}H} (DMSO-d_6): -120.49 (d, 1F, J = 8.7 Hz), -124.07 (d, 1F, J = 8.7 Hz). ^{13}C NMR (DMSO-d_6): 14.49 (s, CH_3), 42.55 (s, $N(CH_2)_2$), 43.95 (s, $N(CH_2)_2$), 45.27 (s, $N(CH_2)_2$), 50.08 (s, $N(CH_2)_2$), 60.84 (s, OCH_2), 61.02 (s, OCH_2), 111.98 (d, C-5, $^{2}J_{CF}$ = 26.5 Hz), 115.94 (м, C-4a), 117.46 (m, C-8a), 131.91 (d, C-7, $^{2}J_{CF}$ = 12.9 Hz), 140.25 (d, C-8, $^{1}J_{CF}$ = 259.7 Hz), 148.51 (d, C-6, $^{1}J_{CF}$ = 259.7 Hz), 154.56 (s, COO), 154.67 (s, COO), 160.30 (s, C-2), 165.20 (s, C(O)). MS, *m/z* (rel. int.): 511 (37) $[M]^+$, 443 (14), 397 (24), 396 (46), 384 (15), 383 (72), 381 (12), 328 (15), 313 (15), 308 (13), 226 (13), 214 (15), 213 (13), 199 (13), 141 (25), 128 (13), 115 (16), 70 (17), 69 (11), 56 (100), 44 (11), 43 (12), 42 (31). Calcd for $C_{22}H_{27}F_2N_5O_5S$: C 51.66; H 5.32; N 13.69. Found: C 51.72; H 5.37; N 13.61.

4.5. Procedures for the Synthesis of 2-Piperazino-substituted 6,7,8-trifluoro-1,3-benzothiazin-4-ones (7, 8)

6,7,8-Trifluoro-2-(piperazin-1-yl)-1,3-benzothiazin-4-one ***(7)***

Trifluoroacetic acid (0.15 mL, 1.3 mmol) was added to a solution of 6,7,8-trifluoro-2-(4-*t*-butoxycarbonylpiperazine)-1,3-benzothiazin-4-one **5f** (0.19 g, 0.46 mmol) in dichloromethane (1.5 mL) at 0 °C. Reaction mixture was stirred at 0 °C for 5 min, then at room temperature during 3 h. Solvent was removed in vacuum, saturated solution of sodium hydrocarbonate (10 ml) was added to the residue, and then product **7** was filtered off and used for the synthesis of compounds **8a-e** without further purification. Yield 0.1 g (70%), mp 229−231 °C. ^{1}H NMR (DMSO-d_6): 2.92 (m, 4H, $N(CH_2)_2$), 3.85 (m, 4H, $N(CH_2)_2$), 4.9 (s, 1H, NH), 8.00 (m, 1H, H-5). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.80 (dd, 1F, F-6, $^{3}J_{FF}$ = 21.5, $^{4}J_{FF}$ = 4.9 Hz), -136.49 (dd, 1F, F-8, $^{3}J_{FF}$ = 20.1, $^{4}J_{FF}$ = 4.9 Hz), -153.80 (dd, 1F, F-7, $^{3}J_{FF}$ = 21.5, $^{3}J_{FF}$ = 20.1 Hz). MS, *m/z* (rel. int.): 301 (16) $[M]^+$, 246 (15), 245 (10), 233 (11), 218 (15), 191 (14), 190 (31), 162 (23), 144 (12), 69 (100), 68 (12), 57 (24), 56 (85), 55 (26), 51 (12), 45 (31), 42 (30). Calcd for $C_{12}H_{10}F_3N_3OS$: C 47.84; H 3.35; N 13.95. Found: C 47.79; H 3.40; N 13.90.

General Procedure for the Synthesis of 1,3-Benzothiazin-4-ones ***8a-c***

Aroylchloride (0.74 mmol) was added to a solution of 6,7,8-trifluoro-2-(piperazin-1-yl)-1,3-benzothiazin-4-one **7** (0.2 g, 0.66 mmol) in dichloromethane (15 mL). Reaction mixture was

stirred at 55 °C for 4 h, and then concentrated in vacuum; the precipitate was filtered off and recrystallized from ethanol.

6,7,8-Trifluoro-2-(4-t-butylbenzoylpiperazino)-1,3-benzothiazin-4-one ***(8a)***

Yield 87%, mp 265−267 °C. ^{1}H NMR (DMSO-d_6): 1.36 (s, 9H, $C(CH_3)_3$), 3.71 (m, 4H, $N(CH_2)_2$), 3.97 (m, 4H, $N(CH_2)_2$), 7.38 (d, 2H, H-3', H-5', ^{3}J = 8.2 Hz), 7,45 (d, 2H, H-2', H-6', ^{3}J = 8.3 Hz), 8.00 (m, 1H, H-5). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.51 (dd, 1F, F-6, $^{3}J_{FF}$ = 21.5, $^{4}J_{FF}$ = 4.6 Hz), -136.24 (dd, 1F, F-8, $^{3}J_{FF}$ = 20.0, $^{4}J_{FF}$ = 4.6 Hz), -153.49 (dd, 1F, F-7, $^{3}J_{FF}$ = 21.5, $^{3}J_{FF}$ 20.0 = Hz). MS, *m/z* (rel. int.): 461 (7) $[M]^+$, 190 (6), 162 (17), 161 (100), 146 (15), 118 (14), 69 (15). Calcd for $C_{23}H_{22}F_3N_3O_2S$: C 59.86; H 4.80; N 9.10. Found: C 59.81; H 4.82; N 9.05.

6,7,8-Trifluoro-2-(4-benzoylpiperazino)-1,3-benzothiazin-4-one ***(8b)***

Yield 85%, mp 153−155 °C. ^{1}H NMR (DMSO-d_6): 3.71 (m, 4H, $N(CH_2)_2$), 3.96 (m, 4H, $N(CH_2)_2$), 7.45 (s, 3H, H-3', H-4', H-5'), 7.59 (m, 1H, H-6'), 8.00 (m, 1H, H-5), 8.11 (m, 1H, H-2'). ^{19}F NMR {^{1}H} (DMSO-d_6): -134.46 (dd, 1F, F-6, $^{3}J_{FF}$ = 21.6, $^{4}J_{FF}$ = 4.9 Hz), -136.24 (dd, 1F, F-8, $^{3}J_{FF}$ = 20.1, $^{4}J_{FF}$ = 4.9 Hz), -153.46 (dd, 1F, F-7, $^{3}J_{FF}$ = 21.6, $^{3}J_{FF}$ = 20.1 Hz). MS, *m/z* (rel. int.): 405 (3) $[M]^+$, 190 (8), 105 (100), 77 (44), 69 (23). Calcd for $C_{19}H_{14}F_3N_3O_2S$: C 56.29; H 3.48; N 10.37. Found: C 56.32; H 3.41; N 10.42.

6,7,8-Trifluoro-2-[4-(2,6-difluorobenzoyl)piperazino)-1,3-benzothiazin-4-one ***(8c)***

Yield 82%, mp 229−231 °C. ^{1}H NMR (DMSO-d_6): 3.49 (m, 2H, $N(CH_2)$), 3.89 (m, 4H, $N(CH_2)_2$), 4.02 (m, 2H, $N(CH_2)$), 7.13 (m, 2H, H-3', H-5'), 7.55 м (m, 1H, H-4'), 8.00 (m, 1H, H-5). ^{19}F NMR {^{1}H} (DMSO-d_6): -113.21 (s, 2F, $C_6H_3F_2$), -134.40 (d, 1F, F-6, $^{3}J_{FF}$ = 21.4 Hz), -136.17 (d, 1F, F-8, $^{3}J_{FF}$ = 16.1 Hz), -153.38 (dd, 1F, F-7, $^{3}J_{FF}$ = 21.4, $^{3}J_{FF}$ = 16.1 Hz). MS, *m/z* (rel. int.): 441 (2) $[M]^+$, 286 (29), 258 (17), 190 (26), 162 (12), 141 (100), 113 (15), 69 (12), 56 (10). Calcd for $C_{19}H_{12}F_5N_3O_2S$: C 51.70; H 2.74; N 9.52. Found: C 51.75; H 2.39; N 9.45.

General Procedure for the Synthesis of 1,3-Benzothiazin-4-ones ***8d,e***

HATU (0.27 g, 0.71 mmol) was added to a solution of substituted benzoic acid (0.63 mmol) in dichloromethane (24 mL), then DIPEA (0.12 mL, 0.71 mmol) and 6,7,8-trifluoro-2-(piperazin-1-yl)-1,3-benzothiazin-4-one **7** (0.2 g, 0.63 mmol) were added. Reaction mixture was stirred at room temperature for 24 h, and then water (47 mL) was added. The organic layer was separated, the product was extracted from water layer with dichloromethane (3×10 mL), dichloromethane solution was washed with brain, dried over Na_2SO_4 and then the solvent was removed in vacuum. The residue was recrystallized from ethanol.

6,7,8-Trifluoro-2-[4-(3-fluorobenzoyl)piperazino]-1,3-benzothiazin-4-one ***(8d)***

Yield 84%, mp 213−215 °C. ^{1}H NMR (DMSO-d_6): 3.73 (m, 4H, N(CH_2)$_2$), 3.99 (m, 4H, N(CH_2)$_2$), 7.26 (m, 3H, H-4', H-5', H-6'), 7.49 (m, 1H, H-2'), 8.00 (m, 1H, H-5). ^{19}F NMR {^{1}H} (DMSO-d_6): -111.78 (s, 1F, C_6H_4F), -134.45 (dd, 1F, F-6, $^{3}J_{FF}$ 21.2, $^{4}J_{FF}$ 4.7), -136.23 (dd, 1F, F-8, $^{3}J_{FF}$ = 20.0, $^{4}J_{FF}$ = 4.7 Hz), -153.46 (dd, 1F, F-7, $^{3}J_{FF}$ = 21.2, $^{3}J_{FF}$ = 20.0 Hz). MS, *m/z* (rel. int.): 423 (8) $[M]^+$, 258 (18), 245 (11), 218 (12), 190 (23), 162 (12), 123 (100), 95 (35), 69 (33), 56 (11). Calcd for $C_{19}H_{13}F_4N_3O_2S$: C 53.90; H 3.09; N 9.92. Found: C 53.85; H 3.02; N 9.85.

6,7,8-Trifluoro-2-[4-(4-ethylbenzoyl)piperazino]-1,3-benzothiazin-4-one ***(8e)***

Yield 83%, mp 226−228 °C. ^{1}H NMR (DMSO-d_6): 1.28 (t, 3H, CH_3, ^{3}J 7.9 Hz), 2.71 (q, 2H, CH_2, ^{3}J = 7.6 Hz), 3.71 (m, 4H, N(CH_2)$_2$), 3.97 (m, 4H, N(CH_2)$_2$), 7.27 (d, 2H, H-3', H-5', ^{3}J = 7.9 Hz), 7.38 (d, 2H, H-2', H-6', ^{3}J = 7.9 Hz), 8.00 (m, 1H, H-5). ^{19}F NMR {^{1}H} (DMSO-d_6), δ, м.д.: -134.46 (dd, 1F, F-6, $^{3}J_{FF}$ = 21.5, $^{4}J_{FF}$ = 4.6 Hz), -136.21 (dd, 1F, F-8, $^{3}J_{FF}$ = 20.1, $^{4}J_{FF}$ = 4.6 Hz), -153.47 (dd, 1F, F-7, $^{3}J_{FF}$ = 21.5, $^{3}J_{FF}$ = 20.1 Hz). MS, *m/z* (rel. int.): 433 (5) $[M]^+$, 190 (4), 133 (100), 105 (10), 69 (13). Calcd for $C_{21}H_{18}F_3N_3OS$: C 58.19; H 4.19; N 9.69. Found: C 58.11; H 4.12; N 9.65.

4.6. Antimycobacterial assay

To evaluate the inhibitory efficiency of molecules on Mycobacterium tuberculosis (MTB), *M. tuberculosis* $H_{37}R_v$, which is susceptible to all classical antituberculosis drugs, was used. The minimal inhibitory concentration (MIC) for *M. tuberculosis* $H_{37}R_v$ for each compound was determined by a micro broth dilution method. All molecules tested were dissolved in dimethylsulfoxide and their 1/2 dilutions were prepared in 5 mL tubes using Löwenstein-Jensen medium. A few colonies from freshly grown *M. tuberculosis* $H_{37}R_v$ were suspended in Löwenstein-Jensen medium to obtain 1.0 McFarland turbidity and diluted ten times using the same medium and the tubes were incubated at 37 °C medium with a different concentration of the tested molecule and to a positive control tube containing only clear growth medium. After 24 hours the tubes were placed in a vertical position and the free edge of the buried 0.3 mL of the substance in the test compounds concentrations: 12.5, 6.25, 3.1, 1.5, 0.7, 0.37, 0.15 μg/mL. The tubes were then placed in thermostat at a temperature of 37 °C and incubated for 10 days. Growth estimate for the MTB were determined by standard methods, where the appearance of zones of growth retardation MTB (over 10 mm) indicated the presence of tuberculostatic properties in concentration of the compounds under study. Penetration size stunting MTB (in mm) is proportional to the degree of tuberculostatic activity. Growth delay of 100 mm or more is considered as a complete growth

inhibition MTB. The multi-drug-resistant (MDR) tuberculosis strain has been isolated from tuberculosis patients in Ural Research Institute for Phthisiopulmonology (Russia). The minimal inhibitory concentrations against *Mycobacterium tuberculosis avium, Mycobacterium tuberculosis terrae,* and MDR tuberculosis strains were evaluated similarly.

4.7. Evaluation of acute toxicity in vivo

All experimental protocols were conducted in accordance to the standard protocol approved by the Committee of the Ethical Use of Animals of the Ural Research Institute for Phthisiopulmonology (CEUA/URIP). The synthesized compounds were evaluated for their approximate LD_{50} in white healthy mice (17−20 g body weight) divided into 3 groups of 5 animals each for testing of one compound [21, 22]. Toxicity tests were carried out via a single per oral introduction of compound in a 1 % starch aqueous solution. The volume introduced did not exceed 0.5 mL for mice. The observation period was 14 days. The median lethal doses LD_{50} were used as the criteria of toxicity.

Acknowledgment

The work was carried out with financial support from the Russian Scientific Foundation (grant 15-13-00077-P) and from the Ministry of Education of Russian Federation (State Contract 4.6351.2017/8.9, research of 1,3-benzothiazinones **8**).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j. jfluchem.

References

[1] S. Chetty, M. Ramesh, A. Singh-Pillay, M.E.S. Soliman. Recent advancements in the development of anti-tuberculosis drugs. Bioorg. Med. Chem. Lett. 27 (2017) 370-386.

[2] B. Villemagne, C. Crauste, M. Flipo, A. R. Baulard, B. Déprez, N. Willand. Tuberculosis: The drug development pipeline at a glance. Eur. J. Med. Chem. 51 (2012) 1-16.

[3] M. R. Pasca, G. Degiacomi, A. L. J. L. Ribeiro, F. Zara, P. DeMori, B. Heym, M. Mirrione, R. Brerra, L. Pagani, L. Pucillo, P. Troupioti, V. Makarov, S. T. Cole, G. Riccardi. Clinical Isolates of Mycobacterium tuberculosis in Four European Hospitals Are Uniformly Susceptible to Benzothiazinones. Antimicrob. Agents Chemother. (2010) 1616–1618.

[4] V. Makarov, B. Lechartier, M. Zhang, J. Neres, A. M. van der Sar, S. A. Raadsen, R. C. Hartkoorn, O. B. Ryabova, A. Vocat, L. A. Decosterd, N. Widmer, T. Buclin, W. Bitter, K.

Andries, F. Pojer, P. J. Dyson, S. T. Cole. Towards a new combination therapy for tuberculosis with next generation benzothiazinones. EMBO Mol. Med. 6 (2014) 372–383.

[5] V. Kumar, S. Patel, R. Jain. New structural classes of antituberculosis agents. Med. Res. Rev. 38 (2018) 684–740.

[6] C. Gao, T.-H. Ye, N.-Y. Wang, X.-X. Zeng, L.-D. Zhang, Y. Xiong, X.-Y. You, Y. Xia, Y. Xu, C.-T. Peng, W.-Q. Zuo, Y. Wei, L.-T. Yu. Synthesis and structure–activity relationships evaluation of benzothiazinone derivatives as potential anti-tubercular agents. Bioorg. Med. Chem. Lett. 23 (2013) 4919–4922.

[7] C. Gao, T.-H. Ye, N.-Y. Wang, X.-X. Zeng, L.-D. Zhang, Y. Xiong, X.-Y. You, Y. Xia, Y. Xu, C.-T. Peng, W.-Q. Zuo, Y. Wei, L.-T. Yu. Synthesis and antitubercular evaluation of 4-carbonyl piperazine substituted 1,3-benzothiazin-4-one derivatives. Bioorg. Med. Chem. Lett. 25 (2015) 1373-1376.

[8] T. Karoli, B. Becker, J. Zuegg, U. Möllmann, S. Ramu, J. X. Huang, M A. Cooper. Identification of Antitubercular Benzothiazinone Compounds by Ligand-Based Design. J. Med. Chem. 55 (2012) 7940−7944.

[9] V. Makarov, G. Manina, K. Mikusova, U. Mollmann, O. Ryabova, B. Saint-Joanis, N. Dhar, M. R. Pasca, S. Buroni, A. P. Lucarelli, A. Milano, E. De Rossi, M. Belanova, A. Bobovska, P. Dianiskova, J.Kordulakova, C. Sala, E. Fullam, P. Schneider, J. D. McKinney, P. Brodin, T. Christophe, S. Waddell, P. Butcher, J. Albrethsen, I. Rosenkrands, R. Brosch, V. Nandi, S. Bharath, S. Gaonkar, R. K. Shandil, V. Balasubramanian, T. Balganesh, S. Tyagi, J. Grosset, G. Riccardi, S. T. Cole. Benzothiazinones kill Mycobacterium tuberculosis by blocking arabinan synthesis. Science 324 (2009) 801−804.

[10] A. I. Rudolph. Antitubercular Benzothiazinones: Synthesis, Activity, Properties and SAR (dis.), Martin-Luther-Universität, Halle-Wittenberg, 2014.

[11] A. Richter, I. Rudolph, U. Möllmann, K. Voigt, C. Chung, O. M. P. Singh, M. Rees, A. Mendoza-Losana, R. Bates, L. Ballell, S. Batt, N. Veerapen, K. Fütterer, G. Besra, P. Imming, A. Argyrou. Novel insight into the reaction of nitro, nitroso and hydroxylamino benzothiazinones and of benzoxacinones with Mycobacterium tuberculosis DprE1. Scientific Reports (2018) 13473.

[12] A.S. Shestakov, M.A. Prezent, E.O. Zlatoustovskaya, K.S. Shikhaliev, A.V. Falaleev, O.E. Sidorenko. Alkylation of 1,3-benzothiazin-4-one 2-oxo-, 2-arylimino-, and 2-thioxo derivatives. Chem. Heterocycl. Comp. 51 (2015) 370–376.

[13] V.A. Makarov. Patent EP2380886, 26 October 2011.

[14] R. Zhang, K. Lv, B. Wang, L. Li, B. Wang, M. Liu, H. Guo, A. Wanga, Y. Lu. Design, synthesis and antitubercular evaluation of benzothiazinones containing an oximido or amino nitrogen heterocycle moiety. RCS Adv. 7 (2017) 1480–1483

[15] L. Xiong, C. Gao, Y.-J. Shi, X. Tao, J. Rong, K.-L. Liu, C.-T. Peng, N.-Y. Wang, Q. Lei, Y.-W. Zhang, L.-T. Yu, Y.-Q. Weia. Identification of a new series of benzothiazinone derivatives with excellent antitubercular activity and improved pharmacokinetic profiles. RCS Adv. 8 (2018) 11163–11176.

[16] H. Inami, J. Shishikura, T. Yasunaga, K. Ohno, H. Yamashita, K. Kato, S. Sakamoto. Synthesis, structure–activity relationships, and anticonvulsant activities of 2-amino-4H-pyrido[3,2-*e*][1,3]thiazin-4-one derivatives as orally active AMPA receptor antagonists. Bioorg. Med. Chem. 23 (2015) 1788–1799.

[17] E.V. Nosova, G.N. Lipunova, A.A. Laeva, V.N. Charushin. Fluorine-containing heterocycles: XV. Reactions of polyfluorobenzoyl isothiocyanates with aminoazines and aminoazoles. Russ. J. Org. Chem. 42 (2006) 1544–1550.

[18] E.V. Nosova, G.N. Lipunova, M.A. Kravchenko, A.A. Laeva, V.N. Charushin. Synthesis and tuberculostatic activity of fluorine-containing derivatives of quinolone, quinazolinone, and benzothiazinone. Pharm. Chem. Journ. 42 (2008) 169–174.

[19] V.N. Charushin, E.V. Nosova, A.D. Poteeva, S.K. Kotovskaya, G.N. Lipunova, M.A. Kravchenko, S.N. Skornyakov, I.D. Medvinsky. Patent RF2663848, 10 August 2018.

[20] Handbook of Anti-Tuberculosis Agents, Tuberculosis 88 (2008) 85–170.

[21] J.T. Litchfield Jr., F. Wilcoxon, J. Pharmacol. Exp. Ther. 96 (1949) 99–113.

[22] Progress in medicinal chemistry, in: W.G. Smith, G.P. Ellis, G.B. West, Eds., Pharmacological Screening Tests, Butterworths, 1961, 1–33.