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# Synthesis and Properties of New Fluorine-Containing Thieno[2,3-*b*]pyridine Derivatives

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Received March 21, 2019; revised March 21, 2019; accepted March 27, 2019

**Abstract**—Cyanothioacetamide reacted with 1,1,5,5-tetrafluoroacetylacetone to give 4,6-bis(difluoromethyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and alkylation of the latter with α-chloroacetamides afforded 3-amino-4,6-bis(difluoromethyl)thieno[2,3-*b*]pyridine-2-carboxamides. The structure of the key compounds was proved using two-dimensional NMR techniques. *In silico* analysis of potential biological activity and bioavailability of the synthesized compounds was performed.

**Keywords:** cyanothioacetamide, Guareschi–Thorpe reaction, Thorpe–Ziegler cyclization, thieno[2,3-*b*]pyridines, *in silico* biological activity, organic fluorides

**DOI:** 10.1134/S1070363219090032

One of the priority problems attracting permanent attention of chemists is search for compounds with specific behavior. In this respect, especially promising are organofluorine compounds due to their relative synthetic accessibility via standard methods, on the one hand, and specific properties dtermined by the presence of fluorine atoms, on the other. Replacement of hydrogen by fluorine does not lead to an appreciable distortion of geometric parameters but essentially changes physicochemical properties and biological activity [1–4]. Owing to a combination of practically useful properties and specific features of chemical behavior, fluorinated derivatives of nitrogen heterocycles have become the subjects of keen interest (for reviews, see [5–12]).

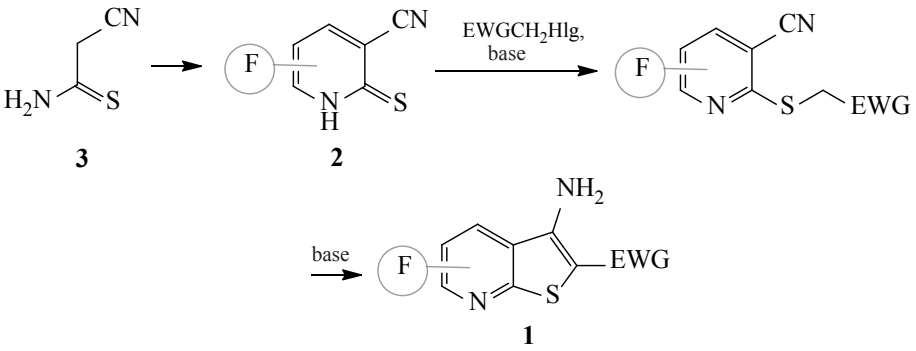
In continuation of our studies in the field of functionally substituted thieno[2,3-*b*]pyridine derivatives [13–19], in the present work we synthesized new fluorine-containing thienopyridines and performed *in silico* analysis of their potential biological activity and bioavailability parameters.

Numerous known examples [20–35] of synthesis of fluorinated thieno[2,3-*b*]pyridine derivatives **1** are based on the tandem C-alkylation/Thorpe–Ziegler cyclization of fluorinated 3-cyanopyridine-2(1*H*)-thiones **2**. The latter can be prepared in turn by condensation of cyanothioacetamide (**3**) [36] with fluorinated 1,3-bielectrophiles such as unsaturated ketones, β-keto esters, or 1,3-diketones (Scheme 1).

It should be noted that in most cases, the initial reactants for the synthesis of **2** were most accessible compounds with a trifluoroacetyl fragment, so that the range of the introduced fluorinated fragments (with a few exceptions [25, 31]) was limited to the trifluoromethyl group. The broad spectrum of biological activity of fluorine-containing thieno[2,3-*b*]pyridine derivatives should also be noted. For instance, compounds **4** [22] and **5** [27] (Scheme 2) showed *in vitro* activity against hepatitis C virus. Pyridothienopyrimidine **6** displayed antidiabetic properties [24, 37]. Thienopyridines **7** [38, 39] and **8** [40] are potent IκB kinase-β inhibitors promising for the treatment of autoimmune diseases. According to patent data, amides **9** inhibit cytokine TNF-α with a broad spectrum of action [41], and tricyclic compounds **10** are phosphodiesterase-4 inhibitors [42]. The importance of research in this field is also determined by the quite favorable pharmacological profile of the 3-aminothieno[2,3-*b*]-pyridine fragment itself [43–45].

We previously described [46] a procedure for the synthesis of 4,6-bis(difluoromethyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**11**), a convenient precursor to fluorine-containing thienopyridine derivatives, by the Guareschi–Thorpe reaction of cyanothioacetamide

**Scheme 1.**




EWG—electron withdrawing substituent, (F)—fluorine-containing substituent.

(**3**) and tetrafluoroacetylacetone. Taking into account that the yield of **11** according to the reported procedure [46] was fairly low, we tried to improve the synthesis of **11** and studied its transformation to thienopyridine derivatives. By treatment of **11** with chloroacetamides in the presence of excess alkali we obtained previously unknown 3-amino-4,6-bis(difluoromethyl)thieno[2,3-*b*]-pyridine-2-carboxamides **12a** and **12b** (Scheme 3).

Compounds **12a** and **12b** were isolated as yellow powders readily soluble in acetone and ethyl acetate. Their structure was confirmed by $^{1}H$, $^{13}C$ (DEPTQ), and $^{19}F$ NMR, IR, and high-resolution mass spectra, as well as by two-dimensional NMR spectra ($^{1}H$–$^{13}C$ HSQC, $^{1}H$–$^{13}C$ HMBC, $^{1}H$–$^{15}N$ HSQC, $^{1}H$–$^{15}N$ HMBC) of 3-amino-4,6-bis(difluoromethyl)thieno[2,3-*b*]pyridine-2-carboxamide (**12a**) (Scheme 4, Table 1). The $^{1}H$ NMR spectra of **12a** and **12b** characteristically showed two triplets in the region δ 7.07–7.81 ppm ($^{2}J_{HF}$ = 53.6–54.4 Hz) due to protons of the difluoromethyl groups. The signals of $NH_2$ and 4-$CHF_2$ were shifted downfield (relative to those of the fluorine-free analog of **12** and the 6-$CHF_2$ signal), which

**Scheme 2.**

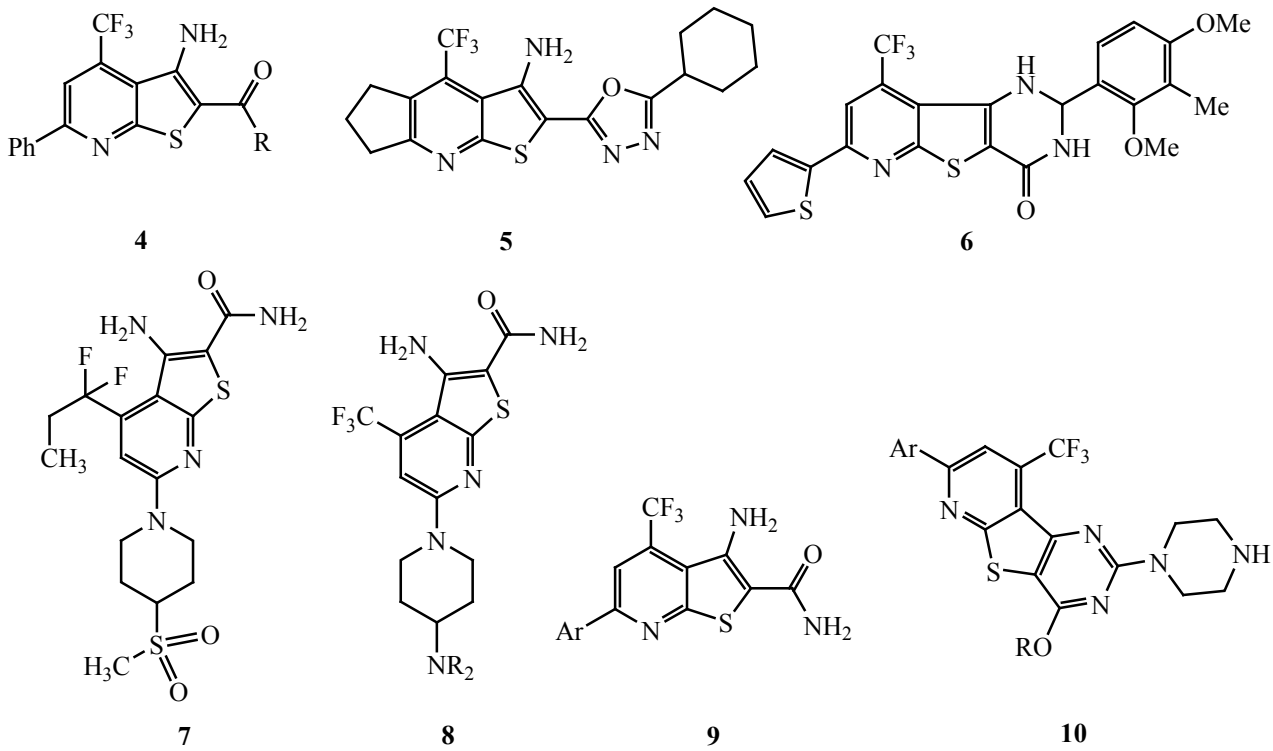


**Table 1**. Principal correlations in the 2D $^{1}H–^{13}C$ and $^{1}H–^{15}N$ HSQC and HMBC spectra of 3-amino-4,6-bis(difluoromethyl)-thieno[2,3-*b*]pyridine-2-carboxamide (**12a**)[a]

| $\delta_H$, ppm | $\delta_C$ or $\delta_N$, ppm | | | |
|---|---|---|---|---|
| | $^{1}H–^{13}C$ HSQC | $^{1}H–^{13}C$ HMBC | $^{1}H–^{15}N$ HSQC | $^{1}H–^{15}N$ HMBC |
| 6.81 s (2H, $NH_2$) | – | 103.3 ($C^2$), 123.7 ($C^{3a}$), 144.7 ($C^3$) | 64.6 ($NH_2$) | – |
| 7.17 t (1H, $C^6CHF_2$) | 113.1* ($C^6\underline{C}HF_2$) | 112.9* ($C^5$), 151.7 ($C^6$) | – | – |
| 7.58 br. s (2H, $CONH_2$) | – | – | 107.7 ($CONH_2$) | – |
| 7.78 t (1H, $C^4CHF_2$) | 112.1* ($C^4\underline{C}HF_2$) | 112.9* ($C^5$), 123.7 ($C^{3a}$), 138.9 ($C^4$) | – | – |
| 7.87 s (1H, $C^5CH$) | 112.9* ($C^5$) | 112.1* ($C^4\underline{C}HF_2$), 113.1* ($C^6\underline{C}HF_2$), 123.7 ($C^{3a}$), 138.9 ($C^4$), 151.7 ($C^6$) | – | 301.3 ($N_{Py}$) |

[a] Opposite phase signals in the DEPTQ $^{13}C$ NMR spectrum (CH) are marked with an asterisk.

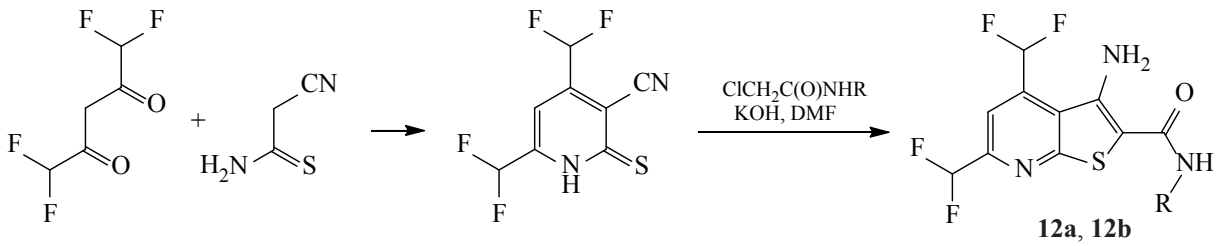
may be rationalized by intramolecular hydrogen bonding 4-$CHF_2\cdots$H–NH. The $^{13}C$ NMR spectra of **12a** and **12b** contained triplets of $C^4$ ($\delta_C$ 138.9–139.0 ppm, $^{2}J_{CF}$ = 22.8–23.5 Hz), $C^6$ ($\delta_C$ 151.7–152.0 ppm, $^{2}J_{CF}$ = 25.7 Hz), and $CHF_2$ ($\delta_C$ 112.1–113.1 ppm, $^{1}J_{CF}$ = 238.4–239.2 Hz) and a quintet (multiplet) of $C^5$ at $\delta_C$ 112.9–113.2 ppm. Fluorine nuclei resonated in the $^{19}F$ NMR spectra as two doublets at $\delta_F$ –111.7 and –115.6 ppm, which is consistent with published data for other difluoromethyl-substituted pyridine derivatives [25]. In the IR spectra of **12a** and **12b** we observed absorption bands typical of functional groups present in their molecules, as well as a very strong C–F stretching band at 1043–1034 $cm^{-1}$.

It is known that replacement of hydrogen by fluorine increases the lipophilicity of a compound and significantly affects protein–ligand interactions [4]. We performed *in silico* analysis of biological activity and bioavailability parameters of fluorine-containing compounds **11**, **12a**, and **12b** in comparison with their fluorine-free analogs.

By using OSIRIS Property Explorer online service [47] we calculated *c* Log*P* [logarithm of the *n*-octanol–water partition coefficient, log ($c_o/c_w$)], solubility (log *S*), topological polar surface area (TPSA), toxicological parameters (i.e., risks of mutagenic, oncogenic, and reproductive side effects), drug likeness, and drug score (general pharmacological potential) so that to find out whether the compounds under study conform to Lipinski's "rule of five" (*c* Log *P* ≤ 5.0, molecular weight MW ≤ 500, TPSA ≤ 140, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5) [48–50]. The results are summarized in Table 2.

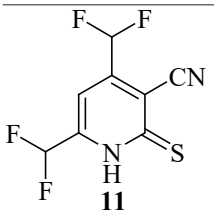
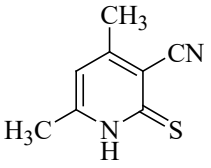
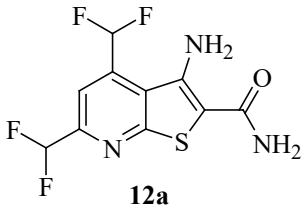
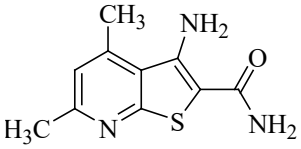
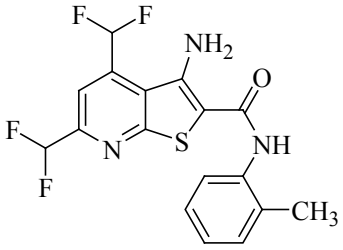
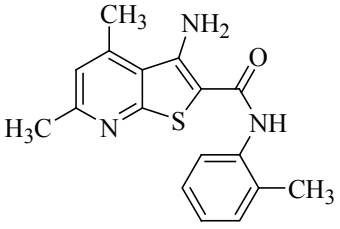
It is seen that compounds **12a** and **12b** should be appreciably more lipophilic than their hydrogen analogs and that the opposite pattern is observed for compound **11**. In all cases, the *c* Log *P* values do not exceed 5.0, indicating probable good intestinal absorption and permeability [48–50]. The molecular weights of all compounds are lower than 400, in keeping with Lipinski's "rule of five."

**Scheme 3.**




R = $CONH_2$ (**a**), 2-$CH_3C_6H_3NHCO$ (**b**).

**Table 2.** Toxicity risks and physicochemical parameters of compounds **11**, **12a**, and **12b** and their fluorine-free analogs **11-H**, **12a-H**, and **12b-H**, predicted by OSIRIS Property Explorer

| Compound | Toxicity risk[a] | | | | Physicochemical parameters | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | *c*Log*P* | log*S* | MW | TPSA | drug likeness | drug Score |
|  **11** | – | – | – | – | 0.19 | –3.63 | 236 | 67.91 | –7.03 | 0.438 |
|  **11-H** | – | – | – | – | 0.65 | –2.69 | 164 | 67.91 | –3.26 | 0.487 |
|  **12a** | – | – | – | – | 1.64 | –4.54 | 293 | 110.2 | –1.6 | 0.445 |
|  **12a-H** | – | – | – | – | 0.93 | –3.77 | 221 | 110.2 | 1.39 | 0.78 |
|  **12b** | – | – | ± | – | 4.04 | –6.31 | 383 | 96.25 | –0.01 | 0.28 |
|  **12b-H** | – | – | ± | – | 3.33 | –5.54 | 311 | 96.25 | 3.03 | 0.47 |

[a] "+" stands for high risk, "±" stands for moderate risk, and "–" stands for no toxicity; "A," "B," "C," and "D" denote mutagenicity, carcinogenicity, irritant action, and reproductive effects, respectively.

**Table 3.** ADMET parameters and probable biological activities of compounds **11**, **12a**, and **12b** predicted by SwissADME and SwissTargetPrediction

| Comp. no. | Gastrointestinal absorption[a] | BBB penetration[a] | Cytochrome P450 inhibition | | | | | Probable targets | Bioavailability index |
|---|---|---|---|---|---|---|---|---|---|
| | | | CYP1A2 | CYP2C19 | CYP2C9 | CYP2D6 | CYP3A4 | | |
| **11** | High | + | + | – | – | – | – | – | 0.55 |
| **12a** | High | – | + | – | – | – | – | MAPT | 0.55 |
| **12b** | Low | – | + | + | + | – | + | MAPT, MBNL1, MBNL2, MBNL3 | 0.55 |

[a] "+" and "–" denote the presence or absence of effect, respectively.

None of the fluorine-containing compounds showed a positive drug likeness value or a high drug score (>0.5). On the other hand, the results of calculations predict low toxicity of **11**, **12a**, and **12b**. According to the log *S* values, the examined compounds are moderately soluble, and the solubility of compound **12b** is the lowest as might be expected.

The TPSA parameter characterizes the surface area of polar molecular fragment. Increased TPSA value corresponds to reduced cell membrane or blood–brain barrier (BBB) permeability, and lower TPSA values are generally more favorable in terms of drug likeness. All compounds meet the condition TPSA ≤ 140 (Table 2).

Potential biological activity, probable targets, and ADMET (absorption, distribution, metabolism, excretion, toxicity) parameters were predicted using SwissADME [51], SwissTargetPrediction [52], PASS Online [53], and Molinspiration Property Calculation Service [54]. According to the PASS Online data, compounds **11**, **12a**, and **12b** could be expected to exhibit anti-arthritic and anti-allergic activities with a probability of more than 80%, as well as activity in autoimmune disorders. In addition, compounds **12a** and **12b** were predicted to show analgesic effect. Molinspiration Property Calculation Service predicted kinase inhibitory activity of **12a** and **12b** with a Molinspiration bioactivity score of –0.32 and –0.26, respectively.

High gastrointestinal absorption was predicted for compounds **11** and **12a**, whereas only compound **11** could penetrate the BBB (Table 3). According to SwissTargetPrediction, microtubule-associated protein tau (MAPT) is the most probable target for thienopyridine **12a**, and MAPT and muscleblind-like splicing regulator (MBNL) protein family are the most probable targets for thienopyridine **12b**. The bioavailability index for all compounds was estimated at 0.55, which indicated consistency with the Lipinski rule [55].

In summary, the proposed synthetic approach can be used for the preparation of new thieno[2,3-*b*]pyridine derivatives containing a difluoromethyl group. The structure of the synthesized compounds has been studied in detail using a combination of spectral methods. *In silico* analysis of biological activity and pharmacological potential has revealed substantial differences between fluorinated thienopyridines and their fluorine-free analogs, primarily in their solubilities and lipophilicities, and the results encourage further research in this field.

## EXPERIMENTAL

The NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer at 400.17 ($^{1}$H), 100.63 ($^{13}$C), 40.55 ($^{15}$N), or 376.50 MHz ($^{19}$F) using DMSO-$d_6$ as solvent. The chemical shifts were measured relative to tetramethylsilane or residual proton and carbon signals of the solvent ($^{1}$H, $^{13}$C), $MeNO_2$ ($^{15}$N, external), or $CFCl_3$ ($^{19}$F). The IR spectra were recorded on a Bruker Vertex 70 spectrometer with Fourier transform, equipped with an diamond ATR accessory (spectral resolution ± 4 cm$^{-1}$). The high-resolution mass spectra were obtained with a Bruker maXis time-of-flight spectrometer (electrospray ionization from solutions in acetonitrile). The purity of the isolated compounds was checked by TLC on Sorbfil-A plates using acetone–hexane (1 : 1) as eluent; spots were visualized by treatment with iodine vapor or under UV light.

Cyanothioacetamide (**3**) was synthesized by passing gaseous hydrogen sulfide through a solution of malono-

nitrile in ethanol in the presence of triethylamine [56]. 1,1,5,5-Tetrafluoroacetylacetone was provided by *PiM Invest* scientific and industrial association (http://fluorine1.ru).

**4,6-Bis(difluoromethyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (11)** was synthesized according to a modified procedure [46]. Cyanothioacetamide (**3**, 2.9 g, 29.06 mmol) was added with vigorous stirring in a stream of nitrogen to a solution of 1,1,5,5-tetrafluoroacetylacetone (5.00 g, 29.06 mmol) in 13 mL of ethanol, and a catalytic amount of morpholine (0.3 mL) was then added dropwise. When thioamide **3** dissolved completely, the solution was stirred for 6 h in a nitrogen atmosphere and was left to stand for 72 h at 4°C. The precipitate was filtered off and washed with diethyl ether. An additional amount of the product separated from the mother liquor on further keeping. Overall yield 4.80 g (70%). The spectral parameters were identical to those given in [46].

**3-Amino-4,6-bis(difluoromethyl)thieno[2,3-*b*]-pyridines 12a and 12b** (*general procedure*). A 10% aqueous solution of potassium hydroxide (2.2 mL, 4.25 mmol) was added with stirring to a solution of 1.00 g of 4,6-bis(difluoromethyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**11**, 4.23 mmol) in 4 mL of DMF heated to 70°C. 2-Chloroacetamide or 2-chloro-*N*-(2-methylphenyl)acetamide (4.25 mmol) was then added, and themixture was stirred for 0.5 h at 70°C. An additional 2.2 mL of 10% aqueous potassium hydroxide was added, and the mixture was stirred for 0.5 h more at 70°C. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, and dried. Compounds **12a** and **12b** were thus isolated in an analytically pure form.

**3-Amino-4,6-bis(difluoromethyl)thieno[2,3-*b*]-pyridine-2-carboxamide (12a).** Yield 72%, light yellow powder. IR spectrum, ν, $cm^{-1}$: 3427, 3392 s, 3346, 3294, 3149 br (N–H), 1684 s (C=O), 1043 s (C–F). $^1$H NMR spectrum, δ, ppm: 6.81 br.s (2H, $NH_2$), 7.17 t (1H, 6-$CHF_2$, $^2J_{HF}$ = 54.4 Hz), 7.58 br.s (2H, $CONH_2$), 7.78 t (1H, 4-$CHF_2$, $^2J_{HF}$ = 53.6 Hz), 7.87 s (1H, 5-H). $^{13}$C NMR spectrum (DEPTQ),[1] $\delta_C$, ppm: 103.3 ($C^2$), 112.1* t (4-$CHF_2$, $^1J_{CF}$ = 238.5 Hz), 112.9* quint ($C^5$, $^3J_{CF}$ = 4.4 Hz), 113.1* t (6-$CHF_2$, $^1J_{CF}$ = 239.2 Hz), 123.7 br.s ($C^{3a}$), 138.9 ($C^4$, $^2J_{CF}$ = 22.8 Hz), 144.7 ($C^3$), 151.7 ($C^6$, $^2J_{CF}$ = 25.7 Hz), 159.0 ($C^{7a}$), 166.4 (C=O). $^{15}$N NMR spectrum, $\delta_N$, ppm: 64.6 ($NH_2$), 107.7 ($CONH_2$), 301.3 ($N^7$). $^{19}$F NMR spectrum, $\delta_F$, ppm: –115.6 d (6-$CHF_2$, $^2J_{HF}$ = 54.5 Hz), –111.7 d (4-$CHF_2$, $^2J_{HF}$ = 53.1 Hz). Mass spectrum: *m*/*z* 316.0140 $[M + Na]^+$; calculated for $C_{10}H_7F_4N_3NaOS$: 316.0138.

**3-Amino-4,6-bis(difluoromethyl)-*N*-(2-methylphenyl)thieno[2,3-*b*]pyridine-2-carboxamide (12b).** Yield 62%, yellow powder. IR spectrum, ν, $cm^{-1}$: 3445, 3418, 3331 br (N–H), 1657 (C=O), 1034 s (C–F). $^1$H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 6.84 br.s (2H, $NH_2$), 7.07–7.34 m (5H, 6-$CHF_2$, $H_{arom}$), 7.81 t (1H, 4-$CHF_2$, $^2J_{HF}$ = 53.6 Hz), 7.91 s (1H, 5-H), 9.67 br.s (1H, CONH). $^{13}$C NMR spectrum (DEPTQ), $\delta_C$, ppm: 17.9* (Me), 103.2 ($C^2$), 112.2* t (4-$CHF_2$, $^1J_{CF}$ = 238.4 Hz), 113.1* t (6-$CHF_2$, $^1J_{CF}$ = 239.2 Hz), 113.2* m ($C^5$), 123.6 br.s ($C^{3a}$), 126.1* ($CH_{arom}$), 126.4* ($CH_{arom}$), 127.2* ($CH_{arom}$), 130.3* ($CH_{arom}$), 134.4 ($C_{arom}$), 135.9 ($C_{arom}$), 139.0 ($C^4$, $^2J_{CF}$ = 23.5 Hz), 145.2 ($C^3$), 152.0 ($C^6$, $^2J_{CF}$ = 25.7 Hz), 159.3 ($C^{7a}$), 163.4 (C=O). $^{19}$F NMR spectrum, $\delta_F$, ppm: –115.6 d (6-$CHF_2$, $^2J_{HF}$ = 54.5 Hz), –111.7 d (4-$CHF_2$, $^2J_{HF}$ = 53.1 Hz). Mass spectrum: *m*/*z* 406.0598 $[M + Na]^+$; calculated for $C_{17}H_{13}F_4N_3NaOS$: 406.0608.

[1] Hereinafter, opposite phase signals are marked with an asterisk.


## FUNDING

This study was performed under financial support by the Ministry of Science and Higher Education of the Russian Federation (project no. 4.5547.2017/8.9, V.V. Dotsenko, I.V. Aksenova; project no. 4.1196.2017/4.6, N.A. Aksenov) and by the Russian Foundation for Basic Research (project no. 19-43-230 007 r_a, D.S. Buryi).


## CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

## REFERENCES


1. *Fluorine in Medicinal Chemistry and Chemical Biology*, Ojima, I., Ed., Chichester: Wiley, 2009.
2. Bégué, J.P. and Bonnet-Delpon, D., *Bioorganic and Medicinal Chemistry of Fluorine*, Hoboken: Wiley, 2008.
3. Chambers, R.D., *Fluorine in Organic Chemistry*, Oxford: Blackwell, 2004.
4. Böhm, H.J., Banner, D., Bendels, S., Kansy, M., Kuhn, B., Müller, K., Obst-Sander, U., and Stahl, M., *ChemBioChem*, 2004, vol. 5, no. 5, p. 637. https://doi.org/10.1002/cbic.200301023
5. *Fluorine in Heterocyclic Chemistry*, Nenajdenko, V., Ed., Cham: Springer, 2014, vol. 1. https://doi.org/10.1007/978-3-319-04346-3
6. *Fluorine in Heterocyclic Chemistry*, Nenajdenko, V., Ed., Cham: Springer, 2014, vol. 2.

https://doi.org/10.1007/978-3-319-04435-4

7. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Petrov, V.A., Ed., Hoboken: Wiley, 2009.
8. Nenajdenko, V.G. and Balenkova, E.S., *Arkivoc*, 2011, part (i), p. 246. https://doi.org/10.3998/ark.5550190.0012.104
9. Nenajdenko, V.G., Sanin, A.V., and Balenkova, E.S., *Molecules*, 1997, vol. 2, no. 12, p. 186. https://doi.org/10.3390/21200186
10. Furin, G.G., *Chem. Heterocycl. Compd.*, 2006, vol. 42, no. 3, p. 285. https://doi.org/10.1007/s10593-006-0087-1
11. Furin, G.G. and Zhuzhgov, E.L., *Chem. Heterocycl. Compd.*, 2002, vol. 38, no. 2, p. 129. https://doi.org/10.1023/A:1015320822860
12. Elwahy, A.H. and Shaaban, M.R., *Curr. Org. Synth.*, 2010, vol. 7, no. 5, p. 433. https://doi.org/10.2174/157017910792246117
13. Dotsenko, V.V., Krivokolysko, S.G., Krivokolysko, B.S., and Frolov, K.A., *Russ. J. Gen. Chem.*, 2018, vol. 88, no. 4, p. 682. https://doi.org/10.1134/S1070363218040114
14. Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Mendeleev Commun.*, 2003, vol. 13, no. 6, p. 267. https://doi.org/10.1070/MC2003v013n06ABEH001851
15. Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Mendeleev Commun.*, 2004, vol. 14, no. 1, p. 30. https://doi.org/10.1070/MC2004v014n01ABEH001882
16. Dotsenko, V.V., Krivokolysko, S.G., Chernega, A.N., and Litvinov, V.P., *Russ. Chem. Bull., Int. Ed.*, 2002, vol. 51, no. 8, p. 1556. https://doi.org/10.1023/A:1020939712830
17. Dotsenko, V.V., Krivokolysko, S.G., Litvinov, V.P., and Chernega, A.N., *Russ. Chem. Bull., Int. Ed.*, 2002, vol. 51, no. 2, p. 362. https://doi.org/10.1023/A:1015436500899
18. Dotsenko, V.V., Chigorina, E.A., and Krivokolysko, S.G., *Chem. Heterocycl. Compd.*, 2017, vol. 53, no. 5, p. 626. https://doi.org/10.1007/s10593-017-2103-z
19. Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Monatsh. Chem.*, 2008, vol. 139, no. 3, p. 271. https://doi.org/10.1007/s00706-007-0784-1
20. Kumar, G.S., Poornachandra, Y., Reddy, K.R., Kumar, C.G., and Narsaiah, B., *Synth. Commun.*, 2017, vol. 47, no. 20, p. 1864. https://doi.org/10.1080/00397911.2017.1354379
21. Bakhite, E.A., Abdel-Rahman, A.E., and Al-Taifi, E.A., *Arab. J. Chem.*, 2014, vol. 7, no. 6, p. 936. https://doi.org/10.1016/j.arabjc.2014.05.035
22. Wang, N.Y., Zuo, W.Q., Xu, Y., Gao, C., Zeng, X.X., Zhang, L.D., You, X.Y., Peng, C.T., Shen, Y., Yang, S.Y., Wei, Y.Q., and Yu, L.T., *Bioorg. Med. Chem. Lett.*, 2014, vol. 24, no. 6, p. 1581. https://doi.org/10.1016/j.bmcl.2014.01.075
23. Ho, Y.W. and Yao, W.H., *Dyes Pigm.*, 2006, vol. 70, no. 1, p. 60. https://doi.org/10.1016/j.dyepig.2005.04.009
24. Ma, F., Liu, J., Zhou, T., Lei, M., Chen, J., Wang, X., Zhang, Y., Shen, X., and Hu, L., *Eur. J. Med. Chem.*, 2018, vol. 152, p. 307. https://doi.org/10.1016/j.ejmech.2018.04.028
25. Rodinovskaya, L.A., Shestopalov, A.M., Gromova, A.V., and Shestopalov, A.A., *J. Comb. Chem.*, 2008, vol. 10, no. 2, p. 313. https://doi.org/10.1021/cc7001793
26. Rateb, N.M., *J. Sulfur Chem.*, 2011, vol. 32, no. 6, p. 611. https://doi.org/10.1080/17415993.2011.628994
27. Zuo, W.Q., Wang, N.Y., Zhu, Y.X., Liu, L., Xiao, K.J., Zhang, L.D., Gao, C., Liu, Z.H., You, X.Y., Shi, Y.J., Peng, C.T., Ran, K., Tang, H., and Yu, L.T., *RSC Adv.*, 2016, vol. 6, no. 46, p. 40 277. https://doi.org/10.1039/C6RA01179A
28. Dyachenko, V.D., Tkachev, R.P., and Dyachenko, A.D., *Russ. J. Gen. Chem.*, 2009, vol. 79, no. 1, p. 121. https://doi.org/10.1134/S1070363209010186
29. Nikishin, K.G., Kislyi, V.P., Nesterov, V.N., Shestopalov, A.M., Struchkov, Yu.T., and Semenov, V.V., *Russ. Chem. Bull.*, 1998, vol. 47, no. 3, p. 465. https://doi.org/10.1007/BF02495655
30. Nikishin, K.G., Nesterov, V.N., Kislyi, V.P., Shestopalov, A.M., Struchkov, Y.T., and Semenov, V.V., *Russ. Chem. Bull.*, 1998, vol. 47, no. 4, p. 698. https://doi.org/10.1007/BF02495978
31. Rodinovskaya, L.A., Fedorov, A.E., Shestopalov, A.M., Belyakov, P.A., and Nikishin, K.G., *Russ. Chem. Bull., Int. Ed.*, 2013, vol. 62, no. 10, p. 2214. https://doi.org/10.1007/s11172-013-0321-9
32. Rodinovskaya, L.A., Sharanin, Yu.A., Litvinov, V.P., Shestopalov, A.M., Promonenkov, V.K., Zolotarev, B.M., and Mortikov, V.Yu., *J. Org. Chem. USSR*, 1985, vol. 21, no. 11, p. 2230.
33. Artyomov, V.A., Rodinovskaya, L.A., Shestopalov, A.M., and Litvinov, V.P.,

*Tetrahedron*, 1996, vol. 52, no. 3, p. 1011. https://doi.org/10.1016/0040-4020(95)00935-3
34. Kislyi, V.P., Nikishin, K.G., Kruglova, E.Y., Shestopalov, A.M., Semenov, V.V., Gakh, A.A., and Buchanan, A.C., *Tetrahedron*, 1996, vol. 52, no. 33, p. 10841. https://doi.org/10.1016/0040-4020(96)00632-1
35. Shestopalov, A.M., Kislyi, V.P., Kruglova, E.Y., Nikishin, K.G., Semenov, V.V., Buchanan, A.C., and Gakh, A.A., *J. Comb. Chem*., 2000, vol. 2, no. 1, p. 24. https://doi.org/10.1021/cc990036r
36. Dyachenko, V.D., Dyachenko, I.V., and Nenajdenko, V.G., *Russ. Chem. Rev*., 2018, vol. 87, no. 1, p. 1. https://doi.org/10.1070/RCR4760
37. Zhou, T.T., Ma, F., Shi, X.F., Xu, X., Du, T., Guo, X.D., Wang, G.H., Yu, L., Rukachaisirikul, V., Hu, L.H., Chen, J., and Shen, X., *J. Mol. Endocrinol*., 2017, vol. 59, no. 2, p. 151. https://doi.org/10.1530/JME-17-0121
38. Latli, B., Eriksson, M., Hrapchak, M., Busacca, C.A., and Senanayake, C.H., *J. Labelled Compd. Radiopharm*., 2016, vol. 59, no. 8, p. 300. https://doi.org/10.1002/jlcr.3398
39. Ginn, J.D., Sorcek, R.J., Turner, M.R., and Young, E.R.R., US Patent no. 2007 293 533, 2007.
40. Chen, Z., Cirillo, P.F., Disalvo, D., Liu, W., Marshall, D.R., Wu, L., and Young, E.R.R., WO Patent no. 2005 056 562, 2005.
41. Reichelt, C., Ludwig, A., and Leistner, S., EP Patent no. 1 683 799, 2006.
42. Reichelt, C., Ludwig, A., Schulze, A., Daghish, M., Leistner, S., Kroedel, A., and Heinicke, J., WO Patent no. 2006 010 567, 2006.
43. Litvinov, V.P., Dotsenko, V.V., and Krivokolysko, S.G., *Russ. Chem. Bull., Int. Ed*., 2005, vol. 54, no. 4, p. 864. https://doi.org/10.1007/s11172-005-0333-1
44. Litvinov, V.P., Dotsenko, V.V., and Krivokolysko, S.G., *Adv. Heterocycl. Chem*., 2007, vol. 93, p. 117. https://doi.org/10.1016/S0065-2725(06)93003-7
45. Litvinov, V.P., Dotsenko, V.V., and Krivokolysko, S.G., *Khimiya tienopiridinov i rodstvennykh sistem* (Chemistry of Thienopyridines and Related Systems), Moscow: Nauka, 2006, p. 6.
46. Buryi, D.S., Aksenov, N.A., and Dotsenko, V.V., *Fluorine Notes*, 2018, no. 4 (119). https://doi.org/10.17677/fn20714807.2018.04.02
47. Sander, T., *OSIRIS Property Explorer*, Idorsia Pharmaceuticals, Switzerland. http://www.organic-chemistry.org/prog/peo/
48. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., *Adv. Drug Delivery Rev*., 1997, vol. 23, nos. 1–3, p. 4. https://doi.org/10.1016/S0169-409X(96)00423-1
49. Lipinski, C.A., *Drug Discovery Today: Technol*., 2004, vol. 1, no. 4, p. 337. https://doi.org/10.1016/j.ddtec.2004.11.007
50. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., *Adv. Drug Delivery Rev*., 2012, vol. 64, Suppl., p. 4. https://doi.org/10.1016/j.addr.2012.09.019
51. Daina, A., Michielin, O., and Zoete, V., *Sci. Rep*., 2017, vol. 7, article no. 42 717. https://doi.org/10.1038/srep42717
52. Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., and Zoete, V., *Nucleic Acids Res*., 2014, vol. 42, no. W1, p. W32. https://doi.org/10.1093/nar/gku293
53. *PASS Online*, Laboratory for Structure-Function Based Drug Design, Institute of Biomedical Chemistry (IBMC), Moscow, Russia. http://www.pharmaexpert.ru/passonline/predict.php
54. *Molinspiration Property Calculation Service*, Molinspiration Cheminformatics, Slovak Republic, 2002. www.molinspiration.com
55. Martin, Y.C., *J. Med. Chem*., 2005, vol. 48, no. 9, p. 3164. https://doi.org/10.1021/jm0492002
56. Dotsenko, V.V., Krivokolysko, S.G., Polovinko, V.V., and Litvinov, V.P., *Chem. Heterocycl. Compd*., 2012, vol. 48, no. 2, p. 309. https://doi.org/10.1007/s10593-012-0991-5