Polyfunctional molecules in processes of aromatic nucleophilic substitution

3*. Pentafluoropyridines as scaffolds for synthesis of liquid-phase combinatorial libraries based on S_NAr processes

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A possibility of using polyfluorinated pyridines as multiply modified molecules, *i.e.*, scaffolds, in processes of aromatic nucleophilic substitution (S_NAr) for the synthesis of liquid-phase combinatorial libraries was studied. The real and "virtual" combinatorial libraries of diaryl ethers were synthesized by the reactions of pentafluoropyridine with phenol and its derivatives. Some criteria for the estimation of the quality of the libraries were formulated. A rational methodology for the preparation of representative combinatorial mixtures on the basis of processes of the S_NAr type in polyfluorinated arenes was proposed. The libraries can be used in highly efficient biological screening of low-molecular-weight regulators of transferase functioning.

Key words: aromatic nucleophilic substitution, combinatorial library, polyfluoropyridines, aryl ethers.

Application of methods of combinatorial chemistry for biological screening makes it possible to accelerate the elucidation of physiologically active substances of medical and agricultural design.[2—4] One of the approaches to the synthesis of liquid-phase combinatorial libraries is the use of polyhalogenated arenes as scaffolds in processes of the S_NAr types, for example, for search for low-molecular-weight regulators of transferase functioning.[5] In fundamental medical biological investigations combinatorial libraries can be used in studying the mechanisms of enzymatic processes. In fact, fast revealing of a structure—reactivity relationship by a comparison of structures of the most reactive compounds with the structure of less reactive components of the representative library can allow one to conclude about the mechanisms of interaction of low-molecular-weight inhibitors and enzymes.

Among aromatic compounds promising for the synthesis of combinatorial libraries, there are polyfluorinated arenes capable of subsequent substitution of several halogen atoms for nucleophilic reagents of different types.[1,5—10] It was observed[11] that among many matrices used in search for physiologically active substances the heterocyclic scaffolds are met most frequently. All the available data[1,6,8—10] indicate a possibility of using the multiple modification of polyfluorinated pyridines for the synthesis of soluble combinatorial libraries on their basis.

In the previous works, we performed processes of multiple modification of substrates **1** and **2** for the synthesis of pyridine-containing dioxines[9] and nucleosides[1,10] and new reagents for biochemical studies.[8] The main aims of the present work are the experimental substantiation of a possibility to use polyfluorinated pyridines as scaffolds in reactions with nucleophiles of different types, synthesis of "virtual" and real combinatorial mixtures of aromatic ethers, and development of a rational methodology for estimation of the representative libraries obtained on the basis of the S_NAr processes in polyfluorinated arenes.

For this purpose we primarily revealed a possibility of multiple modification of compounds **1—3** in the reactions with nucleophiles of different types (compounds **4—9**). It was found that the interaction of polyfluorinated pyridines even with such weak nucleophiles as pentafluorophenoxide or nitrophenoxide ions (generated from the corresponding phenols by potash in DMF) afforded substitution products of three F atoms in molecules **4** and **5** in high yields. The successive accumulation of strongly donating fragments of the amino groups in the aromatic framework (compounds **6—9**) should substantially diminish the nucleophilic mobility of the remained halogen atoms. Nevertheless, the high electron-withdrawing potential of the polyfluorinated pyridine framework and the high nucleophilic mobility of the F atom provide triple modifi-

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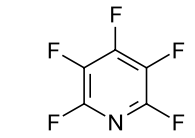

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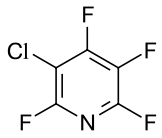

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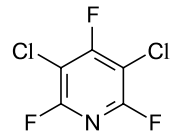

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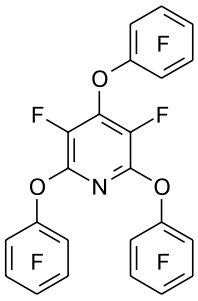

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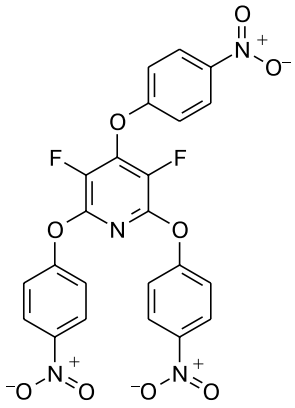

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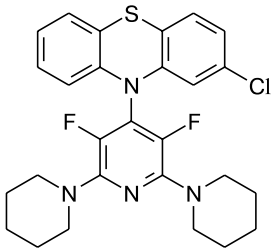

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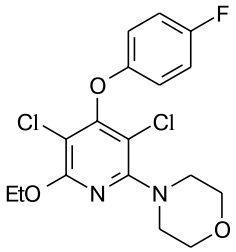

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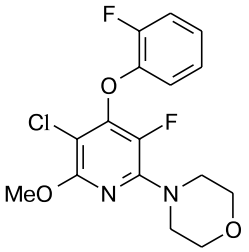

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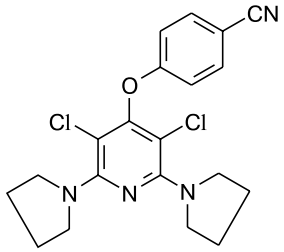

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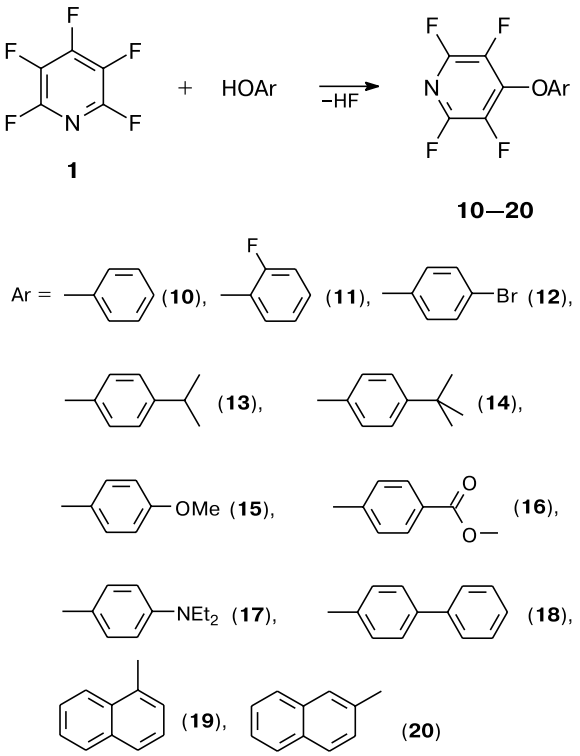
cation of a molecule under mild conditions. The study of the dynamics of disappearance of substrates **1—3** and accumulation of the corresponding diaryl ethers by ^{19}F NMR and TLC analyses of the reaction mixtures revealed the stepwise and highly selective formation of products of mono-, di-, and trisubstitution in high yield of each product. As should be expected,[1,6—10] in all substrates the F atoms in position 4 of the pyridine ring are substituted first. In substrate **2** the second nucleophile adds predominantly to the *para*-position with respect to the Cl atom, and the fraction of the corresponding *o*-isomer does not exceed 5%. The synthesis of trisubstituted compounds **4—9** in rather high yields illustrates a possibility of selective modification of the aromatic framework by nucleophilic reagents of different nature: phenoxides, amines, and alkoxides.

The very wide range of the reactivity change of the tested nucleophilic reagents should be mentioned. This range covers the most part of typical nucleophilic reactants in reactions of the S_NAr type, including those that were used for the synthesis of libraries of potential regulators of transferase functioning.[5] This fact predetermines a possibility of synthesis of the representative liquid-phase combinatorial libraries based on polyfluorinated pyridines for fast revealing low-molecular-weight regulators of transferase functioning using highly productive biological screening.

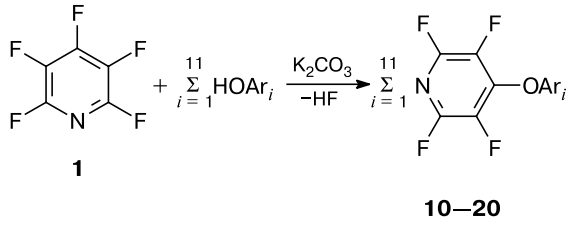
The processes studied correspond to the known conditions of synthesis of the liquid-phase combinatorial mixtures: they occur under mild conditions of continuous, as a rule, one-pot synthesis and with a minimum number of by-products. Thus, polyfluoropyridines can be considered as possible scaffolds of the first, second, and third degrees of modification. In the last case, a set of only ten reactants is needed to synthesize the combinatorial libraries consisting, for example, of a thousand of components.

In the present study, we synthesized the libraries ("virtual" and real, Schemes 1 and 2, respectively) consisting of a small number of aromatic ethers formed in the unambiguous reaction of substitution of the F atom in pentafluoropyridine for aryloxy groups. Note that the frameworks of diaryl ethers are presented in such preparations as pyriproxyfen, fusilade, fenoxycarb, chlomethoxynyl, *etc.*

Scheme 1



Scheme 2



It seemed reasonable to perform the study by comparing the ^{19}F NMR spectra of the reaction products formed in the "virtual" and real libraries. The ^{19}F NMR method was chosen, because it is most informative[1,10,12] for the solution of the stated problems. First we determined the optimal reaction conditions under which pentafluoropyridine reacted completely with an equimolar amount of each nucleophile presented in Scheme 1. The substitution of the F atom in position 4 of pentafluoropyridine appeared as an exponential decrease in the signal intensity at δ_F 29.9 and the up- and downfield shifts of the signals from the halogen atoms in the 2,6- and 3,5-positions of the ethers, respectively, relative to the signals of the precursor (Table 1).

The correspondence between the disappearance of the substrate and accumulation of the reaction product was observed at any moment. All the ^{19}F NMR and TLC data,

Table 1. Chemical shifts of multiplets (δ_F) and ratios of their relative intensities (I_{rel}) in the ^{19}F NMR spectra of compounds **1**, **10—13**, and **16—20** in DMF

Compound	δ_F				I_{rel}
	F(2), F(6)	F(3), F(5)	F(4)	F(2′)	
1	74.60	1.90	29.9	—	2 : 2 : 1
10	73.10	7.50	—	—	1 : 1
11	72.72	6.82	—	29.7	2 : 2 : 1
12	72.62	8.21	—	—	1 : 1
13	72.25	7.89	—	—	1 : 1
16	72.95	8.60	—	—	1 : 1
17	72.13	7.72	—	—	1 : 1
18	72.45	8.14	—	—	1 : 1
19	72.52	7.75	—	—	1 : 1
20	72.54	8.25	—	—	1 : 1

as well as the analysis of the amount of potassium fluoride that formed in the reaction mixtures, indicated that the only reaction products are the corresponding ethers **10—20**. Unlike pentafluoronitrobenzene,[4] even no traces of possible products of substitution F atoms in other positions of the substrate were observed for pentafluoropyridine. Of all the nucleophiles studied (see Scheme 1), the least reactive is phenol containing the acceptor substituent (*p*-COOMe) in the *para*-position. In addition, of all the substituents designated in Scheme 1, just the methoxycarbonyl group is least stable in the presence of bases. Nevertheless, ether **16** was isolated from the reaction mixture in the individual state in high yield. Thus, it is shown that the reaction under study proceeds unambiguously, which corresponds to the main conditions of synthesis of liquid-phase combinatorial mixtures, and pentafluoropyridine can be considered as the scaffold on the basis of which the libraries of tetrafluoropyridines substituted at position 4 are synthesized.

The ^{19}F NMR spectra of ethers **10—20** formed *in situ* (see Scheme 1) in quantitative yields were used for comparison of the "virtual" libraries in two variants. In one of them, the spectra were superimposed using the NUTS program. In the second variant, to check the correctness of computer summation of the spectra, a combinatorial mixture was prepared from equimolar parts of the reaction mixture of each ether, and the spectrum of the obtained mixture was recorded. The number, position, and relative intensities of signals were identical in the both cases. Taking into account the data obtained at the first stage, we synthesized the real library of diaryl ethers by the involvement of 1 equiv. of pentafluoropyridine in the reaction with a mixture of 1/11 equiv. of each phenol (see Scheme 2).

The spectra of the real and "virtual" (second variant) libraries are presented in Fig. 1.

The general view of the spectra of the libraries in an interval covering the signals of all detected F atoms is

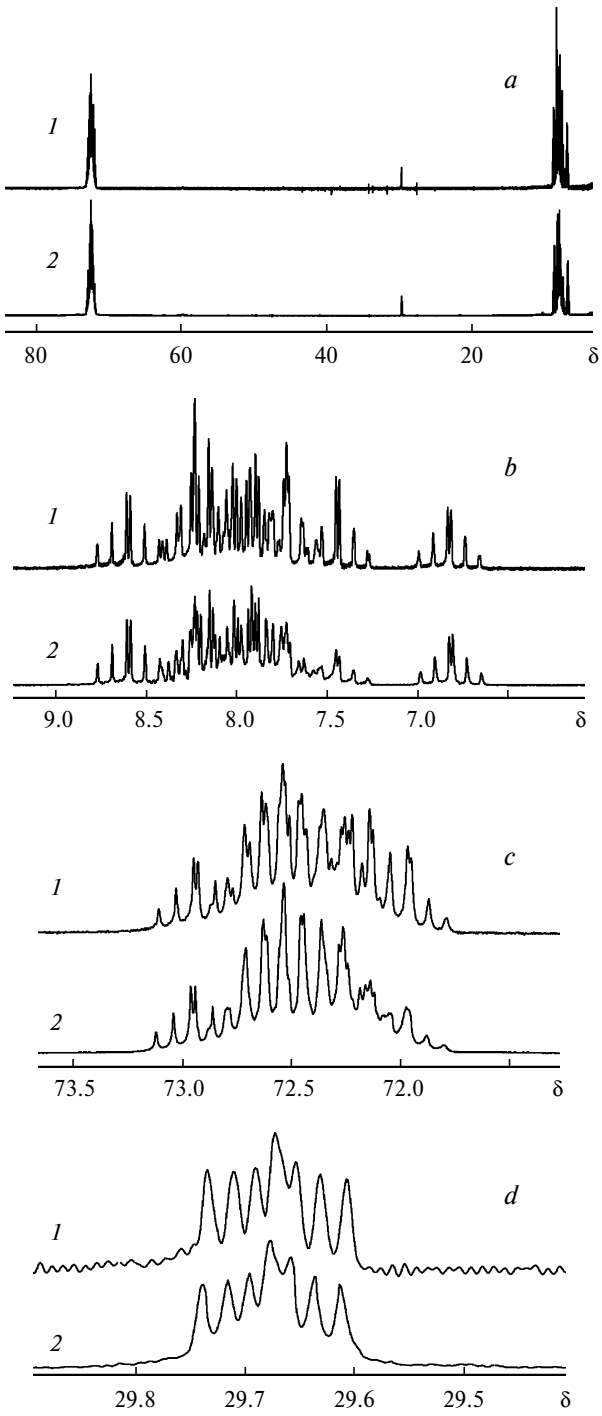


Fig. 1. ^{19}F NMR spectra of the real (*1*) and "virtual" (*2*) libraries of ethers **10—20**: general view (*a*) and regions of the spectra corresponding to the F atoms in positions 3, 5 (*b*), 2, 6 (*c*), and in the benzene ring of ether **11** (*d*).

shown in Fig. 1, *a*. The signals of the F(3), F(5), and F(2), F(6) lie in the ranges δ_F 6.6—8.8 (see Fig. 1, *b*) and 71.6—73.2 (see Fig. 1, *c*), respectively; the multiplets at δ_F 29.5—29.8 (see Fig. 1, *d*) belong to the F atom in the benzene ring of ether **11**. As follows from Fig. 1, the interval of chemical shifts of the F(3), F(5) atoms is larger than that for the F(2), F(6) atoms, and the number of separately observed signals in this interval is also higher. The individual multiplets (centers at δ_F 6.82 and 8.60) from ethers **11** and **16** can be observed in this interval. Thus, the F(3) and F(5) atoms lying near the aryloxy groups are more sensitive to a change in the nature of the substituent in the benzene fragments of aromatic ethers.

A comparison of the spectra of the "virtual" and real libraries suggests some criteria for the obtained combinatorial library.

1. The numbers of individual peaks and multiplets in the spectra of the "virtual" and real libraries coincide almost completely.

2. The ratio of intensities and distances between individual peaks or groups of signals are in accord.

3. The chemical shifts of singlets or centers of multiplets coincide.

4. Any signals are absent upon the mutual computer subtraction of the spectra of equal intensity of the both libraries.

The last criterion includes three preceding criteria and can be considered as the necessary and sufficient one for the estimation of the quality of the libraries.

Good coincidence between the spectra of the "virtual" and real libraries makes it possible to draw the expected but not evident *a priori* conclusion that the chemical properties of each nucleophile in a mixture with other nucleophiles remain unchanged. No mutual influence of the aromatic reaction products on the spectral characteristics of each component of the combinatorial mixture is observed. The exhaustive analysis of the ^{19}F NMR spectra of many individual components of the libraries can be problematic because of superposition of the signals of the fluorine derivatives containing substituents with similar electronic effects. It is most likely that the completeness of conversion of reactants cannot virtually be estimated and the presence of other reaction routes cannot be revealed. In this case, the criterion of quality of the representative library can be the quality of its small part synthesized from the least and most electron-donating nucleophiles and from reactants containing potentially labile substituents. For reactants of these types it seems reasonable to use the above described approach based on the comparison of the spectra of the "virtual" and real libraries and isolation and proof of the structures of only a restricted number of products for which we are not sure that the reaction proceeds unambiguously. Data of different kind on the quantitative dependences between the structures of the reactants and their reactivity can serve as an orientation for choosing the optimal conditions for the synthesis of the libraries.

We hope that the positions formulated in the present work can be useful for the synthesis of other libraries based on the S_NAr reactions in polyfluorinated arenes.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker WP 200SY spectrometer at 295 K and with frequencies of 200.13 and 188.28 MHz, respectively, and chemical shift values were measured relative to the internal standards Me_4Si and C_6F_6. Mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument. Melting points were determined on a Kofler S 30 A/G stage (Germany).

Preliminarily distilled polyfluoropyridines **1—3** (Aldrich) were used; purity of the fractions was monitored by ^{19}F and ^{1}H NMR spectroscopy. The melting points of the phenols used coincided with published data. Solvents were purified according to known procedures[13] and stored over molecular sieves 4 Å.

The completeness of the reactions and individual character of the synthesized compounds were monitored by TLC and HPLC. TLC was carried out on plates with silica gel Kieselgel $60F_{254}$ (Merk) in systems of $CHCl_3$ or $CHCl_3$ with a necessary additive of MeOH. Analytical HPLC was carried out on a Milikhrom-1 microcolumn liquid chromatograph, column Nucleosil 100-5 C-18, 5 μm (Macherey—Nagel), eluting for 20 min with the gradient of the MeCN concentration from 70 to 90% in 0.1% TFA (rate 100 μL min^{-1}). The accumulation of KF was determined using a fluorine-selective electrode.

Synthesis of ethers 10—20 for the synthesis of the "virtual" library (see Scheme 1). A mixture of DMF (2 mL), pentafluoropyridine (0.2 g, 1.18 mmol), K_2CO_3 (0.2 g, 1.45 mmol), and the corresponding arylhydroxy derivative (1.18 mmol) was stirred in a sealed vessel at ~20 °C without light. The reaction mixtures and purity of the isolated compounds were analyzed by ^{19}F NMR, TLC, and HPLC. After 1 day, the substrate and nucleophiles in the reaction mixtures already were not observed, and the amount of KF was 1.18 mmol (~100% of the theoretical yield). To record the ^{19}F NMR spectra, the reaction mixture was stopped to stir, a precipitate was let to settle, a transparent liquid above the precipitate was sampled with a pipette, and C_6F_6 (1.45 mmol) was added to the sample. At the end of the reaction, the ratios of signal intensities of the standard (C_6F_6) and organic products for each ether corresponded to the expected values. The combinatorial mixture was prepared from equimolar parts of the reaction mixtures of each ether, and the ^{19}F NMR spectrum of the obtained mixture was recorded (see Fig. 1, spectra *2*).

Synthesis of the real combinatorial library of ethers 10—20 (see Scheme 2). Pentafluoropyridine (0.4 g, 2.36 mmol), K_2CO_3 (0.4 g, 2.90 mmol), and a mixture of 2.36 mmoles of 11 nucleophiles shown in Scheme 1 (0.215 mmol of each nucleophile) were added to DMF (5 mL). The reaction was carried out and monitored as described above, and then the ^{19}F NMR spectrum was recorded (see Fig. 1, spectra *1*).

2,4,6-Tris(2,3,4,5,6-pentafluorophenoxy)-3,5-difluoropyridine (4). A mixture of pentafluoropyridine (1.19 g, 7.04 mmol), pentafluorophenol (6.5 g, 35.2 mmol), and K_2CO_3 (3 g, 21.8 mmol) in DMF (15 mL) was stirred for 18 h at 80 °C. The reaction mixture was poured on ice, and the precipitate was filtered off, washed with H_2O, dried *in vacuo* above $CaCl_2$, and crystallized from an ethanol—water (3 : 1) mixture and then from hexane. Compound **4** was obtained in a yield of 3.75 g (80%, hereinafter the yields are given based on the corresponding substrates **1—3**), m.p. 102—103 °C. Found (%): C, 41.52; F, 48.91; N, 2.31. $C_{23}F_{17}NO_3$. Calculated (%): C, 41.78; F, 48.84; N, 2.12. Found: *m/z* 661 $[M]^+$. ^{19}F NMR (CCl_4), δ: −0.55 (m, 4 F, F(3′), F(5′), 2-OC_6F_5, 6-OC_6F_5); 0.94 (m, 2 F, F(3′), F(5′), 4-OC_6F_5); 3.62 (s, 2 F, F(3), F(5)); 4.44 (m, 3 F, F(4′), 2-OC_6F_5, 4-OC_6F_5, 6-OC_6F_5); 6.71 (m, 2 F, F(2′), F(6′), 4-OC_6F_5); 9.71 (m, 4 F, F(2′), F(6′), 2-OC_6F_5, 6-OC_6F_5).

2,4,6-Tris(4-nitrophenoxy)-3,5-difluoropyridine (5). A mixture of pentafluoropyridine (1.19 g, 7.04 mmol), *p*-nitrophenol (4.9 g, 35.2 mmol), and K_2CO_3 (3 g, 21.8 mmol) in DMF (8 mL) was stirred for 35 h at 80 °C. The reaction mixture was poured on ice, and a precipitate was filtered off, washed with H_2O, dried *in vacuo* above $CaCl_2$, and crystallized from acetone and then from acetonitrile. Compound **5** was obtained in a yield of 4.34 f (70%), m.p. 209—210 °C. Found (%): C, 52.34; H, 2.26; F, 7.14; N, 10.68. $C_{23}H_{12}F_2N_4O_9$. Calculated (%): C, 52.48; H, 2.30; F, 7.22; N, 10.64. Found: *m/z* 526.0580 $[M]^+$. $C_{23}H_{12}F_2N_4O_9$. Calculated: M = 526.0572. ^{1}H NMR spectrum (CCl_4—DMAA-d_9), δ: 7.47 (d, 4 H, H(2′), H(6′), 2-C_6H_4O, 6-C_6H_4O, *J* = 9.1 Hz); 7.59 (d, 2 H, H(2′), H(6′), 4-C_6H_4O, *J* = 9.1 Hz); 8.22 (d, 4 H, H(3′), H(5′), 2-C_6H_4O, 6-C_6H_4O, *J* = 9.1 Hz); 8.29 (d, 2 H, H(3′), H(5′), 4-C_6H_4O, *J* = 9.1 Hz). ^{19}F NMR (CCl_4—DMAA-d_9): δ: 10.12 (s, F(3), F(5)).

4-(2-Chlorophenothiazin-10-yl)-2,3,5,6-tetrafluoropyridine. Pentafluoropyridine (3 g, 17.75 mmol) was added to a solution of 2-chlorophenothiazine (2.09 g, 8.94 mmol) in DMF (50 mL), and then a 60% suspension of NaH (0.9 g, 22.5 mmol) in mineral oil was added with stirring for 2 h. The reaction mixture was stirred at ~20 °C until 2-chlorophenothiazine disappeared (TLC monitoring). The reaction mixture was poured on ice, and the precipitate was filtered off, washed with water, dried *in vacuo* above $CaCl_2$, and recrystallized from Pr^nOH. 4-(2-Chlorophenothiazin-10-yl)-2,3,5,6-tetrafluoropyridine was obtained in a yield of 1.56 g (45%), m.p. 140—141 °C. Found (%): C, 53.55; H, 1.86; F, 19.90; N, 7.55; S, 8.42. $C_{17}H_7ClF_4N_2S$. Calculated (%): C, 53.34; H, 1.84; F, 19.85; N, 7.32; S, 8,38. Found: *m/z* 381.9955 $[M]^+$. $C_{17}H_7ClF_4N_2S$. Calculated: M = 381.9955. ^{1}H NMR ($CDCl_3$), δ: 6.25—6.38 (m, 2 H, H(7), H(8)); 6.89—7.17 (m, 5 H, H(1), H(3), H(4), H(6), H(9)). ^{19}F NMR ($CDCl_3$), δ: 19.06 (m, 2 F, F(3), F(5)); 75.43 (m, 2 F, F(2), F(6)).

2,6-Bis(piperid-1-yl)-4-(2-chlorophenothiazin-10-yl)-3,5-difluoropyridine (6). Piperidine (2 mL, 20.2 mmol) was added to a solution of 4-(2-chlorophenothiazin-10-yl)-2,3,5,6-tetrafluoropyridine (1.56 g, 4.1 mmol) in DMSO (10 mL), The reaction mixture was stirred for 16 h at ~20 °C and poured on ice. The precipitate was filtered off, washed with H_2O, dried *in vacuo* above $CaCl_2$, and recrystallized from Pr^nOH. Compound **6** was obtained in a yield of 1.83 g (87%), m.p. 148—149 °C. Found (%): C, 62.99; H, 5.26; Cl, 6.98; F, 7.32; N, 10.89; S, 6.16. $C_{27}H_{27}ClF_2N_4S$. Calculated (%): C, 63.21; H, 5.30; Cl, 6.91; F, 7.41; N, 10.92; S, 6,25. Found: *m/z* 512.1615 $[M]^+$. $C_{27}H_{27}ClF_2N_4S$. Calculated: M = 512.1613. ^{1}H NMR (CCl_4), δ: 1.65 (br.s, 12 H, CH_2—C); 3.40 (br.s, 8 H, CH_2—N); 6.20—6.32 (m, 3 H, H(3′), H(7′), H(8′)); 6.75—6.97 (m, 4 H, H(1′), H(4′), H(6′), H(9′)). ^{19}F NMR (CCl_4), δ: 16.84 (s, F(3), F(5)).

3,5-Dichloro-6-ethoxy-4-(4-fluorophenoxy)-2-(morpholin-1-yl)pyridine (7). *p*-Fluorophenol (0.153 g, 1.367 mmol) and triethylamine (0.152 g, 1.503 mmol) were added to a solution of 3,5-dichlorotrifluoropyridine (**3**) (0.276 g, 1.367 mmol) in DMF

(1.0 mL), and the mixture was stored for 30 min at ~20 °C. Then morpholine (0.119 g, 1.367 mmol) and triethylamine (0.152 g, 1.503 mmol) were added, the mixture was kept for 25 min at ~20 °C, then a 20% solution of EtONa (1.535 g, 4.511 mmol) in EtOH was added dropwise, and the mixture was stored for 10 min at ~20 °C. (Hereinafter the stepped substitution of the F atoms was monitored by ^{19}F NMR and TLC.) The reaction mixture was poured on ice, and the precipitate was filtered off, washed with H_2O, dried *in vacuo* above NaOH, and recrystallized from EtOH. Compound **7** was obtained in a yield of 0.370 g (70%), m.p. 99—102 °C. Found (%): C, 52.61; H, 4.45; Cl, 18.26; F, 4.98; N, 7.30. $C_{17}H_{17}Cl_2FN_2O_3$. Calculated (%): C, 52.73; H, 4.43; Cl, 18.31; F, 4.91; N, 7.23. ^{1}H NMR (CCl_4), δ: 1.44, (t, 3 H, Me, J = 7.1 Hz); 3.31 (t, 4 H, CH_2N, J = 4.4 Hz); 3.73 (t, 4 H, CH_2O, J = 4.4 Hz); 4.38 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1 Hz); 6.76 (m, 2 H, H(2′), H(6′), C_6H_4F); 6.92 (m, 2 H, H(3′), H(5′), C_6H_4F). ^{19}F NMR (CCl_4), δ: 41.09 (m, F(4′), C_6H_4F).

5-Chloro-3-fluoro-4-(2-fluorophenoxy)-6-methoxy-2-(morpholin-1-yl)pyridine (8). *o*-Fluorophenol (0.3363 g, 3.00 mmol) and triethylamine (1.0626 g, 10.50 mmol) were added to a solution of 3-chlorotetrafluoropyridine (**2**) (0.5859 g, 3.16 mmol) in DMF (3 mL), and the mixture was stored for 2.2 days at ~20 °C. Then morpholine (0.2614 g, 3.00 mmol) was added, the mixture was stored for 14 days at ~20 °C, a 29.4% solution of MeONa (1.1025 g, 6.0 mmol) in MeOH was added dropwise with stirring, and the mixture was stored for 9 days at ~20 °C. The reaction mixture was poured on ice, and the precipitate was filtered off, washed with water, dried *in vacuo* above NaOH, and crystallized from EtOH. Compound **8** was obtained in a yield of 0.675 g (63%), m.p. 83—84 °C. Found (%): C, 53.98; H, 4.30; Cl, 10.60; F, 10.60; N, 7.65. $C_{16}H_{15}ClF_2N_2O_3$. Calculated (%): C, 53.86; H, 4.24; Cl, 9.94; F, 10.65; N, 7.85. ^{1}H NMR ($CDCl_3$), δ: 3.47 (t, 4 H, CH_2N, J = 4.5 Hz); 3.77 (t, 4 H, CH_2O, J = 4.5 Hz); 3.93 (s, 3 H, OMe); 6.75—7.21 (m, 4 H, H(3′), H(4′), H(5′), H(6′), C_6H_4F). ^{19}F NMR ($CDCl_3$), δ: 3.34 (s, 1 F, F(3)); 25.26 (m, 1 F, F(2′), C_6H_4F).

2,6-Bis(pyrrolidin-1-yl)-3,5-dichloro-4-(4-cyanophenoxy)pyridine (9). 4-Cyanophenol (0.148 g, 1.237 mmol) and triethylamine ((0.138 g, 1.36 mmol) were added to a solution of 3,5-dichlorotrifluoropyridine (**3**) (0.25 g, 1.237 mmol) in DMF (1.0 mL), and the mixture was stored for 30 min at ~20 °C. Then pyrrolidine (0.194 g, 2.72 mmol) was added, the mixture was stored for 10 min at ~20 °C, triethylamine (0.275 g, 2.72 mmol) was added, and the mixture was stored for 1.5 h at 65 °C. The reaction mixture was poured into water with ice, and the precipitate that formed was filtered off, washed with water, dried *in vacuo* above NaOH, and crystallized from EtOH. Compound **9** was obtained in a yield of 0.463 g (93%), m.p. 186—188 °C. Found (%): C, 59.41; H, 4.99; Cl, 17.36; N, 13.73. $C_{20}H_{20}Cl_2N_4O$. Calculated (%): C, 59.56; H, 4.99; Cl, 17.58; N, 13.89. Found: m/z 402.1 $[M]^+$. $C_{20}H_{20}Cl_2N_4O$. Calculated: M = 402.1. ^{1}H NMR (CCl_4), δ: 1.90, (br.s, 8 H, CH_2C); 3.63 (br.s, 8 H, CH_2N); 6.92 (d, 2 H, H(2′), H(6′), OC_6H_4, J = 8.8 Hz); 7.53 (d, 2 H, H(3′), H(5′), OC_6H_4, J = 8.8 Hz).

4-(4-Carboxymethylphenoxy)-2,3,5,6-tetrafluoropyridine (16). Methyl *p*-hydroxybenzoate (0.190 g, 1.18 mmol) and K_2CO_3 (0.2 g, 1.45 mmol) were added to pentafluoropyridine (0.2 g, 1.18 mmol) in DMF (2 mL). The mixture was stirred at ~20 °C, and after the end of the process the reaction mixture was filtered off, the filtrate was added to ice-cold water (15 mL), and the precipitate was filtered off, dried *in vacuo* above NaOH, and crystallized from hexane. Compound **16** was obtained in a yield of 0.31 g (96%), m.p. 90.5—91.0 °C. According to the HPLC data, the content of the major substance was 99%. Found (%): C, 51.45; H, 2.39; F, 25.52; N, 4.68. $C_{13}H_7F_4NO_3$. Calculated (%): C, 51.84; H, 2.34; F, 25.23; N, 4.65. ^{1}H NMR (CCl_4), δ: 3.88 (s, 3 H, OMe); 7.04 (d, 2 H, H(3′), H(5′), J = 8.5 Hz); 8.02 (d, 2 H, H(2′), H(6′), J = 8.5 Hz). ^{19}F NMR (DMF), δ: 8.61 (m, 2 F, F(3), F(5)); 72.89 (m, 2 F, F(2), F(6)). The spectra of the products isolated and formed *in situ* are identical.

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