A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2025** (5) 202512393

N-Difluoromethylpyrazoles: in-demand and now available fluorinated building blocks

Bogdan Ugrak, Tatyana Dutova, Vyacheslav Rusak, and Evgeny Tretyakov*

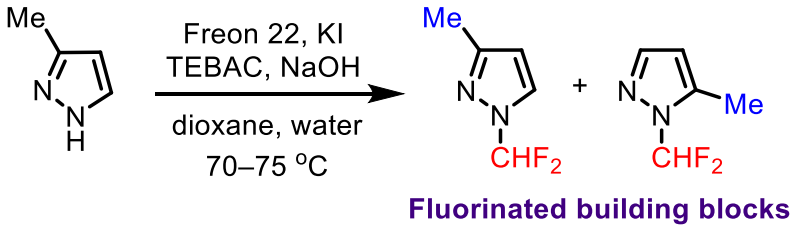
N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Av. 47, Moscow 119991, Russian Federation

E-mail: tretyakov@ioc.ac.ru

Received 04-24-2025 **Accepted** 06-18-2025 **Published on line** 06-27-2025

Abstract

A method for the difluoromethylation of 3(5)-methylpyrazole to synthesize 1-(difluoromethyl)-3-methyl-1*H*-pyrazole and 1-(difluoromethyl)-5-methyl-1*H*-pyrazole was developed. These isomers were employed to prepare various 4-substituted *N*-difluoromethylated pyrazole derivatives for the first time. The synthesized derivatives can be used as precursors for obtaining a comprehensive series of *N*-difluoromethyl–substituted pyrazoles for applications in various research fields, from materials science to medicine.



Keywords: Pyrazole; difluoromethylation; isomer separation; *N*-difluoromethylpyrazoles

Introduction

Compounds carrying a difluoromethyl moiety are common in the pharmaceutical industry and are among substances used for crop protection as well as other commercial products of practical significance.[1–4] The difluoromethyl moiety has substantial lipophilicity while possibly serving as a hydrogen bond donor for potential replacement of hydroxyl groups inter alia.[5] Drugs containing difluoromethoxy- or difluoromethylsulfonyl groups typically possess low toxicity. This is a major factor allowing for applications of such substances in medicinal chemistry. Some compounds containing a difluoromethyl moiety have been approved for medicinal use, for instance, anesthetic agent desflurane, antiulcer medicine pantoprazole, hypotensive drug foridone (riodipine or riosidine), and antipsoriasis agent diftorant. Several derivatives of *N*-(difluoromethyl)pyridin-2(1*H*)-one have been characterized and found to be enzyme inhibitors and therefore have aroused research attention as possible drugs.[6] In the agrochemical industry, herbicides carfentrazone-ethyl and sulfentrazone have been employed for a while. These substances are *N*-difluoromethyl derivatives of 1,2,4-triazol-5-one. Potent herbicidal activity has also been documented for several other *N*-difluoromethylazole–derived compounds.[7–10]

As a clear example, we should mention the latest research articles on milvexian, which is in Phase 2 clinical trials right now (Figure 1). Results of a Phase 2 study indicate that milvexian is effective at preventing postoperative venous thromboembolism (in patients who had undergone knee arthroplasty) while posing only a low risk of bleeding.[11–13] In 2018, it was declared that Janssen was expected to form a partnership with Bristol Myers Squibb to develop and commercialize this medication for severe cardiovascular diseases.[14] It is also worth citing an article on the design, synthesis, and pharmacological assessment of a second-generation inhibitor (TDI-11861) of soluble adenylyl cyclase (sAC, ADCY10); the compound has slow dissociation rates and improved druglike properties for use as a male nonhormonal contraceptive.[15] Compound C-48 has manifested excellent potency toward kinases TYK2 and JAK1 with IC_{50} at 6 and 37 nM, respectively, and shows >23-fold selectivity toward JAK2; compound C-48 also has remarkable metabolic stability and higher anti-inflammatory efficacy as compared to tofacitinib in models of acute ulcerative colitis. Furthermore, the strong anti-inflammatory effect of compound C-48 has been found to be mediated by modulation of the expression of related TYK2/JAK1-regulated genes as well as by the formation of cells of T helper (Th) 1, Th2, and Th17 lineages. Altogether, these properties make this compound promising as a drug with selective dual TYK2/JAK-inhibitory properties.[16]

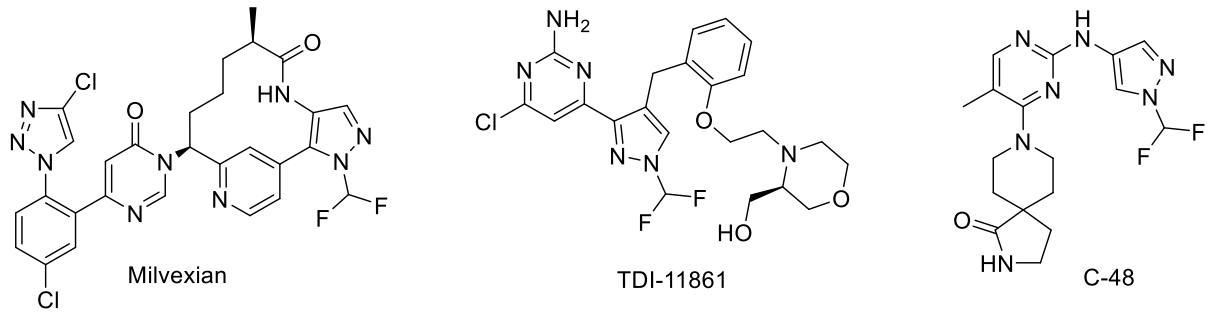


Figure 1. Difluoromethylated pyrazole derivatives.

In addition, diverse pyrazole derivatives, including those carrying difluoromethyl groups, are currently actively employed in coordination chemistry. To demonstrate good potential of *N*-difluoromethylated

pyrazoles as ligands, here we give some examples of the preparation and subsequent structural characterization of metal complexes with difluoromethylated pyrazoles. For instance, we have utilized the electron-withdrawing ability of the difluoromethyl substituent to alter packing mode of substituted pyrazoles[17] and to vary a donor ability of the spin-labeled pyrazole nucleus in manganese complexes. Notably, only in the case of a difluoromethyl-substituted ligand, was a manganese complex with head-to-head chain-polymeric structure obtained successfully.[18]

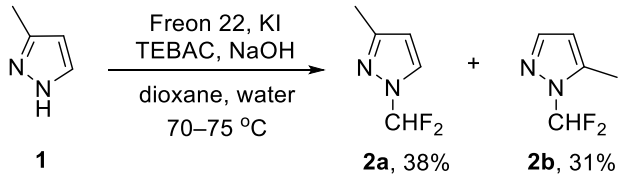
The difluoromethylation of organic molecules can be carried out in kilogram amounts by means of inexpensive reagents such as fluoroform or chlorodifluoromethane (Freon 22).[19] Difluoromethylation reactions of thiophenols, phenols, and different heterocycles have been described in several reviews.[20–22] The difluoromethylation of polydentate (ambidentate) heterocyclic structures, e.g., substituted azoles, leads to the formation of an isomeric mixture, the separation of which remains a difficult problem.[23–26] For instance, the difluoromethylation of 3-methylpyrazole **1** under various conditions produces a mixture of isomers (1-difluoromethyl-3-methylpyrazole [**2a**] and 1-difluoromethyl-5-methylpyrazole [**2b**]) at a 1:1 ratio with 60% yield of the isomeric mixture.[27] All attempts to separate the mixture of isomers by either fractional distillation or preparative HPLC have failed. Accordingly, the reaction products from the *N*-difluoromethylation of 4(5)-methylimidazole have been described as inseparable.

In the present paper, we focused on comprehensive characterization of the *N*-difluoromethylation of 3(5)-methylpyrazole and for the first time resolved the issue of separation of 1-(difluoromethyl)-5-methyl-1*H*-pyrazole and 1-(difluoromethyl)-3-methyl-1*H*-pyrazole. It was found that the difluoromethylation products can be used as bench reagents for obtaining functionalized 1-difluoromethyl compounds derived from pyrazole.

Results and Discussion

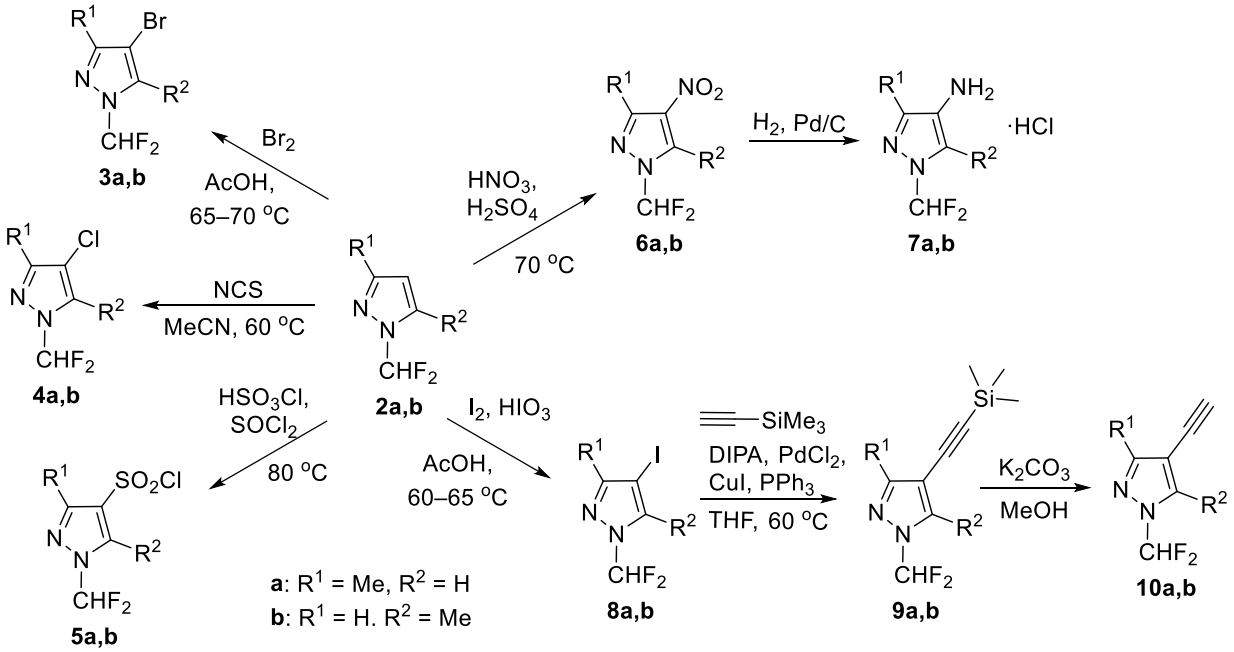
All available difluoromethylation methods for scalability and cost efficiency were reviewed. Xiao and colleagues have demonstrated that difluoromethylene phosphobetaine could serve as a precursor of difluorocarbene upon heating, and this approach has been utilized for the difluoromethylation of the pyrazole core.[28] Not so long ago, it was found that under mild conditions, pyrazoles can be *N*-difluoromethylated by means of $BrCF_2PO(OEt)_2$.[29] Petko and Yagupolskii in 2019 conducted a systematic study on the *N*-difluoromethylation of monosubstituted polydentate azoles with $ClCF_2H$ and $ClCF_2CO_2Na$.[27] Recently, Hong and Li designed a scalable mild method for the *N*-difluoromethylation of azoles using $ClCF_2H$.[30]

After examination of the aforementioned techniques and based on our experience with obtaining **2a** and **2b**, we followed the following approach: $ClCF_2H$ was bubbled at 70–75 °C into a stirred solution of 3(5)-methylpyrazole, triethyl benzylammonium chloride, and KI in a mixture of dioxane and a 13% aqueous NaOH solution. The reaction took place smoothly generating the respective mixture of isomers **2a** and **2b** (Scheme 1). In spite of very close boiling points of the isomers (117.3 and 118.6 °C, respectively), we for the first time successfully separated these products in gram amounts on an efficient distillation column (for details see the Experimental Section).



Scheme 1

The synthesis of both pure isomers **2a** and **2b** and their excellent stability under various conditions made it possible to obtain various derivatives of *N*-difluoromethylpyrazole. Particularly, derivatives **2a** and **2b** were successfully subjected to bromination with bromine in acetic acid at 65–70 °C thus giving 4-bromopyrazoles **3a** and **3b** with ~80–90% yield. The reaction of isomers **2a** and **2b** with *N*-chlorosuccinimide (NSC) at 60 °C in MeCN gave 4-chloroderivatives **4a,b** with an 80% yield. Furthermore, 1-difluoromethylpyrazole-4-sulfonyl chlorides **5a,b** were prepared with high yield from precursors **2a,b** through their interaction with $SOCl_2$ and HSO_3Cl at 80 °C. Importantly, 4-aminopyrazoles **7a,b** as hydrochlorides were synthesized from **2a,b** in two stages through the formation of 4-nitro-derivatives **6a,b** with overall yields of 50–70%. Compounds **2a,b** were also added into an electrophilic iodination reaction; in this way, the reaction with iodic acid and iodine gave substituted 4-iodopyrazoles **8a,b**; they were isolated with 70% yields (Scheme 2). Finally, iodo derivatives **8a,b** were subjected to the Sonogashira cross-coupling reaction with trimethylsilylacetylene to obtain acetylenic derivatives **9a,b;** the latter—after cleavage of the Si–C bond—were converted to 2-ethynylpyrazoles **10a,b**. The structures of compounds **2**–**10** were proven by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy (see ESI). Note that for compounds **2a** and **2b**, we were able to measure chemical shifts ^{15}N and coupling constants ^{15}N–^{19}F. It was found that geminal constant ^{2}J is 16.7 Hz, and vicinal constant ^{3}J is slightly more than 1 Hz.



Scheme 2

Thus, a feasible procedure for the difluoromethylation of 3(5)-methylpyrazole was developed. The method paves the way to gram scale synthesis of respective 1-(difluoromethyl)-3-methyl or 1-

(difluoromethyl)-5-methyl pyrazoles. The most general procedure involves bubbling of chlorodifluoromethane into a dioxane–water solution of the substrate, a base, and a phase transfer catalyst. Isomeric compounds 1-(difluoromethyl)-3-methyl-1*H*-pyrazole and 1-(difluoromethyl)-5-methyl-1*H*-pyrazole having very similar boiling points were separated with the help of an efficient distillation column. The isomers were subjected to chemical transformation to prepare derivatives of *N*-difluoromethylated pyrazoles with high yields. The derivatives thus synthesized may be helpful as excellent bench reagents for the synthesis of a comprehensive series of difluoromethyl-containing derivatives to investigate structure–property correlations in various research fields: e.g., medicine and materials science.

Experimental Section

General. Chemicals were obtained from commercial sources and were used without further purification. All solvents were purified by standard procedures. Quantitative analysis of reaction mass, fractions, and products was performed on an LKHM-80 gas-liquid chromatograph equipped with a flame ionization detector, together with a capillary column 50 m long with a deposited XE-60 phase; the temperature of the evaporator and detector was 250 °C, the temperature of the column thermostat was 50 °C, and the volume of the injected sample was 0.1 µl. Chromatograms were recorded and calculated using the Waters-740 module. Pyrrolidone-2 served as an internal standard.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 200.13, 50.32, and 188.31 MHz, respectively, on a Bruker AC-200 spectrometer. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. ^{15}N NMR spectra were acquired at 50.70 MHz on a Bruker Advance-500 spectrometer using nitromethane as an internal standard (high-field chemical shifts are shown with a minus sign). Chemical shifts of ^{15}N and KCCB ^{15}N–^{19}F were measured using reverse polarization (^{1}H to ^{15}N) with broadband isolation from protons (INEPT).[31]

High-resolution mass spectra were recorded on a Bruker maXis Q-TOF instrument equipped with an electrospray ionization (ESI) ion source. The measurements were carried out in the positive ion mode (+) (grounded spray needle, 4500 V high-voltage capillary; HV end plate offset: –500 V) and in the negative ion mode (–) (grounded spray needle, –4000 V high-voltage capillary; HV end plate offset: 500 V) with a scan range of *m/z* 50−1200. External calibration of the mass spectrometer was performed using a low-concentration tuning mix solution (Agilent Technologies). Direct injection with a syringe was performed for all of the analyzed solutions in appropriate solvents (flow rate: 3 µL·min^{-1}). Nitrogen was used as the nebulizer gas (0.4 bar) and dry gas (4.0 L·min^{-1}, 180 °C). All recorded spectra were processed using the Bruker Data Analysis 4.0 software package.

Synthesis of the mixture of 1-(difluoromethyl)-3-methyl-1*H*-pyrazole (2a) and 1-(difluoromethyl)-5-methyl-1*H*-pyrazole (2b). To a mixture of a 13% NaOH aqueous solution (200 g of NaOH in 1350 ml of water) and dioxane (800 ml), 3-methyl-1*H*-pyrazole (820 g, 10 mol), KI (5 g, 0.03 mol), and triethylbenzylammonium chloride (5 g, 0.02 mol) were added. The reaction mixture was heated to 70 °C, and Freon 22 gas (difluorochloromethane) was passed into the reaction mixture at a rate of 1 bubble per minute for ~4 h until pH decreased to 7.0–7.5. The reaction mixture was cooled to room temperature, NaOH (200 g, 5 mol) was added, and the heating was continued for the next 4 h. The last step was repeated two more times (a total of 800 g of NaOH was added), and the total reaction time was 16 h. The organic layer was separated. It weighed

nearly 2 kg and consisted of 60% of a mixture of 1-(difluoromethyl)-3-methyl-1*H*-pyrazole and 1-(difluoromethyl)-3-methyl-1*H*-pyrazole (ratio 1:1) and 40% of dioxane.

The organic layer was placed in a cube of a nozzle distillation column. Its parameters were as follows: a glass rectification column with a spirally prismatic nozzle made of stainless-steel wire (6 × 8 mm) with a nozzle layer height of 2100 mm; the efficiency of the column was 30 theoretical plates, as determined by means of a reference mixture of benzene with carbon tetrachloride; the internal diameter of the column was 50 mm, and a cube with a volume of 3 liters with external heating was employed; the coolant was PMS-5; pillars of the column were equipped with thermal compensation heating from nichrome thread and had thermal isolation; the head of the column was equipped with a total condenser.

The first fraction (~850 g) was collected at 760 mm Hg in temperature range 80–115 °C and then discarded; the fraction consisted of 10% of water, 85% of dioxane, and 5% of 1-difluoromethyl-3-methylpyrazole. The cubic residue (~1150 g) was placed in another distillation column with the following parameters: a steel distillation column with a spirally prismatic nozzle made of stainless-steel wire (2 × 3 mm) with a nozzle layer height of 7000 mm; the efficiency of the column was 110 theoretical plates, as determined using a reference mixture of benzene with carbon tetrachloride; the internal diameter of the column was 20 mm, and a steel cube with a volume of 2 liters with external heating was utilized; pillars of the column were equipped with thermal compensation heating; the head of the column was equipped with a total condenser and an automatic phlegm regulator.

The end of the selection of the 2nd fraction was controlled according to the concentration of **2a** in the cubic residue by the gas chromatography method. The cubic residue was distilled in a rotary evaporator to remove resinous impurities. The distillation results are compiled in Table 1.

Table 1. Results of separation of **2a** and **2b** by the distillation method

	Downloaded		Retrieved					
			1st fraction, b.p 117.1 °C; R 50-70 [a]		2nd fraction, [b] b.p 117.3-118.4 °C; R 100		Cube	
	% mass	g	% mass	g	% mass	g	% mass	g
2a	52.5	603.7	98.8	436.8	45.9	156.1	2.3	8.3
2b	47.5	546.3	1.2	5.3	54.1	184.0	97.7	351.6
Total	100	1150	100	442.1	100	340.1	100	359.9

[a] R is a phlegm number. [b] 2nd fraction can be recycled to the rectification stage of the mixture.

2a. Yield 442.1 g (38.4%), bp 117.3 °C, n_D^{20} 1.4199. ^{1}H NMR ($CDCl_3$): δ = 2.26 (s, 3 H, CH_3), 6.19 (d, $^3J_{H\text{-}H}$ = 2.6 Hz, 1 H, H^4), 7.10 (t, $^2J_{H\text{-}F}$ = 61.2 Hz, 1 H, HCF_2), 7.65 (d, $^3J_{H\text{-}H}$ = 2.6 Hz, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 12.38 (s, CH_3), 108.06 (s, C^4), 110.38 (t, $^1J_{C\text{-}F}$ = 248.1 Hz, CHF_2), 126.75 (s, C^5), 150.98 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –92.55 (d, $^2J_{F\text{-}H}$ = 61.2 Hz, CHF_2). ^{15}N NMR ($CDCl_3$): δ = –79.87 (t, $^3J_{N\text{-}F}$ = 1.3 Hz, N^2), –168.70 (t, $^2J_{N\text{-}F}$ = 16.7 Hz, N^1). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_7F_2N_2]^+$ 133.0572; found 133.0568.

2b. Yield 359.9 g (31.3%), bp 118.6 °C, n_D^{20} 1.4208. ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 6.09 (d, $^3J_{H\text{-}H}$ = 2.0 Hz, 1 H, H^4), 7.20 (t, $^2J_{H\text{-}F}$ = 60.0 Hz, 1 H, CHF_2), 7.44 (d, $^3J_{H\text{-}H}$ = 2.0 Hz, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 9.66 (t, $^5J_{C\text{-}F}$ = 2.5 Hz, CH_3), 108.54 (s, C^4), 112.36 (t, $^1J_{C\text{-}F}$ = 248.4 Hz, CHF_2), 138.82 (s, C^5), 140.80 (t, $^4J_{C\text{-}F}$ = 2.0 Hz, C^3). ^{19}F NMR ($CDCl_3$): δ = –93.04 (d, $^2J_{F\text{-}H}$ = 60.0 Hz, CHF_2). ^{15}N NMR ($CDCl_3$): δ = –73.74 (t, $^3J_{N\text{-}F}$ = 1.2 Hz, N^2), –165.80 (t, $^2J_{N\text{-}F}$ = 16.7 Hz, N^1). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_7F_2N_2]^+$ 133.0572; found 133.0568.

4-Bromo-1-(difluoromethyl)-3-methyl-1*H*-pyrazole (3a). Pyrazole **2a** (1.3 g, 0.01 mol) was dissolved in acetic acid (5 ml), and bromine (1.6 g, 0.01 mol) was added with stirring under ambient conditions. The reaction mixture was heated at 65–70 °C for 6 h, cooled to room temperature, and diluted with water (20 ml). Then, the mixture was neutralized with a 30% NaOH aqueous solution to pH 7.0–7.5 and extracted with methyl *tert*-butyl ether (2 × 20 ml). The combined organic solutions were washed with water (2 × 15 ml) and brine (20 ml) and dried over Na_2SO_4. The solvent was removed in vacuum at 30 °C, and the residue was purified by distillation thus giving the title product. Yield 1.75 g (83%), bp 65 °C/20 mm Hg, colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 7.06 (t, 1 H, $^2J_{H-F}$ = 60.0 Hz, CHF_2), 7.77 (s, 1, H^5). ^{13}C NMR ($CDCl_3$): δ = 11.86 (s, CH_3), 98.41 (s, C^4), 110.65 (t, $^1J_{C-F}$ = 251.1 Hz, CHF_2), 126.88 (s, C^5), 150.43 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –92.64 (d, $^2J_{F-H}$ = 60.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_6BrF_2N_2]^+$ 210.9677; found 210.9667.

4-Bromo-1-(difluoromethyl)-5-methyl-1*H*-pyrazole (3b). Pyrazole **2b** (2.0 g, 0.015 mol) was dissolved in acetic acid (10 ml), and bromine (2.4 g, 0.015 mol) was added with stirring under ambient conditions. The reaction mixture was heated at 65–70 °C for 6 h, cooled to room temperature, and diluted with water (30 ml). Next, the mixture was neutralized with a 30% NaOH aqueous solution to pH 7.0–7.5 and extracted with methyl *tert*-butyl ether (2 × 30 ml). The organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was purified by distillation to obtain the title compound. Yield 2.75 g (87%), bp 62–63 °C/20 mm Hg, colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H, CH_3), 7.16 (t, $^2J_{H-F}$ = 60.0 Hz, 1 H, CHF_2), 7.50 (s, 1 H, H^3). ^{13}C NMR ($CDCl_3$): δ = 9.45 (t, $^4J_{H-F}$ = 2.0 Hz, CH_3), 98.03 (s, C^4), 112.53 (t, $^1J_{C-F}$ = 250.0 Hz, CHF_2), 137.45 (s, C^5), 141.44 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –93.02 (d, $^2J_{F-H}$ = 60.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_6BrF_2N_2]^+$ 210.9677; found 210.9677.

4-Chloro-1-(difluoromethyl)-3-methyl-1*H*-pyrazole (4a). A mixture of pyrazole **2a** (6.6 g, 0.05 mol) and NSC (6.7 g, 0.05 mol) in acetonitrile (40 ml) was heated at 60 °C for 6 h. The solvent was removed on a rotary evaporator while the bath temperature was kept below 30 °C, and MTBE (50 ml) was introduced. The reaction mixture was washed with water and brine and dried over Na_2SO_4. The solvent was evaporated in vacuum thereby giving the pure product. Yield 6.8 g (82%), yellowish liquid. ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 7.04 (t, $^2J_{H-F}$ = 61.2 Hz, 1 H, CHF_2), 7.73 (s, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 10.94 (s, CH_3), 110.83 (t, $^1J_{C-F}$ = 250.6 Hz, CHF_2), 113.50 (s, C^4), 124.42 (s, C^5), 148.96 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –92.69 (d, $^2J_{F-H}$ = 61.2 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_6ClF_2N_2]^+$ 167.0182; found 167.0172.

4-Chloro-1-(difluoromethyl)-5-methyl-1*H*-pyrazole (4b). A mixture of pyrazole **2b** (6.6 g, 0.05 mol) and NSC (6.7 g, 0.05 mol) in acetonitrile (40 ml) was heated at 60 °C for 6 h. The solvent was removed on a rotary evaporator while the bath temperature was kept below 30 °C, and MTBE (50 ml) was added. The reaction mixture was washed with water and brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to obtain the pure product. Yield 6.6 g (79%), yellowish liquid. ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 7.14 (t, $^2J_{H-F}$ = 58.4 Hz, 1 H, CHF_2), 7.48 (s, 1 H, H^3). ^{13}C NMR ($CDCl_3$): δ = 8.50 (t, $^4J_{C-F}$ = 2.5 Hz, CH_3), 112.75 (s, C^4), 112.76 (t, $^1J_{C-F}$ = 250.6 Hz, CHF_2), 135.71 (s, C^5), 139.49 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –93.69 (d, $^2J_{F-H}$ = 58.4 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_6ClF_2N_2]^+$ 167.0182; found 167.0172.

1-(Difluoromethyl)-3-methyl-1*H*-pyrazole-4-sulfonyl chloride (5a). To a cold mixture (ice bath) of chlorosulfonic acid (4 ml, 0.06 mol) and thionyl chloride (1.4 ml, 0.02 mol), pyrazole **2a** (2 g, 0.015 mol) was added under stirring. The reaction mixture was allowed to warm to room temperature and then was heated at 80 °C for 20 h. After cooling, the mixture was cautiously poured into ice (~30 g), extracted with diethyl ether (2 × 20 ml), washed with cooled water, treated with charcoal, and dried with Na_2SO_4. The solvent was removed in vacuum at 25 °C thereby affording the title product. Yield 2.9 g (83%), yellowish oil. ^{1}H NMR ($CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 7.16 (t, 1 H, $^2J_{H-F}$ = 60.2 Hz, CHF_2), 8.41 (s, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 12.22 (s, CH_3), 110.21

(t, $^1J_{C\text{-}F}$ = 256.1 Hz, CHF_2), 127.63 (s, C^4), 131.03 (s, C^5), 149.62 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –94.87 (d, $^2J_{F\text{-}H}$ = 60.2 Hz, CHF_2). HRMS (ESI): *m/z* $[M - H]^-$ calcd for $[C_5H_4ClF_2N_2O_2S]^-$ 228.9656; found 228.9656.

1-(Difluoromethyl)-5-methyl-1*H*-pyrazole-4-sulfonyl chloride (5b). To cold (ice bath) chlorosulfonic acid (2.7 ml, 0.04 mol), pyrazole **2b** (1.3 g, 0.01 mol) was added under stirring. The reaction mixture was allowed to warm to room temperature and then was heated at 80 °C for 15 h. After cooling to room temperature, thionyl chloride (1.4 ml, 0.02 mol) was introduced, and the heating was continued for 5 h. The reaction mixture was cooled, cautiously poured into ice (~20 g), extracted with diethyl ether (2 × 15 ml), washed with cooled water, treated with charcoal, and dried with Na_2SO_4. The solvent was removed in vacuum at 25 °C. The yield of the title product: 1.9 g (84%), colorless solid, mp 31–32 °C. ^1H NMR ($CDCl_3$): δ = 2.81 (s, 3 H, CH_3), 7.29 (t, $^2J_{H\text{-}F}$ = 58.0 Hz, 1 H, CHF_2), 7.95 (s, 1 H, H^3). ^{13}C NMR ($CDCl_3$): δ = 9.80 (t, $^4J_{C\text{-}F}$ = 2.5 Hz, CH_3), 112.54 (t, $^1J_{C\text{-}F}$ = 254.6 Hz, CHF_2), 127.61 (s, C^4), 139.64 (s, C^5), 143.41 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –94.16 (d, $^2J_{F\text{-}H}$ = 58.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M - H]^-$ calcd for $[C_5H_4ClF_2N_2O_2S]^-$ 228.9656; found 228.9663.

1-(Difluoromethyl)-3-methyl-4-nitro-1*H*-pyrazole (6a). Fuming HNO_3 (2.5 ml, d 1.5 g/ml) was added during 10 min to an ice-cooled solution of pyrazole **2a** (5.3 g, 0.04 mol) in 98% H_2SO_4 (12 ml, d 1.8 g/ml). The reaction mixture was allowed to warm to ambient conditions, with subsequent heating at 70 °C for 6 h. After cooling to 0 °C, the mixture was cautiously poured into ice (~100 g) and kept at 0 °C for 30 min. A white precipitate was filtered off, washed with ice-cold water, and air-dried to obtain a white solid. Yield 6.3 g (86%), mp 30–31 °C. ^1H NMR ($CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 7.14 (t, $^2J_{H\text{-}F}$ = 60.0 Hz, 1 H, CHF_2), 8.54 (s, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 12.92 (s, CH_3), 110.36 (t, $^1J_{C\text{-}F}$ = 255.6 Hz, CHF_2), 127.57 (s, C^5), 135.47 (br. s, C^4), 147.35 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –95.01 (d, $^2J_{F\text{-}H}$ = 60.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M - H]^-$ calcd for $[C_5H_4F_2N_3O_2]^-$ 176.0277; found 176.0278.

1-(Difluoromethyl)-5-methyl-4-nitro-1*H*-pyrazole (6b). Fuming HNO_3 (3.15 ml, d 1.5 g/ml) was added during 10 min to an ice-cooled solution of pyrazole **2b** (6.6 g, 0.05 mol) in 98% H_2SO_4 (14 ml, d 1.8 g/ml). The reaction mass was allowed to warm to ambient conditions with subsequent heating at 70 °C for 10 h. After cooling to 0 °C, the mixture was cautiously poured into ice (~120 g) and incubated at 0 °C for 30 min. A white precipitate was then filtered off, washed with ice-cold water, and air-dried thus giving a white solid (product). Yield 7.8 g (88%), mp 110 °C. ^1H NMR ($CDCl_3$): δ = 2.85 (s, 3 H, CH_3), 7.25 (t, 1 H, $^2J_{H\text{-}F}$ = 58.0 Hz, CHF_2), 8.13 (s, 1 H, H^3). ^{13}C NMR ($CDCl_3$): δ = 9.71 (t, $^4J_{C\text{-}F}$ = 2.6 Hz, CH_3), 112.83 (t, $^1J_{C\text{-}F}$ = 254.1 Hz, CHF_2), 135.20 (br. s, C^4), 137.26 (s, C^3), 140.10 (s, C^5). ^{19}F NMR ($CDCl_3$): δ = –93.99 (d, $^2J_{F\text{-}H}$ = 58.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M - H]^-$ calcd for $[C_5H_4F_2N_3O_2]^-$ 176.0277; found 176.0267.

1-(Difluoromethyl)-3-methyl-1*H*-pyrazol-4-amine hydrochloride (7a). A mixture of pyrazole **6a** (8.8 g, 0.05 mol) and 10% Pd/C (0.7 g) in ethanol (50 ml) was stirred under H_2 (75 atm) in an autoclave for 3 h at room temperature. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure thus affording a dark liquid. The product was diluted with 2-propanol (10 ml) and DCM (40 ml), and next, a solution of HCl in diethyl ester (20 ml, 20% w/w) was introduced dropwise with stirring and cooling (ice bath). A precipitate was filtered off, washed with diethyl ester (20 ml), and air-dried to obtain a light-beige solid. Yield 7.3 g (80%), mp 235 °C (with decomposition). ^1H NMR (DMSO-d_6): δ = 2.27 (s, 3 H, CH_3), 7.78 (t, $^2J_{H\text{-}F}$ = 58.0 Hz, 1 H, CHF_2), 8.33 (s, 1 H, H^5), 10.30 (br. s, NH_3^+). ^{13}C NMR (DMSO-d_6): δ = 10.83 (s, CH_3), 109.75 (t, $^1J_{C\text{-}F}$ = 248.1 Hz, CHF_2), 114.70 (s, C^4), 124.21 (s, C^5), 145. 90 (s, C^3). ^{19}F NMR (DMSO-d_6): δ = –93.97 (d, $^2J_{F\text{-}H}$ = 58.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_8F_2N_3]^+$ 148.0681; found 148.0675.

1-(Difluoromethyl)-5-methyl-1*H*-pyrazol-4-amine hydrochloride (7b). A mixture of pyrazole **6b** (5.3 g, 0.03 mol) and 10% Pd/C (0.45 g) in ethanol (30 ml) was stirred under H_2 (75 atm) in an autoclave at room temperature for 3 h. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure thus affording a dark liquid. The product was diluted with 2-propanol (5 ml) and DCM (30

ml), after which a solution of HCl in diethyl ester (10 ml, 20 wt.%) was added dropwise with stirring and cooling (ice bath). A precipitate was filtered off, washed with diethyl ester (15 ml), and air-dried to obtain a light-beige solid. Yield 3.3 g (60%), mp 225 °C (with decomposition). ^{1}H NMR (DMSO-d_6): δ = 2.47 (s, 3H, CH_3), 7.80 (s, 1 H, H^5), 7.85 (t, $^2J_{H-F}$ = 58.0 Hz, 1 H, CHF_2), 10.30 (br. s, NH_3). ^{13}C NMR (DMSO-d_6): δ = 8.58 (s, CH_3), 111.06 (t, $^1J_{C-F}$ = 248.6 Hz, CHF_2), 114.55 (s, C^4), 134.25 (s, C^5), 136.93 (s, C^3). ^{19}F NMR (DMSO-d_6): δ = –94.59 (d, $^2J_{F-H}$ = 58.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_8F_2N_3]^+$ 148.0681; found 148.07.

1-(Difluoromethyl)-4-iodo-3-methyl-1*H*-pyrazole (8a). A mixture of pyrazole **2a** (1.3 g, 0.01 mol), I_2 (1.02 g, 0.004 mol), HIO_3 (0.35 g, 0.002 mol), and 30% H_2SO_4 (0.55 ml, d 1.22 g/ml) in acetic acid (10 ml) was heated at 60–65 °C for 6 h. After cooling to room temperature, the reaction mixture was poured into ice (~50 g). A white precipitate formed, which was collected by filtration, washed with ice-cold water, and air-dried thus giving the title product. Yield 1.75 g (68%), white solid, mp 54–55 °C, bp 64 °C/5.1 mm Hg. ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 7.07 (t, $^2J_{H-F}$ = 60.4 Hz, 1 H, CHF_2), 7.79 (s, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 13.45 (s, CH_3), 64.61 (s, C^4), 110.28 (t, $^1J_{C-F}$ = 251.1 Hz, CHF_2), 131.55 (s, C^5), 153.47 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –92.54 (d, $^2J_{F-H}$ = 60.4 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_6IF_2N_2]^+$ 298.9538; found 298.9538.

1-(Difluoromethyl)-4-iodo-5-methyl-1*H*-pyrazole (8b). A mixture of pyrazole **2b** (1.3 g, 0.01 mol), I_2 (1.02 g, 0.004 mol), HIO_3 (0.35 g, 0.002 mol), and 30% H_2SO_4 (0.55 ml, d 1.22 g/ml) in acetic acid (10 ml) was heated at 60–65 °C for 6 h. After cooling to room temperature, it was poured into ice (~50 g). A white precipitate formed, which was collected by filtration, washed with ice-cold water, and air-dried to obtain the title product. Yield 1.91 g (74%), white solid, mp 47–48 °C, bp 74 °C/12 mm Hg. ^{1}H NMR ($CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 7.16 (t, 1 H, $^2J_{H-F}$ = 58.0 Hz, CHF_2), 7.53 (s, 1 H, H^3). ^{13}C NMR ($CDCl_3$): δ = 11.30 (t, $^4J_{C-F}$ = 3.0 Hz, CH_3), 65.24 (s, C^4), 112.21 (t, $^1J_{C-F}$ = 250.3 Hz, CHF_2), 140.65 (s, C^5), 145.70 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –92.85 (d, $^2J_{F-H}$ = 58.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_5H_6IF_2N_2]^+$ 298.9538; found 298.9543.

1-(Difluoromethyl)-4-ethynyl-3-methyl-1*H*-pyrazole (10a). Diisopropylamine (16 ml, 0.11 mol, d 0.72 g/ml) was added to a mixture of pyrazole **8a** (15 g, 0.058 mol), $PdCl_2$ (0.5 g, 0.0028 mol), CuI (1.1 g, 0.0058 mol), and PPh_3 (3.0 g, 0.011 mol) in dry THF (110 ml). The flask was purged with argon, and trimethylsilylacetylene (13 ml, 0.091 mol, d 0.69 g/ml) was introduced. The reaction mixture was heated at 60 °C for 2.5 h, cooled, and filtered through celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in diethyl ester (100 ml), washed with water (2 × 50 ml), dried over Na_2SO_4, and concentrated. The crude product was distilled (80 °C/5 mm Hg) thereby giving **9a** in the form of a colorless liquid (11.4 g, 86%). The product (11.4 g, 0.05 mol) was dissolved in methanol (110 ml), and K_2CO_3 (8.3 g, 0.06 mol) was added. The mixture was stirred under ambient conditions for 2 h and filtered, and the solvent was removed on a rotary evaporator while the bath temperature was kept below 35 °C. The residue was diluted with diethyl ester (100 ml), washed with water (2 × 50 ml), dried over Na_2SO_4, and distilled to obtain the title product. Yield 4 g (51%), colorless liquid, bp 56 °C/13.5 mm Hg. ^{1}H NMR ($CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 3.15 (s, 1 H, CH), 7.07 (t, $^2J_{H-F}$ = 61.2 Hz, 1 H, CHF_2), 7.86 (s, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 11.97 (s, CH_3), 73.67 (s, -C≡), 81.17 (s, ≡CH), 105.35 (s, C^4), 110.44 (t, $^1J_{C-F}$ = 251.6 Hz, CHF_2), 129.95 (s, C^5), 153.72 (s, C^3). ^{19}F NMR ($CDCl_3$): δ = –93.17 (d, $^2J_{F-H}$ = 61.2 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_7H_7F_2N_2]^+$ 157.0572; found 157.0570.

1-(Difluoromethyl)-4-ethynyl-5-methyl-1*H*-pyrazole (10b). Diisopropylamine (11 ml, 0.078 mol, d 0.72 g/ml) was added to a mixture of pyrazole **8b** (10 g, 0.038 mol), $PdCl_2$ (0.35 g, 0.002 mol), CuI (0.74 g, 0.0038 mol), and PPh_3 (2.0 g, 0.0076 mol) in dry THF (70 ml). The flask was purged with argon, and trimethylsilylacetylene (9 ml, 0.062 mol, d 0.69 g/ml) was introduced. The reaction mass was heated at 60 °C for 2.5 h, cooled, and filtered through celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (100 ml), washed with brine (50 ml), dried over Na_2SO_4, and concentrated. Crude product **9b** (7.1 g, 80%) was dissolved in methanol (70 ml), and K_2CO_3 (6.0 g, 0.043 mol) was added. The reaction mixture was

stirred under ambient conditions for 2 h and filtered, and the solvent was removed on a rotary evaporator while the bath temperature was kept below 45 °C. The residue was diluted with ethyl acetate (100 ml), washed with water (2 × 50 ml), dried over Na_2SO_4, and distilled thereby giving the title product. Yield 2.5 g (52%), colorless liquid, 78 °C/45 mm Hg. ^{1}H NMR ($CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.16 (s, 1 H, CH), 7.18 (t, 1 H, $^2J_{H-F}$ = 58.0 Hz, CHF_2), 7.59 (s, 1 H, H^5). ^{13}C NMR ($CDCl_3$): δ = 9.67 (t, $^4J_{C-F}$ = 2.5 Hz, CH_3), 73.72 (s, -C≡), 81.12 (s, ≡CH), 105.48 (s, C^4), 112.29 (t, $^1J_{C-F}$ = 250.0 Hz, CHF_2), 143.03 (s, C^3), 143.07 (s, C^5). ^{19}F NMR ($CDCl_3$): δ = –93.53 (d, $^2J_{F-H}$ = 58.0 Hz, CHF_2). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $[C_7H_7F_2N_2]^+$ 157.0572; found 157.0575.

Supplementary Material

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all compounds and ^{15}N NMR spectra of **2a** and **2b** are available in the supplementary material file associated with this manuscript.

References

1. *Fluorinated Heterocyclic Compounds: Synthesis*, *Chemistry and application* (Ed. V. A. Petrov), John Wiley & Sons: Hoboken, 2009, p 516. https://doi.org/10.1002/9780470528952
2. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed.; Wiley-VCH Verlag GmbH: Weinheim, 2013, p 379. https://doi.org/10.1002/9783527651351
3. *Fluorine in Heterocyclic Chemistry, Vol. 1, 5-Membered Heterocycles and Macrocycles* (Ed. V. Nenajdenko), Springer: Heidelberg, 2013, p 681.
4. Politanskaya, L. V.; Selivanova, G. A.; Panteleeva, E. V.; Tretyakov, E. V.; Platonov, V. E.; Nikul'shin, P. V.; Vinogradov, A. S.; Zonov, Ya. V.; Karpov, V. M.; Mezhenkova, T. V.; Vasilyev, A. V.; Koldobskii, A. B.; Shilova, O. S.; Morozova, S. M.; Burgart, Ya. V.; Shchegolkov, E. V; Saloutin, V. I.; Sokolov, V. B.; Aksinenko, A. Yu.; Nenajdenko, V. G.; Moskalik, M. Yu.; Astakhova, V. V.; Shainyan, B. A.; Tabolin, A. A.; Ioffe, S. L.; Muzalevskiy, V. M.; Balenkova, E. S.; Shastin, A. V.; Tyutyunov, A. A.; Boiko, V. E.; Igumnov, S. M.; Dilman, A. D.; Adonin, N. Yu.; Bardin, V. V.; Masoud, S. M.; Vorobyeva, D. V.; Osipov, S. N.; Nosova, E. V.; Lipunova, G. N.; Charushin, V. N.; Prima, D. O.; Makarov, A. G.; Zibarev, A. V.; Trofimov, B. A.; Sobenina, L. N.; Belyaeva, K. V.; Sosnovskikh, V. Ya.; Obydennov, D. L.; Usachev, S. A. *Russ. Chem. Rev*. **2019**, *88*, 425. https://doi.org/10.1070/RCR4871
5. Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626. https://doi.org/10.1021/jo00111a021
6. Yu, G.; Rao, P. N. P.; Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Velazquez, C. A.; Suresh, M. R.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2168. https://doi.org/10.1016/j.bmcl.2010.02.040
7. Dayan, B. E.; Armstrong, B. M.; Weete, G. D. *J. Agric. Food Chem.* **1998**, *46*, 2024. https://doi.org/10.1021/jf970988p
8. Elmarakby, S. A.; Supplee, D.; Cook, R. *J. Agric. Food Chem.* **2001**, *49*, 5285. https://doi.org/10.1021/jf010601p

9. Kobayashi, O.; Takatsuna, R.; Niikura, N.; Matsukawa, T.; Nakamura, S.; Hirai, K.; Koshi, S.; Kawanishi, N.; Yamada, O. *JP Patent* 201656157 A, **2016**.
10. Mykhailiuk, P. K. *Chem. Rev*. **2021**, *121*, 1670. https://doi.org/10.1021/acs.chemrev.0c01015
11. Weitz, J. I.; Strony, J.; Ageno, W.; Gailani, D.; Hylek, E. M.; Lassen, M. R.; Mahaffey, K. W.; Notani, R. S.; Roberts, R.; Segers, A.; Raskob, G. E. *N. Engl. J. Med*. **2021**, *385*, 2161. https://doi.org/10.1056/NEJMoa2113194
12. Wong, P. C.; Crain, E. J.; Bozarth, J. M.; Wu, Yi.; Dilger, A. K.; Wexler, R. R.; Ewing, W. R.; Gordon. D.; Luettgen, J. M. *J. Thromb Haemost*. **2022**, *20*, 399. https://doi.org/10.1111/jth.15588
13. Dilger, A. K.; Pabbisetty, K. B.; Corte, J. R.; De Lucca, I.; Fang, T.; Yang, W.; Pinto, D. J. P.; Wang, Yu.; Zhu, Ye.; Mathur, A.; Li, J.; Hou, X.; Smith, D.; Sun, D.; Zhang, H.; Krishnananthan, S.; Wu, D.-R.; Myers, Jr. J. E.; Sheriff, S.; Rossi, K. A.; Chacko, S.; Zheng, J. J.; Galella, M. A.; Ziemba, T.; Dierks, E. A.; Bozarth, J. M.; Wu, Yi.; Crain, E.; Wong, P. C.; Luettgen, J. M.; Wexler, R. R.; Ewing, W. R. *J. Med. Chem*. **2022**, *65*, 1770. https://doi.org/10.1021/acs.jmedchem.1c00613
14. A Study on BMS-986177 for the Prevention of a Stroke in Patients Receiving Aspirin and Clopidogrel (AXIOMATIC-SSP). U.S. National Library of Medicine, **2023** (accessed 30 May 2024); ClinicalTrial.gov.
15. Miller, M.; Rossetti, T.; Ferreira, J.; Ghanem, L.; Balbach, M.; Kaur, N.; Levin, L. R.; Buck, J.; Kehr, M.; Coquille, S.; van den Heuvel, J.; Steegborn, C.; Fushimi, M.; Finkin-Groner, E.; Myers, R. W.; Kargman, S.; Liverton, N. J.; Huggins, D. J.; Meinke, P. T. *J. Med. Chem*. **2022**, *65*, 15208. https://doi.org/10.1021/acs.jmedchem.2c01133
16. Yang, T.; Cui, X.; Tang, M.; Qi, W.; Zhu, Z.; Shi, M.; Yang, L.; Pei, H.; Zhang, W.; Xie, L.; Xu, Ya; Yang, Z.; Chen, L. *J. Med. Chem*. **2022**, *65*, 3151. https://doi.org/10.1021/acs.jmedchem.1c01137
17. Serykh, A.; Tretyakov, E.; Fedyushin, P.; Ugrak, B.; Dutova, T.; Lalov, A.; Korlyukov, A.; Akyeva, A.; Syroeshkin, M.; Bogomyakov, A.; Romanenko, G.; Artiukhova, N.; Egorov, M.; Ovcharenko, V. *J. Mol. Struct*. **2022**, *1269*, 133739. https://doi.org/10.1016/j.molstruc.2022.133739
18. Kudryavtseva, E.; Serykh, A.; Ugrak, B.; Dutova, T.; Nasyrova, D.; Korlyukov, A.; Zykin, M.; Efimov, N.; Bogomyakov, A.; Tretyakov, E. *Crystals*, **2023**, *13*, 1528. https://doi.org/10.3390/cryst13101528
19. Thomoson, C. S.; Wang, L.; Dolbier, W. R. *J. Fluor. Chem.* **2014**, *168*, 34. https://doi.org/10.1016/j.jfluchem.2014.08.015
20. Ni, C.; Hu, J. *Synthesis* **2014**, 842. https://doi.org/10.1061/9780784413753.127
21. Lu, Y.; Liu, C.; Chen, Q-Y. *Curr. Org. Chem*. **2015**, *19,* 1638. https://doi.org/10.2174/1385272819666150615235605
22. Yierien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. Eur. J*. **2017**, *23*, 14676. https://doi.org/10.1002/chem.201702311
23. Jończyk, A.; Nawrot, E.; Kisielewski, M. *J. Fluor. Chem.* **2005**, *126*, 1587. https://doi.org/10.1016/j.jfluchem.2005.09.013
24. Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12390. https://doi.org/10.1002/anie.201306703
25. Petko, K. I.; Yagupolskii, L. M. *J. Fluor. Chem.* **2001**, *108*, 211.

https://doi.org/10.1016/S0022-1139(01)00350-5
26. Fuchibe, K.; Koseki, Y.; Aono, T.; Sasagawa, H.; Ishikawa, S. *J. Fluor. Chem.* **2012**, *153*, 52. https://doi.org/10.1016/j.jfluchem.2011.09.012
27. Petko, K. I.; Sokolenko, T. M.; Filatov, A. A.; Polovinko, V. V.; Rusanov, E. B.; Dudko, V. A.; Yagupolskii, Yu. L. *Chem. Heterocycl. Compd.* **2019**, *55*, 359. https://doi.org/10.1007/s10593-019-02465-x
28. Deng, X. Y.; Lin, J. H.; Zheng, J.; Xiao, J. C. *Chem. Commun*. **2015**, *51*, 8805. https://doi.org/10.1039/C5CC02736E
29. Mao, T.; Zhao, L.; Huang, Y.; Lou, Y. G.; Yao, Q.; Li, X. F.; He, C. Y. *Tetrahedron Lett*. **2018**, *59*, 2752. https://doi.org/10.1016/j.tetlet.2018.06.003
30. Hong, Z.; Hou, X.; Zhao, R.; Li, J.; Pawluczyk, J.; Wang, B.; Kempson, J.; Khandelwal, P.; Smith, L. M.; Glunz, P.; Mathur, A. *J. Fluor. Chem*. **2020**, *234*, 109514. https://doi.org/10.1016/j.jfluchem.2020.109514
31. Pachler, K. G. R.; Wessels, P. G. *J. Magn. Reason*, **1973**, 377.