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Synthesis of an 8-pentafluorosulfanyl analog of the antimalarial agent mefloquine

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ABSTRACT

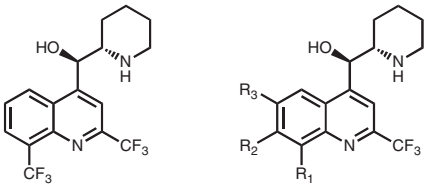
The 8-SF_5 analog of mefloquine was synthesized in nine steps from commercially available starting materials and in five steps from a novel *ortho*-SF_5–substituted aniline intermediate.

The geographic extension of *Plasmodium falciparum* necessitates the development of new antimalarial drugs that are active against resistant parasite strains.[1] Mefloquine (**1**) has been shown to have high efficacy for both treatment and prophylaxis of chloroquine-resistant malaria (Fig. 1).[2] However, its present potential is limited due to its adverse central nervous system (CNS) effects, including anxiety, depression, hallucinations, and seizures.[3] One explanation for these undesirable neurological events may be the ability of mefloquine to cross the blood–brain barrier, accumulate in the brain, and interact with several CNS targets.[4] However, despite the relatively high incidence of these side effects, mefloquine continues to be used by virtue of its long half-life, relative safety in pregnancy, activity against chloroquine-resistant strains, and the absence of effective alternatives.

In order to ameliorate the neurotoxicity profile of mefloquine, we set out to develop analogs that are less readily absorbed through the blood–brain barrier but retain the antimalarial profile of the quinoline methanol scaffold.[5] By replacing the 8-trifluoromethyl (CF_3) group in mefloquine with 6- and 7-pentafluorosulfanyl (SF_5) substituents, respectively, we previously prepared two SF_5-analogs that showed equivalent or improved activities compared to the parent compound **1** (Fig. 1, compounds **2** and **3**).[5] Interestingly, **2** and **3** also exhibited better activity and selectivity than their corresponding 6- and 7-CF_3-congeners, **4** and **5**. These encouraging results demonstrate the effective biological mimicry of the CF_3–SF_5 switch in quinoline containing antimalarial drugs and prompted us to prepare the synthetically considerably demanding 8-SF_5-congener **6** of mefloquine.

Introduction of an SF_5 group into an organic compound has been of interest in the design of new materials, pharmaceuticals, and agrochemicals.[6] Compared to CF_3, the symmetrical, octahedral SF_5 group demonstrates higher electronegativity and hydrophobicity, a substantially larger steric effect, and a slightly higher chemical stability.[7] However, due to the relative dearth of practical high-yielding methods for introducing this highly fluorinated functional group, to date there are still only a few SF_5-containing building blocks accessible.[8] For pentafluorosulfanylbenzenes, oxidative fluorination of aromatic disulfides is still the generally preferred procedure, despite its origin dating back half a century ago.[9] Most of the recent routes involve the use of expensive silver(II) fluoride or hazardous fluorine gas, and the yields are generally low (<40%).[10] Furthermore, the disulfide method is only applicable to a few substituted benzenes.

In contrast to *meta*- and *para*-nitro-SF_5-benzene, the corresponding *ortho*-nitro product is not accessible by the disulfide procedure, presumably because the steric hindrance from the *ortho*-nitro group prevents further fluorination of the SF_3 intermediate to give the SF_5 moiety.[11] To date, the only substrate containing an *ortho*-substituent known to be suitable for direct fluorination is the bis-*ortho*-fluorodiphenyl disulfide.[12] The *ortho*-fluorine substituent can then be converted in moderate yield into an amino group by nucleophilic aromatic substitution.



Mefloquine (**1**)

2: R_1 = H, R_2 = H, R_3 = SF_5
3: R_1 = H, R_2 = SF_5, R_3 = H
4: R_1 = H, R_2 = H, R_3 = CF_3
5: R_1 = H, R_2 = CF_3, R_3 = H
6: R_1 = SF_5, R_2 = H, R_3 = H

Figure 1. Mefloquine and its analogs, including the new analog **6**.

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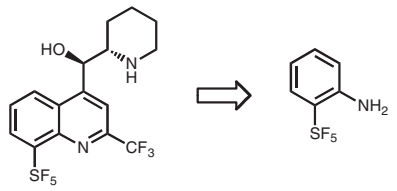
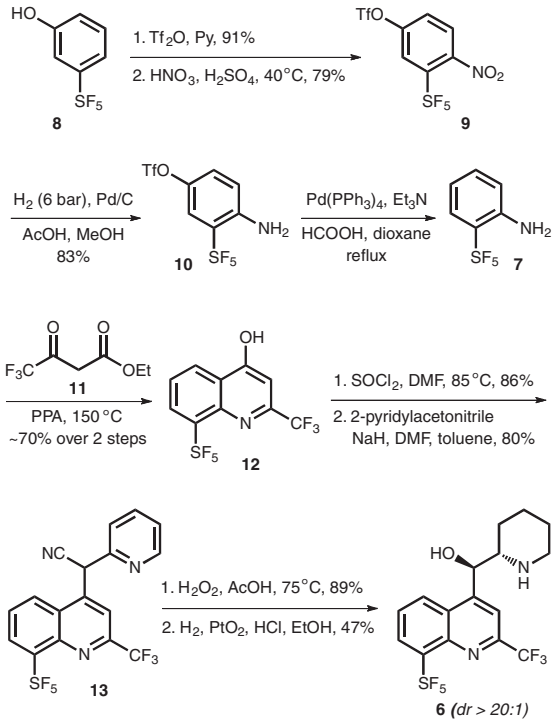


Figure 2. Retrosynthetic strategy for preparation of **6**.

An important first objective of the present study was the preparation of the novel *ortho*-SF_5-aniline **7** from commercially available 3-SF_5-phenol **8** en route to the 8-SF_5 mefloquine analog **6** (Fig. 2).

We envisioned installing the *ortho*-amino group by the regioselective nitration of a suitable pentafluorosulfanyl arene, followed by reduction.[13] Accordingly, we chose the commercially available starting material **8** as the nitration substrate (Scheme 1). However, the *para*-regioselectivity of the nitration of the phenol was poor, since the hydroxyl group is a strong *ortho*-directing substituent. To diminish the *ortho*-effect, **8** was converted into the trifluoromethyl sulfonate in 91% yield, and nitration now proceeded in 79% yield to give exclusively the desired product **9** with the NO_2 group in the *para*-position to the TfO moiety. Subsequent Pd-catalyzed reduction furnished the *ortho*-SF_5-aniline **10** in 83% yield.

Removal of the triflate in **10** proved not to be trivial. Initial attempts using Pd(II) salts and hydrogen transfer conditions led either to the reductive cleavage of the SF_5 group or to unspecific decomposition. However, when a Pd(0) catalyst was employed in the presence of formic acid and triethylamine,[14] the desired product **7** was formed. In our hands, the free base **7** was surprisingly unstable in a neat (oily) form. However, we were able to obtain a crystalline, stable storage form for **7** by converting it into its corresponding hydrochloride salt. When aniline **7** was immediately subjected to a Conrad–Limpach reaction with 4,4,4-trifluoroacetoacetate (**11**) in polyphosphoric acid, the somewhat difficult to purify 8-pentafluorosulfanylquinoline intermediate **12** was obtained in 70% yield and ca. 90% purity. The previously used chlorination conditions with phosphorous oxychloride at 110 °C proved to be too harsh for this quinoline,[5] but the milder thionyl chloride afforded the product in 86% yield. After nucleophilic aromatic substitution with 2-pyridylacetonitrile, oxidation of the carbon-nitrile bond and Pt-catalyzed reduction of the ketone and pyridine moieties in **13** proceeded in moderate to good yields to afford the target molecule **6**.[15] This sequence was used to prepare **6** on 200 mg scale.[16–21]



Scheme 1. Synthesis of 8-SF_5 substituted mefloquine analog **6**.

In conclusion, we have developed an efficient synthetic route to a novel 8-pentafluorosulfanyl analog of mefloquine that utilizes a new preparation of *ortho*-SF_5 aniline **7**. Access to the latter compound is of general utility since it can readily be converted into other SF_5-containing heterocyclic building blocks. The potency and selectivity of **6** against *P. falciparum* strains as well as its CNS effects are currently being evaluated and will be reported in due course.

Acknowledgments

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References and notes

1. (a) Wellems, T. E.; Plowe, C. V. *J. Infect. Dis.* **2001**, *184*, 770; (b) O'Neill, P. M.; Park, B. K.; Shone, A. E.; Maggs, J. L.; Roberts, P.; Stocks, P. A.; Biagini, G. A.; Bray, P. G.; Gibbons, P.; Berry, N.; Winstanley, P. A.; Mukhtar, A.; Bonar-Law, R.; Hindley, S.; Bambal, R. B.; Davis, C. B.; Bates, M.; Hart, T. K.; Gresham, S. L.; Lawrence, R. M.; Brigandi, R. A.; Gomez-Delas-Heras, F. M.; Gargallo, D. V.; Ward, S. A. *J. Med. Chem.* **2009**, *52*, 1408; (c) Nwaka, S.; Hudson, A. *Nat. Rev. Drug Disc.* **2006**, *5*, 941.
2. Trenholme, G. M.; Williams, R. L.; Desjardins, R. E.; Frischer, H.; Carson, P. E.; Rieckmann, K. H.; Canfield, C. J. *Science* **1975**, *190*, 792; Palmer, K. J.; Holliday, S. M.; Brogden, R. N. *Drugs* **1993**, *45*, 430.
3. (a) Tin, F.; Hlaing, N.; Lasserre, R. *Bull. WHO* **1982**, *60*, 913; (b) Weinke, T.; Trautmann, M.; Held, T.; Weber, G.; Eichenlaub, D.; Fleischer, K.; Kern, W.; Pohle, H. D. *Am. J. Trop. Med. Hyg.* **1991**, *45*, 86; (c) Hennequin, C.; Bourée, P.; Bazin, N.; Bisaro, F.; Feline, A. *Arch. Int. Med.* **1994**, *154*, 2360; (d) Schlagenhauf, P.; Steffen, R.; Lobel, H.; Johnson, R.; Letz, R.; Tschopp, A.; Vranjes, N.; Bergqvist, Y.; Ericsson, O.; Hellgren, U.; Rombo, L.; Mannino, S.; Handschin, J.; Stürchler, D. *Trop. Med. Int. Health* **1996**, *1*, 485.
4. (a) Jones, R.; Kunsman, G.; Levine, B.; Smith, M.; Stahl, C. *Forensic Sci. Int.* **1994**, *68*, 29; (b) Pham, Y. T.; Nosten, F.; Farinotti, R.; White, N. J.; Gimenez, F. *Int. J. Clin. Pharmacol. Ther.* **1999**, *37*, 58; (c) Baudry, S.; Pham, Y. T.; Baune, B.; Vidrequin, S.; Crevoisier, C.; Gimenez, F.; Farinotti, R. *J. Pharm. Pharmacol.* **1997**, *49*, 1086; (d) Barraud de Lagerie, S.; Comets, E.; Gautrand, C.; Fernandez, C.; Auchere, D.; Singlas, E.; Mentre, F.; Gimenez, F. *Br. J. Pharmacol.* **2004**, *141*, 1214; (e) Cruikshank, S. J.; Hopperstad, M.; Younger, M.; Connors, B. W.; Spray, D. C.; Srinivas, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12364; (f) Weiss, S. M.; Benwell, K.; Cliffe, I. A.; Gillespie, R. J.; Knight, A. R.; Lerpiniere, J.; Misra, A.; Pratt, R. M.; Revell, D.; Upton, R.; Dourish, C. T. *Neurology* **2003**, *61*, S101; (g) Caridha, D.; Yourick, D.; Cabezas, M.; Wolf, L.; Hudson, T. H.; Dow, G. S. *Antimicrob. Agents Chemother.* **2008**, *52*, 684; (h) Thompson, A. J.; Lochner, M.; Lummis, S. C. *Br. J. Pharmacol.* **2007**, *151*, 666; (i) Gillespie, R. J.; Adams, D. R.; Bebbington, D.; Benwell, K.; Cliffe, I. A.; Dawson, C. E.; Dourish, C. T.; Fletcher, A.; Gaur, S.; Giles, P. R.; Jordan, A. M.; Knight, A. R.; Knutsen, L. J. S.; Lawrence, A.; Lerpiniere, J.; Misra, A.; Porter, R. H. P.; Pratt, R. M.; Shepherd, R.; Upton, R.; Ward, S. E.; Weiss, S. M.; Williamson, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2916.
5. (a) Wipf, P.; Mo, T.; Geib, S. T.; Caridha, D.; Dow, G. S.; Gerena, L.; Roncal, N.; Milner, E. E. *Org. Biomol. Chem.* **2009**, *7*, 4163; (b) Milner, E.; McCalmont, W.; Bhonsle, J.; Caridha, D.; Carroll, D.; Gardner, L.; Gerena, M.; Gettayacamin, C.; Lanteri, T.; Luong, V.; Melendez, J.; Moon, N.; Roncal, J.; Sousa, A.; Tungtaeng, S.; Wipf, P.; Dow, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1347.
6. (a) Kirsch, P.; Hahn, A. *Eur. J. Org. Chem.* **2005**, 3095; (b) Geiser, U.; Schlueter, J. A.; Wang, H. H.; Kini, A. M.; Williams, J. M.; Sche, P. P.; Zakowicz, H. I.; VanZile, M. L.; Dudek, J. D.; Nixon, P. G.; Winter, R. W.; Gard, G. L.; Ren, J.; Whangbo, M.

H. *J. Am. Chem. Soc.* **1996**, *118*, 9996; (c) St. Clair, T. L.; St. Clair, A. K.; Thrasher, J. S. U.S. Patent 5220,070, 1993; (d) Welch, J. T.; Lim, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 6659; (e) Hansen, J. C.; Savu, P. M. U.S. Patent 5286,352, 1994; (f) Lim, D. S.; Choi, J. S.; Pak, C. S.; Welsh, J. T. *J. Pestic. Sci.* **2007**, *32*, 255.

7. (a) Lentz, D.; Seppelt, K. The SF_5, SeF_5 and TeF_5 Groups in Organic Chemistry. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; Wiley-VCH: New York, 1998; p 295; (b) Sæthre, L. J.; Berrah, N.; Bozek, J. D.; Børve, K. J.; Carroll, T. X.; Kukk, E.; Gard, G. L.; Winter, R.; Thomas, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 10729; (c) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088; (d) Brant, P.; Berry, A. D.; DeMarco, R. A.; Carter, F. L.; Fox, W. B.; Hashmall, J. A. *J. Electron Spectrosc. Relat. Phenom.* **1981**, *22*, 119.
8. (a) Massey, A. G.; Packer, K. J. *J. Chem. Soc.* **1961**, 5554; (b) Wessel, J.; Hartl, H.; Seppelt, K. *Chem. Ber.* **1986**, *119*, 453; (c) Hoover, F. W.; Coffman, D. D. *J. Org. Chem.* **1964**, *29*, 3567; (d) Winter, R. W.; Dodean, R.; Smith, J. A.; Anilkumar, R.; Burton, D. J.; Gard, G. L. *J. Fluorine Chem.* **2003**, *122*, 251; (e) Dolbier, W. R., Jr.; Aït-Mohand, S.; Schertz, T. D.; Sergeeva, T. A.; Cradlebaugh, J. A.; Mitani, A.; Gard, G. L.; Winter, R. W.; Thrasher, J. S. *J. Fluorine Chem.* **2006**, *127*, 1302.
9. (a) Sheppard, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 4751; (b) Sheppard, W. A. U.S. Patent 3117,158, 1964.
10. (a) Bowden, R. D.; Comina, P. J.; Greenhall, M. P.; Kariuki, B. M.; Loveday, A.; Philp, D. *Tetrahedron* **2000**, *56*, 3399; (b) Sipyagin, A. M.; Enshov, V. S.; Kashtanov, S. A.; Bateman, C. P.; Mullen, B. D.; Tan, Y. T.; Thrasher, J. S. *J. Fluorine Chem.* **2004**, *125*, 1305.
11. Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3064.
12. Sipyagin, A. M.; Bateman, C. P.; Tan, Y. T.; Thrasher, J. S. *J. Fluorine Chem.* **2001**, *112*, 287.
13. (a) Jaehne; G.; Below, P.; Stengelin, S.; Goessel, M.; Klabunde, T.; Winkler, I., WO Patent 2009/097997, 2009; (b) Kleemann, H.; Weck, R., WO Patent 2005/047240, 2005; (c) Kleenmann, H. WO Patent 2006/027130, 2006.
14. Sissouma, D.; Maingot, L.; Collet, S.; Guingant, A. *J. Org. Chem.* **2006**, *71*, 8384.
15. Adam, S. *Tetrahedron* **1989**, *45*, 1409.
16. Experimental protocol and spectral data for 4-nitro-3-(pentafluorosulfanyl)phenyl trifluoromethane-sulfonate (**9**). A solution of 3-(pentafluorothio)phenol (**8**) (0.998 g, 4.40 mmol) in distilled pyridine (5.0 mL) was treated dropwise at 0 °C with triflic anhydride (0.91 mL, 5.28 mmol). The reaction mixture was stirred for 10 min at 0 °C and at room temperature for 1.5 h, diluted with diethyl ether (40 mL), and extracted with a 1 M solution of copper sulfate (three times). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (10% diethyl ether/pentane) to yield 3-(pentafluorosulfanyl)phenyl trifluoromethane-sulfonate (1.40 g, 91%) as a colorless oil that was used immediately for the next reaction. A solution of this sulfonate (1.40 g, 4.00 mmol) in conc. sulfuric acid (13 mL) was slowly treated with fuming nitric acid (11 mL) at 0 °C. The reaction mixture was stirred for 7.5 h at 40 °C, quenched with ice (40 g), extracted with diethyl ether (40 mL), washed with sat. $NaHCO_3$ (2 × 30 mL) and brine, dried ($MgSO_4$), and concentrated. The yellow residue was purified by chromatography on SiO_2 (10%AcOEt/hexanes) to provide **9** (1.25 g, 79%) as a colorless solid: Mp 70.2–71.8 °C; IR (Neat) 3105, 1549, 1431, 1366, 1250, 1211, 1131, 822, 781, 749 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.48 (d, 1H, J = 2.4 Hz), 8.26 (d, 1H, J = 9.0 Hz), 8.20 (dd, 1H, J = 2.1, 9.0 Hz); ^{13}C NMR (acetone-d_6) δ 150.5, 146.7, 144.8 (app quintet, J = 22.5 Hz), 129.3, 128.6, 124.4 (app quintet, J = 5.3 Hz), 119.7 (q, J = 318.0 Hz); ^{19}F NMR (acetone-d_6) δ 76.4 (quintet, J = 155.1 Hz), 68.7 (d, J = 152.3 Hz), −72.2; EIMS m/z 397 (M^+, 4), 84 (75), 69 (99), 57 (100); HRMS (EI) m/z calcd for $C_7H_3NO_5F_8S_2$ 396.9325, found 396.9311.
17. Experimental protocol and spectral data for 4-amino-3-(pentafluorosulfanyl)phenyl trifluoromethane-sulfonate (**10**). A solution of **9** (126 mg, 0.317 mmol) in acetic acid (1.0 mL) and methanol (1.0 mL) was treated with 10% Pd on carbon (33.8 mg, 0.0317 mmol). The reaction mixture was hydrogenated under 6 bar H_2 pressure in a Parr apparatus for 4 h and filtered through Celite. The filtrate was concentrated, extracted with diethyl ether, washed with sat. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (10% diethyl ether/pentane) to provide **10** (96.7 mg, 83%) as a colorless solid: mp 66.4–66.7 °C; IR (Neat) 3547, 3431, 1634, 1502, 1407, 1247, 1215, 1133, 850, 801 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, 1H, J = 2.7 Hz), 7.20 (dd, 1H, J = 2.7, 9.0 Hz), 6.79 (d, 1H, J = 9.0 Hz), 4.64 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 141.9, 138.9, 138.3 (app quintet, J = 17.2 Hz), 126.0, 122.0 (app quintet, J = 5.3 Hz), 120.2, 118.9 (q, J = 318.8 Hz); ^{19}F NMR ($CDCl_3$) δ 85.6 (quintet, J = 152.3 Hz), 64.4 (d, J = 149.5 Hz), −72.6; EIMS m/z 367 (M^+, 10), 234 (55), 106 (60), 84 (100); HRMS (EI) m/z calcd for $C_7H_5NO_3F_8S_2$ 366.9583, found 366.9571.
18. Experimental protocol and spectral data for 4-hydroxy-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (**12**). To a solution of **10** (1.46 g, 3.98 mmol) in anhydrous degassed dioxane (65 mL) at room temperature were added tetrakis(triphenylphosphine) palladium(0) (0.209 g, 0.199 mmol), triethylamine (2.0 mL, 14.3 mmol), and formic acid (0.54 mL, 14.3 mmol). The reaction mixture was heated at reflux for 1 h under a nitrogen atmosphere, cooled to room temperature, and filtered through Celite. The filtrate was concentrated and extracted with CH_2Cl_2, washed with water (three times) and brine, dried ($MgSO_4$), and concentrated. The brown residue was purified by chromatography on SiO_2 (1% triethylamine and 10% diethyl ether in pentane) to provide crude 2-aminophenylsulfur pentafluoride **7** (0.700 g, 3.19 mmol) as a colorless liquid. A solution of this crude material (0.700 g, 3.19 mmol) in polyphosphoric acid (10 mL) at 110 °C was treated with ethyl 4,4,4-trifluoroacetoacetate (4.3 mL, 29.4 mmol) and heated at reflux at 150 °C for 1 h. The reaction mixture was cooled to room temperature, quenched by addition of 40 g ice, neutralized to pH 5 by adding 5% NaOH solution and NaOH pellets, extracted with EtOAc (two times), washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude brown residue was purified by chromatography on SiO_2 (25% EtOAc/hexanes) to yield **12** (0.980 g, 90% purity, 70% over two steps) as a beige solid: ^1H NMR ($CDCl_3$) δ 8.89 (br s, 1H), 8.65 (d, 1H, J = 7.8 Hz), 8.21 (dd, 1H, J = 1.5, 8.1 Hz), 7.54 (app t, 1H, J = 8.1 Hz), 6.71 (d, 1H, J = 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ 84.9 (quintet, J = 155.1 Hz), 68.6 (d, J = 146.6 Hz), −68.7; EIMS m/z 339 (M^+, 100), 211 (50), 183 (25); HRMS m/z calcd for $C_{10}H_5F_8NOS$ 338.9964, found 338.9954.
19. Experimental protocol and spectral data for **7·HCl**: To a solution of crude 2-(pentafluorosulfanyl)aniline **7** (8.7 mg, 0.040 mmol) in anhydrous diethyl ether (0.20 mL) was added 2 M HCl in diethyl ether (40 μL, 0.079 mmol) at room temperature under N_2. The reaction mixture was stirred for 30 min and filtered. The filtrate was washed with diethyl ether (1 mL) and dried in vacuo to provide **7·HCl** (5.6 mg, 0.025 mmol, 64%) as a colorless solid: Mp 190.6 °C (dec); IR (Neat) 2917, 2850, 1728, 1637, 1476, 1437, 1107, 1031, 843, 811, 721 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.61 (dd, 1H, J = 8.4, 1.2 Hz), 7.30 (t, 1H, J = 8.4 Hz), 6.98 (d, 1H, J = 8.4 Hz), 6.80 (t, 1H, J = 8.4 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 153.9 (app quintet, J = 21.0 Hz), 139.0, 130.7, 126.3 (app quintet, J = 5.4 Hz), 118.5, 115.7; ^{19}F NMR (400 MHz, CD_3OD) δ 81.0 (quintet, J = 159.2 Hz), 61.2 (d, J = 158.0 Hz); MS (EI) m/z 219 ([M−HCl]$^+$, 100), 111 (42), 92 (95); HRMS (EI) m/z calcd for $C_6H_6NF_5S$ (M−HCl) 219.0141, found 219.0144.
20. Experimental protocol and spectral data for δ-(2-pyridyl)-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylaceto-nitrile (**13**). A solution of **12** (0.373 g, 0.990 mmol) in thionyl chloride (4.0 mL) was treated with a catalytic amount of DMF (six drops). The reaction mixture was heated to 80 °C and kept at reflux for 1 h. The mixture was cooled to 0 °C and quenched with 20 g of ice. The suspension was extracted with diethyl ether (20 mL). The organic layer was washed with sat. $NaHCO_3$ (two times) and brine, dried ($MgSO_4$), and concentrated. The yellow residue was purified by chromatography on SiO_2 (15% EtOAc/hexanes) to provide 4-chloro-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (0.304 g, 86%) as a beige solid: mp 108.7–109.6 °C; IR (neat) 1336, 1263, 1185, 1141, 1114, 1021, 1075, 844, 818, 757, 721, 667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (dd, 1H, J = 1.2, 8.4 Hz), 8.46 (dd, 1H, J = 1.2, 7.8 Hz), 7.94 (s, 1H), 7.87 (dd, 1H, J = 8.1, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 151.8 (app quintet, J = 15.0 Hz), 148.4 (q, J = 36.0 Hz), 145.4, 142.0, 133.1 (app t, J = 4.5 Hz), 129.4, 128.2, 128.2, 120.7 (q, J = 274.5 Hz), 118.3; ^{19}F NMR ($CDCl_3$) δ 83.6 (quintet, J = 157.9 Hz), 71.7 (d, J = 177.7 Hz), −68.1; EIMS m/z 357 (M^+, 100), 249 (25), 149 (55), 180 (60), 89 (20); HRMS (EI) m/z calcd for $C_{10}H_4NF_8SCl$ 356.9625, found 356.9633.

A cooled (0–5 °C) suspension of sodium hydride (38.8 mg, 1.54 mmol) in toluene (6.0 mL) and DMF (3.0 mL) was treated for 10 min under argon gas with a solution of 2-pyridylacetonitrile (0.18 mL, 1.66 mmol) in toluene (5.0 mL) and DMF (1.5 mL). The resulting yellow-brown colored suspension was stirred for 1 h at the same temperature. A solution of 4-chloro-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (0.458 g, 1.28 mmol) in toluene (8.0 mL) and DMF (3.0 mL) was added dropwise to the suspension over 5 min. After 0.5 h, the reaction mixture was quenched with ice water (50 mL), extracted with EtOAc, washed with water (three times) and brine, dried ($MgSO_4$), and concentrated. The orange residue was purified by chromatography on SiO_2 (25% EtOAc/hexanes) to provide **13** (0.450 g, 80%) as a light orange solid: Mp 146.2 °C (dec); IR (Neat) 2876, 1368, 1275, 1179, 1144, 1122, 846, 833, 793, 654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.61 (ddd, 1H, J = 0.9, 1.8, 5.1 Hz), 8.47 (d, 1H, J = 8.7 Hz), 8.41 (dd, 1H, J = 0.9, 8.1 Hz), 8.10 (s, 1H), 7.79 (dd, 1H, J = 8.1, 8.4 Hz), 7.78 (ddd, 1H, J = 2.1, 7.8, 7.8 Hz), 7.46 (d, 1H, J = 8.1 Hz), 7.33 (ddd, 1H, J = 0.9, 5.1, 7.5 Hz), 6.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 153.0, 152.4 (app quintet, J = 15.8 Hz), 150.6, 148.7 (q, J = 36.0 Hz), 143.2, 141.9, 138.4, 132.6 (app t, J = 5.3 Hz), 128.6, 128.2, 127.3, 124.3, 122.6, 120.9 (q, J = 273.8 Hz), 117.5, 117.4, 43.4; ^{19}F NMR ($CDCl_3$) δ 83.7 (quintet, J = 157.9 Hz), 71.6 (d, J = 169.2 Hz), −68.1; EIMS m/z 439 (M^+, 60), 428 (25), 273 (25), 89 (30), 78 (100); HRMS (EI) m/z calcd for $C_{17}H_9N_3F_8S$ 439.0389, found 439.0388.
21. Experimental protocol and spectral data for δ-(2-piperidyl)-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinoline-methanol (**6**). A suspension of **13** (197 mg, 0.448 mmol) in acetic acid (2.6 mL) was treated dropwise at room temperature with H_2O_2 (0.35 mL, 4.48 mmol). The reaction mixture was placed in a preheated (75 °C) oil bath until it turned into light yellow. The mixture was quenched with ice water (10 mL), extracted with diethyl ether (10 mL), washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The yellow residue was purified by chromatography on SiO_2 (16% EtOAc/hexanes) to provide 2-pyridyl-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylketone (171 mg, 89%) as a colorless solid: Mp 98.9–99.7 °C; IR (neat) 1687, 1271, 1245, 1211, 1182, 1137, 1114, 844, 829, 759, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62 (ddd, 1H, J = 0.9, 1.8, 4.5 Hz), 8.42 (dd, 1H, J = 1.2, 7.8 Hz), 8.38 (ddd, 1H, J = 0.9, 0.9, 8.1 Hz), 8.12 (dd, 1H, J = 1.2, 8.4 Hz), 8.04 (ddd, 1H, J = 1.8, 7.8, 7.8 Hz), 7.90 (s, 1H), 7.72 (app t, 1H, J = 8.1 Hz), 7.60 (ddd, 1H, J = 1.2, 4.5, 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 194.4, 152.9, 151.8 (app t, J = 15.0 Hz), 149.8, 147.8 (q, J = 35.3 Hz), 147.2, 141.6, 137.8, 132.4 (app t, J = 5.3 Hz), 130.6, 128.5, 127.8, 127.1, 124.4, 121.1 (q, J = 273.8 Hz), 117.2; ^{19}F NMR ($CDCl_3$) δ 84.1 (quintet, J = 157.9 Hz), 71.7 (d, J = 149.5 Hz), −68.0; EIMS m/z 428 (M^+, 65), 399 (100), 273 (95), 272 (30); HRMS (EI) m/z calcd for $C_{16}H_8N_2OF_8S$ 428.0230, found 439.0215.

A solution of 2-pyridyl-8-pentafluorosulfanyl-(2-trifluoro-methyl)-4-quinolylketone (83.2 mg, 0.194 mmol) in conc. hydrochloric acid (79 mL, 0.971 mmol) and abs EtOH (2.0 mL) was treated with platinum oxide (4.4 mg, 0.0194 mmol). The flask was purged with hydrogen twice and hydrogenated under balloon pressure of H_2. After 2 h, no alcohol

intermediate appeared on TLC (50% EtOAc/hexanes to check for the alcohol intermediate by UV, followed by 75% dichloromethane/EtOH to check for the final product by UV and ninhydrin staining) anymore. The mixture was filtered through a pad of florisil, concentrated, extracted with diethyl ether (20 mL), washed with sat. $NaHCO_3$ and NaOH aqueous solution (pH 13) and brine, dried ($MgSO_4$), and concentrated. The yellow residue was purified by chromatography on SiO_2 (5% triethylamine in EtOAc, then 5% triethylamine and 5% MeOH in EtOAc). The crude product (65.0 mg) was crystallized from MeOH to obtain **6** (40.0 mg, 47%) as a colorless solid in a dr >20:1: Mp 182.0 °C (dec); IR (Neat) 3088, 2937, 2600 (br), 1422, 1366, 1267, 1224, 1183, 1113, 846, 826, 785, 721, 652 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) δ 8.75 (d, 1H, J = 8.4 Hz), 8.58 (d, 1H, J = 7.8 Hz), 8.19 (s, 1H), 7.97 (dd, 1H, J = 7.8, 8.4 Hz), 5.58 (d, 1H, J = 3.6 Hz), 3.03 (ddd, 1H, J = 3.0, 4.8, 10.8 Hz), 2.98 (app d, 1H, J = 12.0 Hz), 2.56 (dt, 1H, J = 3.0, 12.0 Hz), 1.72 (app d, 1H, J = 12.6 Hz), 1.47 (app d, 1H, J = 12.6 Hz), 1.42 (app d, 1H, J = 12.6 Hz), 1.39–1.22 (m, 2H), 1.57 (tq, 1H, J = 3.6, 13.2 Hz); ^{13}C NMR (acetone-d_6, 600 MHz) δ 154.5, 152.1 (app quintet, J = 13.5 Hz), 148.4 (q, J = 34.5 Hz), 141.7, 133.1 (app t, J = 4.5 Hz), 131.0, 129.1, 127.9, 122.5 (q, J = 273.0 Hz), 116.5, 73.5, 62.3, 47.6, 27.3, 27.0, 25.1; ^{19}F NMR (acetone-d_6) δ 86.6 (quintet, J = 150.2 Hz), 72.8 (d, J = 144.7 Hz), −67.1; HRMS (ESI) m/z calcd for $C_{16}H_{17}N_2OF_8S$ (M+H) 437.0934, found 437.0923.