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The synthesis and biological activity of pentafluorosulfanyl analogs of fluoxetine, fenfluramine, and norfenfluramine

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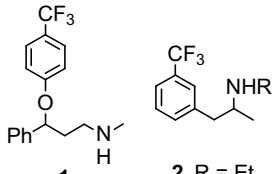
Abstract—The trifluoromethyl group of fluoxetine **1** and fenfluramine and norfenfluramine, **2** and **3**, was substituted by the pentafluorosulfanyl group. On examination of the efficacy of the pentafluorosulfanyl containing compounds as inhibitors of 5-hydroxytryptamine receptors, it was found that substitution could lead to enhanced selectivity and in the case of the pentafluorosulfanyl analog of fenfluramine, **18**, it significantly enhanced potency against the 5-HT_{2b}, 5-HT_{2c}, and 5-HT_6 receptors.

1. Introduction

1.1. Fluoxetine and fenfluramine

The pleiotropic effects of serotonin (5-hydroxytryptamine; 5-HT) on central nervous system targets[1,2] are well known and include influence on complex behaviors such as mood and appetite.[3,4] Two well known clinical agents which affect both those behaviors, fluoxetine **1** and fenfluramine **2**, are especially attractive frameworks on which to probe the influence on 5-HT receptor binding of pentafluorosulfanyl substitution of the trifluoromethyl group.



1 **2** R = Et **3** R = H

The development of fluoxetine, **1**, first reported as a selective serotonin uptake inhibitor in 1974,[5] has been reviewed.[6] In no small part as a consequence of the clinical utility of this compound, the specific indications for use, the mechanism of action, and the occurrence of side effects have been summarized on a regular basis.[7–11] The complexity of the profile of positive and negative effects of fluoxetine on 5-HT receptors[12] suggested that a substitution as simple as replacement of the trifluoromethyl group by the pentafluorosulfanyl group could lead to a different pattern of response.

In contrast to the broadly successful clinical applications of fluoxetine, treatment with the anorectic fenfluramine **2** is associated with the development of cardiac valvulopathy[1,13] which led to the withdrawal of this compound from the marketplace. Following reports in the late 1970s of the profound influence of fenfluramine on appetite,[14] subsequent reviews of the clinical effects of both fenfluramine and the metabolite norfenfluramine **3** documented that initial observation.[15–19] Pursuant to the early reports, the long term efficacy of fenfluramine in the treatment of obesity was established.[20] However, with the report of the adverse effects of both **2** and **3**,[21–24] it is apparent that separation of the detrimental side effects from the efficacious effects on appetite is essential.[25] Much of the efficacy of **2** as an anorectic is thought to be derived from activation of the 5-HT_{2C} receptor,[26] whereas interaction with the 5-HT_{2B} receptor is associated with heart valve hypertrophy.[27] Previously the 5-HT_{2B} receptor had been associated with pulmonary hypertension,[28] but recently the mechanistic details of 5-HT_{2B} receptor binding on overgrowth valvulopathy have been communicated.[29] It is in this context that the pentafluorosulfanyl analogs of fenfluramine and norfenfluramine were prepared.

Keywords: 5-Hydroxytryptamine; Serotonin; Pentafluorosulfanyl group; Fluoxetine; Fenfluramine; Norfenfluramine; 5-HT receptors.
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1.2. Pentafluorosulfanyl arenes

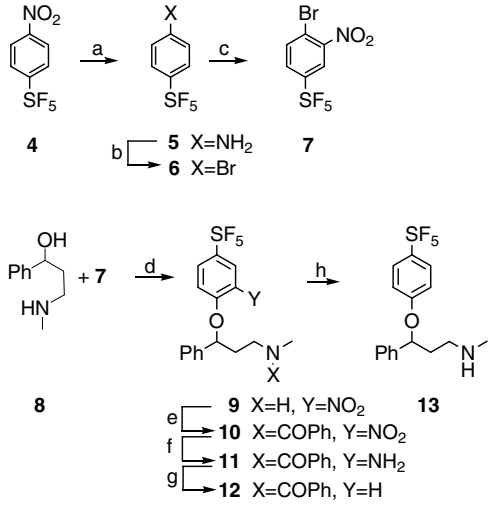
The properties of the pentafluorosulfanyl group can be compared with the trifluoromethyl group. The relative steric demand of the SF_5 group is slightly less than that of a *tert*-butyl group[30,31] and therefore considerably greater than that of a trifluoromethyl group (CF_3). However, the electrostatic surface presented by SF_5 is comparable to CF_3 in that it presents a highly fluorinated surface; a pyramid of electron density as opposed to the inverted cone of density associated with CF_3 group. When the electronic influence of a SF_5 group is contrasted with that of a CF_3 group, the electron-withdrawing effect as assessed by the carbon 1s photoelectron spectra suggests the effect of these electron-withdrawing groups is similar in magnitude.[32,33] However, the electronegativity of the SF_5 group has been proposed to be as high as 3.65 in comparison to a value of 3.36 for the CF_3 group.[34] In electrophilic substitution reactions the Hammet σ_p value for SF_5 was determined to be 0.68 in contrast to a σ_p value for CF_3 of 0.54.[35] This has been further refined to a σ_I value for SF_5 of 0.55 and a σ_R value of 0.11[35] in contrast to σ_I value for CF_3 of 0.39 and a σ_R value of 0.12.[36,37] The decreased resonance and increased inductive contributions are important to note, a trend that is consistent with the electronic effects observed in the estimation of electronegativity.[32,33]

The organic chemistry of the SF_5 group, previously reviewed[31] and extensively developed by Gard,[38] has only recently come under more widespread investigation with the ready availability of previously difficultly accessible building blocks or reagents.[39] However, the potential of pentafluorosulfanylarene building blocks would have had much less impact without the basic understanding and chemical explorations provided by Thrasher.[40] Pentafluorosulfanyl groups are hydrolytically and chemically relatively stable.[41–44] The 'Hydrolytic stability of aromatic pentafluorosulfanyl group equals or exceeds that of the trifluoromethyl group. Aromatic SF_5 groups withstand attack of Brønsted acids and bases and are stable under conditions required for Ni, Pd, or Pt hydrogenation.' 'The weak point of the SF_5 group is reactivity toward alkyl lithium reagents such as *n*-butyllithium however reagents such as *tert*-butyllithium are compatible with the SF_5 group.'[39] To date pentafluorosulfanyl arenes have found applications in liquid crystalline displays[41,42] and in agrochemicals.[40,45]

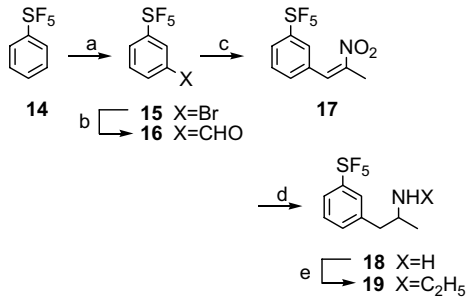
2. Chemistry

Commercially available 1-nitro-4-pentafluorosulfanylbenzene was easily reduced to 1-amino-4-pentafluorosulfanylbenzene **5** under classic conditions with iron powder and concentrated hydrochloric acid.[46] Subsequent Sandmeyer reaction with bromide ion was also affected in an uneventful manner. In contrast to methods for the preparation of the parent compound **1** where the 4-chloro-trifluoromethylbenzene undergoes a ready nucleophilic aromatic displacement reaction with **8**,[47] **6** did not react in our hands. However, following introduction of the sacrificial auxiliary nitro group, 1-bromo-2-nitro-4-pentafluorosulfanylbenzene **7** did undergo the desired displacement reaction albeit in modest yield. It was found that protection of the methylamine group of **9** was necessary for successful diazotization and reductive dediazoniation of easily prepared aminoarene **11**. In the absence of protection the reduction was accompanied by the apparent intramolecular reaction of the reactive amine group. Protection of the methylamino group by benzylation, *tert*-butoxycarbonylation, benzyloxycarbonylation, trimethylsilylation or *tert*-butyldimethylsilylation all failed to lead to the desired reduction product. Fortunately benzoylation to form **10** was effective in suppressing the undesired side reactions. Diazotization and reductive dediazoniation of **11** with *tert*-butylnitrite in DMF proceeded smoothly. Deprotection of the **12** by reduction with diisobutylaluminum hydride led uneventfully to the desired pentafluorosulfanyl fluoxetine analog **13** (Scheme 1).

To prepare the pentafluorosulfanyl analogs of fenfluramine and norfenfluramine readily available pentafluorosulfanylbenzene **14** was used as starting material. Bromination after the method of Dolbier[48,49] led to the preparation of 1-bromo-3-pentafluorosulfanylbenzene **15**. Metalation with *tert*-butyllithium was followed by quenching of the resultant anion with dimethylformamide which on workup afforded the desired aldehyde **16**. Condensation with nitroethane formed the olefin **17** which was subsequently reduced with lithium aluminum hydride. The pentafluorosulfanyl analog of norfenfluramine **18** was reductively alkylated with acetaldehyde and sodium triacetoxyborohydride to form the fenfluramine analog **19** (Scheme 2).



Scheme 1. Reagents and conditions: (a) Fe powder, HCl/ethanol 1:20, 1 h, rt, 86%; (b) HBr, $NaNO_2$, CuBr, 0 °C to rt, overnight, 67%; (c) H_2SO_4, HNO_3, 0 °C to rt, 1 h, 99%; (d) NaH, 55 °C, 2.5 h, 36%; (e) benzoyl chloride, Et_3N in CH_3CN, rt, 15 h, 85%; (f) Fe powder, HCl/ethanol 1:20, 50 min, rt, 90%; (g) *tert*-butyl nitrite, 65 °C, DMF, 1 h 20 min, 33%; (h) Diisobutylaluminum hydride in toluene, 78 °C, 20 min, 80%.



Scheme 2. Reagents and conditions: (a) H_2SO_4, TFA, NBS, 38 h rt, 93%; (b) *t*-BuLi, DMF, ether −78 °C to 0 °C, 50 min, 70%; (c) NH_4Oac, reflux, 4 h, 70%; (d) LAH, THF, reflux, 1.5 h, 59%; (e) Acetaldehyde, $NaBH(OAc)_3$, rt, 8H, 30%.

It is important to note the stability of the aryl-pentafluorosulfanyl group toward strong Brønsted acids such as trifluoroacetic or sulfuric acid and reductants such as LAH, diisobutylaluminium hydride, iron powder–HCl or sodium triacetoxyborohydride. Metallation with *tert*-butyllithium proceeded smoothly, and the resultant aryllithium reagent exhibited no evidence of unusual instability.

3. Results and discussion

The binding and inhibition assays of the materials prepared above were performed as described previously using the resources of the National Institute of Mental Health Psychoactive Drug Screening Program.[1] For initial screening, compounds were tested at concentrations of 10 μmol/L; K_i determinations using seven concentrations of unlabeled ligand spanning four orders of magnitude were obtained on compounds that gave 50% inhibition at 10 μmol/L. K_i values were calculated with the LIGAND program.[1]

As seen in Table 1 below, the pentafluorosulfanyl analogs selectively inhibited binding of the 5-HT receptors. These results confirmed the viability of the pentafluorosulfanyl group as a substituent in a medicinal chemical application.

In secondary screening, the K_i values were determined for those receptors where at the original test concentration of 10 μM there was greater than 50% inhibition. For **13**, substitution of the trifluoro-methyl group diminished the affinity for 5-HT_{2a} and 5-HT_{2c} but had no effect on 5-HT_{2b} (Fig. 1).

However, substitution of the trifluoromethyl group of **2** and **3** by the pentafluorosulfanyl group had a much more dramatic effect on the selectivity of the substituted compounds for the receptors examined.

In Figure 2 it is evident that the pentafluorosulfanyl group enhances the affinity of **19** for 5-HT_{2b}, 5-HT_{2c}, and 5-HT_6 relative to fenfluramine **2**. Of especial note is the increased affinity for 5-HT_{2b} and 5-HT_6, with binding increasing nearly ten-fold. (see Fig. 3) It was binding to 5-HT_{2b} that has been associated with the adverse valvulopathy.[29] Unfortunately the increase in affinity for the 5-HT_{2c} receptor is much less with the result that it is likely that the analog **19** would not be as

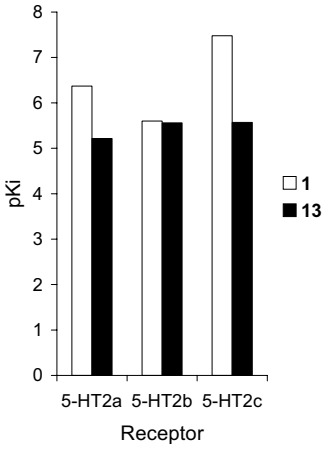


Figure 1. Replacement of the trifluoromethyl group of **1** by pentafluorosulfanyl group **13**. Influence of substitution on receptor binding. Data from the NIMH Psychoactive Drug Screening Program.[1]

Table 1. Percent inhibition of receptor binding from initial screening[a]

Receptor	Compound		
	13	**19**	**18**
5-HT_{1a}	−3[b]	85.5	50
5-HT_{1b}	3.4	63.5	62.9
5-HT_{1d}	12.7	15.2	73.7
5-HT_{1e}	77.8	7.3	23.4
5-HT_{2a}	97.3	53.2	85.9
5-HT_{2b}	71.9	85.3	89.6
5-HT_{2c}	75.8	72.8	94.6
5-HT_3	6.8	14.6	−6.1[b]
5-HT_{5a}	25	62.7	31.3
5-HT_6	1.5	50	50
5-HT_7	12	50	50

[a] Data represent mean% inhibition ($N = 4$ determinations) for 10 μm of compound tested at receptor subtypes.[1]

[b] Negative inhibition (−) represents a stimulation of binding. Compounds at high concentrations non-specifically may increase binding.

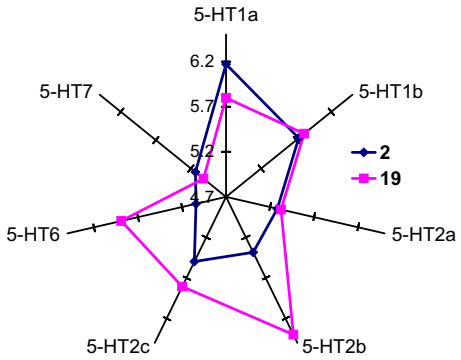


Figure 2. A comparison of pK_i values of **2** and **19** for a series of 5 HT receptors.[1] Additional data in Fig. 3.

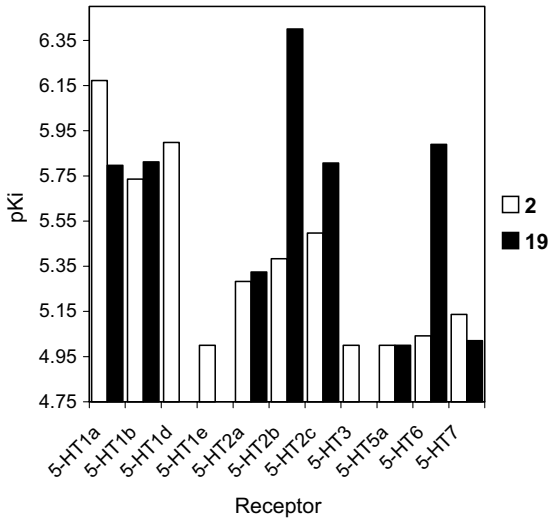


Figure 3. Influence of substitution on receptor binding. Replacement of the trifluoromethyl group of fenfluramine **2** by pentafluorosulfanyl group **19**.[1] For 5-HT_{1d}, 5-HT_{1e}, and 5-HT_3 the activity of **19** was insufficient in initial screening to merit K_i determination.

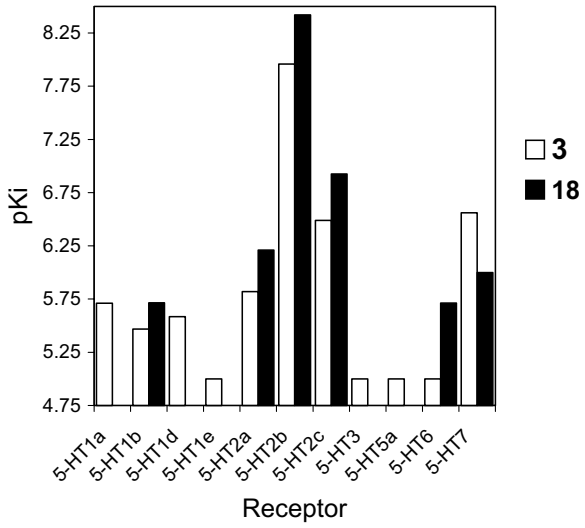


Figure 5. Influence of substitution on receptor binding. Replacement of the trifluoromethyl group of norfenfluramine **3** by pentafluorosulfanyl group **18**.[1] For 5-HT_{1a}, 5-HT_{1d}, 5-HT_{1e}, 5-HT_3, and 5-HT_{5a}, the activity of **18** was insufficient in initial screening to merit K_i determination.

safe as the clinical agent. In contrast, in Figures 4 and 5, while the affinity of **18** relative to **3** for the 5-HT_{2b} is enhanced the increase is much less than in the case of **19** relative to **2**. Perhaps more strikingly, the pentafluorosulfanyl group substitution in the norfenfluramine structure showed the same general pattern of selectivity observed with the parent compound. As determined in the primary inhibition assays there was little affinity for 5-HT_{1a}, 5-HT_{1e}, 5-HT_3, or 5-HT_{5a}, and this selectivity was unaffected by substitution.

4. Conclusion

During the preparation of the pentafluorosulfanyl analogs of fluoxetine, **13**, fenfluramine, **19**, and norfenfluramine **18**, it was shown that the pentafluorosulfanyl group tolerates a wide variety of reaction conditions normally associated with synthetic organic chemical manipulations such as those involving alkyllithium reagents, diazotization and dediazoniation, strong Brønsted acids or reducing conditions. The intermediate pentafluorosulfanyl organolithium reagent formed on metalation of 1-bromo-3-(pentafluorosulfanyl)benzene, **15**, underwent reactions in the expected manner and uneventfully.

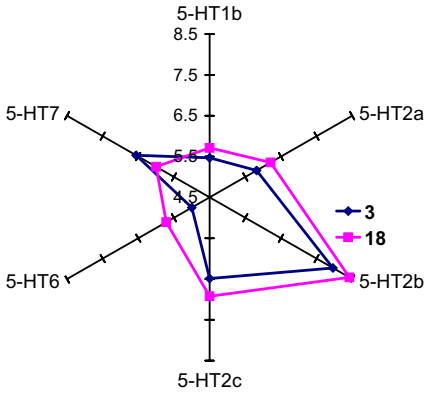


Figure 4. A comparison of pK_i values for **3** and **18** with a series of 5 HT receptors.[1] Additional data in Fig. 5.

The pentafluorosulfanyl group, a novel non-natural octahedral substituent, exhibited totally conventional substituent influences in inhibition and binding studies. All the synthetic materials had some degree of activity while showing discrimination between different receptors. In the case of the fenfluramine and norfenfluramine analogs, the affinity for the 5-HT_{2B} and 5-HT_6 receptors was enhanced. The ten-fold increase in affinity for the 5-HT_6 was equally true for both the fenfluramine and norfenfluramine analogs **19** and **18**, respectively. Enhanced affinity for the 5-HT_6 receptor may be useful in research into the uniqueness and clinical significance of the 5- receptor subfamily. Thus, ligands for 5-HT_6 receptors might be useful to treat: motor disorders, depression, anxiety, mood disorders, memory disorders, Huntington's, Parkinson's, and Alzheimer's disease.[50]

5. Experimental

5.1. Chemistry

Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 Series FT-IR spectrometer. All ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Gemini-300 MHz NMR spectrometer at 300, 75.43, and 282.20 MHz, respectively, and a Bruker-400 MHz spectrometer at 400, 100 and 376 MHz, respectively. The chemical shifts of ^1H and ^{13}C NMR are reported relative to the residual signal of $CDCl_3$ (for ^1H: $\delta = 7.24$; ^{13}C: $\delta = 77.00$) or C_6D_6 (for ^1H: $\delta = 7.15$; ^{13}C: $\delta = 128.00$). All ^{13}C NMR spectra were acquired in the proton-decoupled mode.

^{19}F NMR spectra are reported relative to the resonance assigned to $CFCl_3$ ($\delta = 0$). Thin layer chromatography was performed with silica gel F_{254} (Merck) as the adsorbent on 0.2 mm thick, plastic-backed plates. The chromatograms were visualized under UV (254 nm) or by staining with a $KMnO_4$ aqueous solution followed by heating. Column chromatography was performed using silica gel 60 (70–230 mesh, Merck). Melting points were determined in open capillaries using a Büchi 510 melting point apparatus and are reported uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

5.2. Radioligand binding assays

Radioligand binding assays were performed as described previously using the resources of the National Institute of Mental Health Psychoactive Drug Screening Program.[1]

5.3. Synthesis

5.3.1. 1-Amino-4-pentafluorosulfanylbenzene 4. To a solution of 1-nitro-4-pentafluorosulfanylbenzene (Air Products and Chemicals Inc.) **3** (5.0 g, 20 mmol) in ethanol (200 mL) was added iron powder (6.9 g, 120 mmol) followed by the slow addition of conc. HCl (10 mL) at 0 °C.[46] The reaction mixture was stirred for 38 min at room temperature. The reaction mixture was decanted into the separatory funnel then saturated aqueous NH_4OH was added until the pH has reached 10. The reaction mixture was extracted with dichloromethane and water. The combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was purified by chromatography to afford the white solid of product in 96% (4.25 g, mp = 63–64 °C) yield. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.50 (d, 2H, $J = 9.0$ Hz) 6.60 (d, 2H, $J = 9.0$ Hz) 3.98 (bs, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ_F 87.11 (m, 1F, $^2J_{SF-SF_4} = 150.2$ Hz, SF), 64.02 (d, 4F, $^2J_{SF_4-SF} = 150.2$ Hz, SF_4).

5.3.2. 1-Bromo-4-pentafluorosulfanylbenzene 5. To a solution of 1-amino-4-pentafluorosulfanylbenzene (1.5 g, 6.8 mmol) in acetonitrile (7 mL) was slowly added HBr (48%) (2.3 mL, 21 mmol) followed by the slow addition of sodium nitrite (0.472 g, 6.84 mmol) in water (3 mL) at −25 °C. The reaction mixture was stirred for 30 min at −25 °C. CuBr (1.48 g, 10.3 mmol) was added to the reaction mixture then stirred for 16 h at room temperature. The reaction was quenched with water (20 mL) then made basic (pH 10) by the addition of saturated aqueous sodium carbonate. The reaction mixture was extracted with dichloromethane and water. The combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was purified by chromatography to afford the colorless liquid product in 67% (1.30 g) yield. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.60 (4H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ_F 83.02 (m, 1F, $^2J_{SF-SF_4} = 150.8$ Hz, SF), 62.55 (d, 4F, $^2J_{SF_4-SF} = 150.8$ Hz, SF_4).

5.3.3. 1-Bromo-2-nitro-4-pentafluorosulfanylbenzene 7. To a solution of 1-bromo-4-pentafluorosulfanylbenzene (0.600 g, 2.12 mmol) in conc. H_2SO_4 (11 mL) was slowly added HNO_3 (fuming) (11 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with water (20 mL). The reaction mixture was extracted with dichloromethane and water. The organic layer was washed with saturated sodium bicarbonate solution (2×). The organic layers were dried over $MgSO_4$ and then concentrated. The yellow liquid product was obtained in 99% (0.688 g) crude yield. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ_H 8.23 (d, 1H, $J = 2.5$ Hz), 7.89 (d, 1H, $J = 8.9$ Hz), 7.80 (dd, 1H, $J = 8.9$, 2.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ_F 79.94 (m, 1F, $^2J_{SF-SF_4} = 151.4$ Hz, SF), 62.63 (d, 4F, $^2J_{SF_4-SF} = 151.4$ Hz, SF_4).

5.3.4. 3-(2-Nitro-4-(pentafluorosulfanyl)phenoxy)-*N*-methyl-3- phenylpropan-1-amine 9. To a solution of amino alcohol **8** (1.01 g, 6.10 mmol) in THF (25 mL) was added NaH (0.22 g, 9.2 mmol) at room temperature then stirred for 50 min at 53 °C. 1-Bromo-2-nitro-4-pentafluorosulfanylbenzene **7** (2.0 g, 6.1 mmol) in THF (4 mL) was added dropwise to the reaction mixture. After stirring for 2.5 h, the reaction mixture was allowed to warm to room temperature then the reaction mixture was quenched with water. The reaction mixture was extracted with ethyl acetate, the organic layer separated, and the aqueous layer washed with additional ethyl acetate. The combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo. The crude product was purified by column chromatography to afford 0.91 g of a yellow liquid (36% yield). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.15–8.13 (m, 1H), 7.68–7.63 (m, 1H), 7.38–7.24 (m, 5H), 7.04 (d, $J = 9.4$ Hz, 1H), 4.77–4.71 (m, 1H), 3.56–3.40 (m, 2H), 2.83 (s, 3H), 2.52 (bs, 1H), 2.09–2.01 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 84.2 (AB_4 (nine lines), 1F, SF), 64.1 (d, $J_{AB} = 150.7$ Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 146.8, 143.7, 141.9 (quintet, $J = 19.9$ Hz), 136.4, 129.9 (t, $J = 4.25$ Hz), 128.6, 127.9, 125.5, 125.5–125.3 (m), 117.7, 71.7, 50.3, 40.5, 35.8.

5.3.5. *N*-(3-(2-Nitro-4-(pentafluorosulfanyl)phenoxy)-3-phenylpropyl)-*N*-methylbenzamide 10. To a solution of **9** compound (0.62 g, 1.5 mmol) in acetonitrile (20 mL) was added Et_3N (0.76 g, 1.1 mL, 7.5 mmol) and benzoyl chloride (1.1 g, 0.87 ml, 7.5 mmol) at room temperature then stirred for 15 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution then extracted with dichloromethane. After washing with water, the combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was purified by column chromatography to afford the 0.66 g of yellow semi-solid product (85% yield). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.15–8.01 (m, 3H), 7.64–7.53 (m, 2H), 7.50–7.27 (m, 7H), 6.93 (d, $J = 9.4$ Hz, 1H), 6.04 (t, $J = 6.48$ Hz, 1H), 3.48–3.32 (m, 2H), 2.89 (s, 3H), 2.51–2.39 (m, 1H), 2.35–2.21 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 84.3 (quintet, 1F, SF), 64.1 (d, $J = 150.9$ Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 146.6, 142.1 (quintet, $J = 19.8$ Hz), 139.4, 136.7, 133.2, 130.0–129.8 (m), 129.8, 129.5, 128.7, 128.4, 128.3, 126.2, 125.5–125.2 (m), 117.7, 73.8, 50.3, 39.9, 33.7.

5.3.6. *N*-(3-(2-Amino-4-(pentafluorosulfanyl)phenoxy)-3-phenylpropyl)-*N*-methylbenzamide 11. To a solution of **10** (0.63 g, 1.2 mmol) in ethanol (16 mL) at room temperature was added iron powder (0.68 g, 12 mmol) followed by the slow addition of conc. HCl (0.8 mL). The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was decanted into the separatory funnel whereupon saturated aqueous NH_4OH was added until the pH of the mixture reached 10. After extraction with dichloromethane, the combined organic layers were washed with water, dried over $MgSO_4$, and then concentrated. The crude product was purified by chromatograph to afford 0.54 g the desired product as a colorless liquid (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.19–8.13 (m, 2H), 7.62–7.56 (m, 1H), 7.52–7.43 (m, 4H), 7.43–7.30 (m, 3H), 7.16–7.10 (m, 2H), 7.02–6.96 (m, 1H), 6.23–6.16 (m, 1H), 4.32–4.04 (bs, 2H), 3.17–3.06 (m, 2H), 2.67 (s, 3H), 2.40–2.28 (m, 1H), 2.24–2.11 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 86.4 (quintet, 1F, SF), 63.2 (d, J = 149.7 Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 150.0 (quintet, J = 16.6 Hz), 142.0, 141.1(bs), 140.3, 133.0, 130.1, 129.5, 128.5, 128.3, 128.0, 126.2, 119.9, 115.7–115.3 (m), 112.3, 74.3, 50.6, 41.1, 34.2.

5.3.7. *N*-(3-(4-(Pentafluorosulfanyl)phenoxy)-3-phenylpropyl)-*N*-methylbenzamide 12. To a solution of *tert*-butyl nitrite (0.193 g, 1.87 mmol) in DMF (10 mL) at 65 °C was added **11** (0.607 g, 1.25 mmol) in small amount of DMF. After stirring for 1 h and 20 min, the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$ and then concentrated. The crude product was purified by column chromatography to afford 0.194 g of the product as pale-yellow liquid (33% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.12–8.05 (m, 2H), 7.63–7.27 (m, 10H), 6.53 (d, J = 9.1 Hz, 2H), 6.05–5.99 (m, 1H), 3.56–3.39 (m, 2H), 2.95 (s, 3H), 2.39–2.28 (m, 1H), 2.27–2.14 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 87.9 (quintet, 1F, SF), 64.6 (d, J = 150.0 Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.9, 150.0, 142.7 (t, J = 17.8 Hz), 139.8, 133.2, 130.0, 129.6, 128.7, 128.5, 128.3, 127.2 (t, J = 4.4 Hz), 126.3, 110.5, 74.4, 48.9, 38.6, 33.2.

5.3.8. 3-(4-(Pentafluorosulfanyl)phenoxy)-*N*-methyl-3-phenylpropan-1-amine 13. To a solution of protected amine **12** (0.194 g, 0.412 mmol) in toluene (5 mL) was added diisobutylaluminum hydride (0.12 g, 0.15 mL, 0.82 mmol) in toluene (0.88 mL) at −78 °C. After stirring for 20 min. at room temperature, the reaction mixture was quenched with methanol then filtered through Celite and washed with four portions of ether. The reaction mixture was concentrated to approximately 7 mL then extracted with ether. The combined organic layers were washed with water, dried over $MgSO_4$, and then concentrated. The crude product was purified by column chromatography to afford 0.121 g of the product as a colorless liquid (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55 (dm, J = 9.5 Hz, 2H), 7.40–7.27 (m, 5H), 6.59 (d, J = 9.2 Hz, 2H), 4.70 (t, J = 6.5, 1H), 3.50(t, J = 7.3 Hz, 2H), 2.96 (s, 3H), 2.17 (bs, 3H), 1.98 (quartet, J = 7.0 Hz, 2H)); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 88.2 (quintet, 1F, SF), 64.7 (d, J = 150.2 Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.5, 144.1, 142.3 (t, J = 17.1 Hz), 128.6, 127.9, 127.1 (t, J = 4.5 Hz), 125.6, 110.3, 72.2, 49.0, 38.2, 35.6; Anal. Calcd for $C_{16}H_{18}F_5NOS$: C, 52.31; H, 4.94. Found: C, 52.40; H, 4.96.

5.3.9. 1-Bromo-3-(pentafluorosulfanyl)benzene 15. To a vigorously stirred round-bottomed flask containing pentafluorosulfanylbenzene **14** (3.0 g, 15 mmol), trifluoroacetic acid (7.8 mL), and sulfuric acid (3 mL) mixture were added over 1 h small portions of *N*-bromosuccinimide (3.9 g, 22 mmol).[48] The mixture was stirred for 38 h, then poured onto crushed ice. The organic layer was separated and the aqueous phase extracted with three portions of dichloromethane. The combined organic extracts were washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and then concentrated. The crude product was purified by column chromatography to afford the colorless liquid product in 93% (3.9 g) yield.^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.89 (t, J = 1.9 Hz, 1H), 7.69 (dm, J = 8.4 Hz, 1H), 7.64 (bd, J = 8.0 Hz, 1H), 7.34 (t, J = 8.2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 82.4 (quintet, 1F, SF), 64.1 (d, J = 151.1 Hz, 4F, SF_4).

5.3.10. 3-(Pentafluorosulfanyl)benzaldehyde 16. To a solution of 1-bromo-3-(pentafluorosulfanyl)benzene **15** (0.30 g, 1.1 mmol) in ether (8 mL) was added an 1.7 M solution of *tert*-butyllithium in pentane (0.75 mL, 1.3 mmol) at −78 °C, stirred for 20 min, and then DMF (0.155 g, 2.12 mmol) was added to the reaction mixture. After stirring for 10 min, the temperature of the reaction mixture was allowed to warm to 0 °C then stirred for an additional 20 min. The reaction mixture was quenched with water and extracted with hexane in three portions. The combined organic layers were dried over anhydrous $MgSO_4$ concentrated and purified by column chromatography to afford 0.172 g of a colorless liquid (70% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.04 (s, 1H), 8.28–8.20 (m, 1H), 8.07–7.94 (m, 2H), 7.66 (t, J = 8.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 82.1 (AB_4 (nine lines), 1F, SF), 62.1 (d, J_{AB} = 150.0 Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 190.1, 154.5 (quintet, J = 18.5 Hz), 136.8, 132.3, 131.3 (quintet, J = 4.6 Hz), 129.8, 127.0 (quintet, J = 4.7 Hz).

5.3.11. 1-(Pentafluorosulfanyl)-3-(2-nitroprop-1-enyl)benzene 17. To a solution of aldehyde **16** (0.45 g, 1.9 mmol) in nitroethane (4.8 g, 64 mmol) was added ammonium acetate (0.097 g, 1.3 mmol) at room temperature then was heated under reflux for 4 h. The nitroethane was removed in vacuo. The residue was extracted with dichloromethane and then washed with three portions of water. The combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was purified by column chromatography to afford 0.39 g of a pale-yellow solid product (70% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.05 (s, 1H), 7.84–7.75 (m, 2H), 7.62–7.51 (m, 2H), 2.42 (s, 3H); ^{19}F NMR

(282 MHz, $CDCl_3$, ppm) δ 82.7 (AB_4 (nine lines), 1F, SF), 62.1 (d, $J_{AB} = 150.0$ Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 154.3 (quintet, $J = 17.9$ Hz), 149.5, 133.5, 132.4, 131.2, 129.4, 127.1 (quintet, $J = 4.7$ Hz), 127.0 (quintet, $J = 4.6$ Hz), 13.8.

5.3.12. 1-(3-(Pentafluorosulfanyl)phenyl)propan-2-amine 18. To a solution of LAH (0.555 g, 13.9 mmol) in THF (20 mL) at 0 °C was slowly added **17** (0.73 g, 2.5 mmol). After heating under reflux for 1.5 h, the reaction mixture was quenched at 0 °C by the cautious addition of water until hydrogen evolution ceased. After stirring for 1 h with anhydrous $MgSO_4$, the mixture was filtered, washed with 10% HCl, the acid phase neutralized with 10% NaOH, and then back-extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by column chromatography to afford 0.388 g of a colorless liquid (59% yield). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.63–7.50 (m, 2H), 7.42–7.26 (m, 2H), 3.25–3.08 (m, 1H), 2.72 (dd, $J = 13.4$, 5.6 Hz, 1H), 2.59 (dd, $J = 13.4$, 7.8 Hz, 1H), 1.64 (s, 2H), 1.65 (d, $J = 6.3$ Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 84.3 (AB_4 (nine lines), 1F, SF), 62.3 (d, $J_{AB} = 149.8$ Hz, 4F, SF_4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 154.1 (quintet, $J = 16.4$ Hz), 140.7, 132.4, 128.7, 126.5 (quintet, $J = 4.5$ Hz), 123.9 (quintet, $J = 4.8$ Hz), 48.3, 46.0, 23.2; Anal. Calcd for $C_9H_{12}F_5NS$: C, 41.38; H, 4.63. Found: C, 41.20; H, 4.52.

5.3.13. *N*-Ethyl-1-(3-(pentafluorosulfanyl)phenyl)propan-2-amine 19. To a solution of **18** (0.069 g, 0.26 mmol) in 1,2-dichloroethane (4 mL) at room temperature was added acetaldehyde (0.012 g, 0.40 mmol). After stirring for 2 min, sodium triacetoxyborohydride (0.084 g, 0.40 mmol) was added and the mixture stirred for 4.5 h. On quenching with water, the reaction mixture was extracted with three portions of chloroform. The combined organic layers were washed with sat. $NaHCO_3$, dried over anhydrous $MgSO_4$, concentrated, and the crude product purified by column chromatography to afford 0.023 g of a colorless liquid (30% yield). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.61–7.53 (m, 2H), 7.40–7.29 (m, 2H), 3.00–2.82 (m, 2H), 2.79–2.58 (m, 3H), 2.29–1.79 (bs, 1H), 1.13–1.01 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ 84.3 (AB_4 (nine lines), 1F, SF), 62.2 (d, $J_{AB} = 149.5$ Hz, 4F, SF_4) ; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 154.1 (quintet, $J = 16.9$ Hz), 140.5, 132.5, 128.6, 126.6 (quintet, $J = 4.6$ Hz), 123.9 (quintet, $J = 4.6$ Hz), 54.4, 43.1, 41.4, 19.8, 15.1 Anal. Calcd for $C_{11}H_{16}F_5NS$: C, 45.67; H, 5.57. Found: C, 45.52; H, 5.86.

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