Noncatalytic Electrophilic Oxyalkylation of Anilines with 2-Trifluoroacetyl-1,3-benzothiazole

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Abstract: 2-Trifluoroacetyl-1,3-benzothiazole reacts with anilines to form the corresponding trifluoromethyl-substituted alcohols. The reaction regioselectivity (*ortho*/*para*) was shown to depend strongly on the structure of the aniline. *meta*-Substituted anilines tend to form the corresponding *ortho*-substituted products, in contrary to the previous literature data.

Key words: anilines, Friedel–Crafts alkylation, *ortho*/*para*-substitution, trifluoromethyl alcohols, 1,3-benzothiazole

The substitution of fluorine for hydrogen in organic compounds is widely used to modify their biochemical characteristics.[1] Moreover, many market available pharmaceuticals are fluorine-containing, although fluorine scarcely occurs in organic matter.[2] A trifluoromethyl group, in particular, is one of the most attractive functional groups in organic chemistry, and thus incorporation of this group into organic compounds is still of great interest.[3] Commercially available trifluoromethyl ketones – hexafluoroacetone and trifluoropyruvate – are highly important building blocks commonly used to prepare CF_3-containing compounds.[4] However, despite the great potential of the both hexafluoroacetone and trifluoropyruvate,[4] the chemistry of other trifluoroacetyl ketones had received much less attention so far.[5]

Recently, we started a project aimed at the synthesis and application of various trifluoroacetyl 1,3-azoles **1** (Figure 1).[6] We have already studied the reaction of diverse electron rich heterocycles with **1** to provide the corresponding trifluoromethyl-substituted alcohols.[6d–f] An addition of anilines to **1**, however, received almost no attention so far.[6a] Here, we have performed a systematic study on the interaction of diverse anilines (compounds **2**–**18**, Figure 2) with 2-trifluoroacetyl-1,3-benzothiazole (**1a**).

1 **1a**

Figure 1 2-Trifluoroacetyl-1,3-azoles **1** and 2-trifluoroacetyl-1,3-benzothiazole (**1a**)

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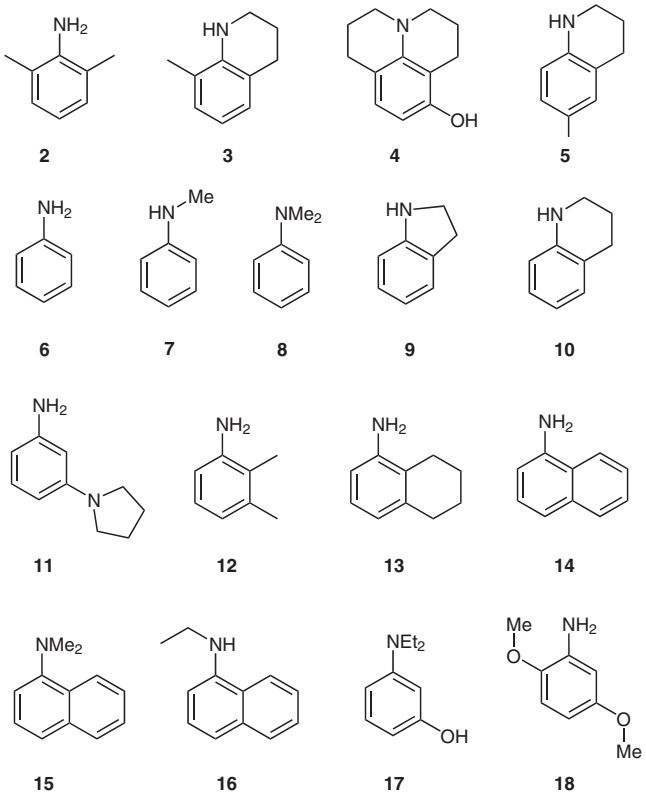
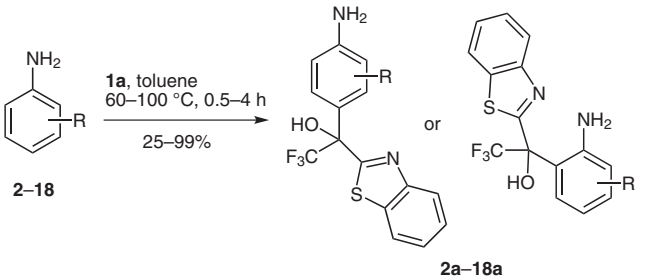


Figure 2 Substituted anilines **2**–**18**

Among the variety of available representatives of **1**,[6a] we selected the highly active 2-trifluoroacetyl-1,3-benzothiazole (**1a**) (Figure 1) as the model compound to test the potential of anilines **2**–**18** in the corresponding reaction of C-oxyalkylation (Scheme 1).



Scheme 1 Synthesis of CF_3-substituted alcohols **2a**–**18a** from anilines **2**–**18** and 2-trifluoroacetyl-1,3-benzothiazole (**1a**)

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2-Trifluoroacetyl-1,3-benzothiazole (**1a**) reacted indeed with all anilines **2–18** under heating in toluene at 60–100 °C for 0.5–4 hours. The target trifluoromethyl alcohols **2a–18a** were obtained in 25–99% yields (Table 1).

Table 1 CF_3-Substituted Alcohols **2a–18a** Prepared

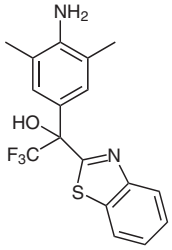
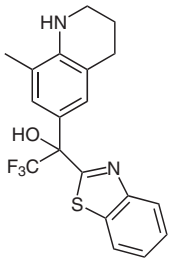
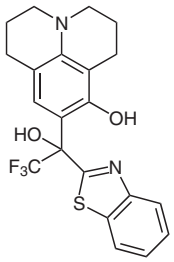
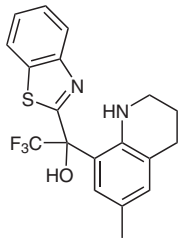
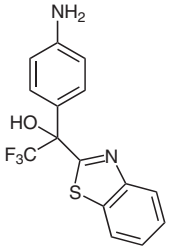
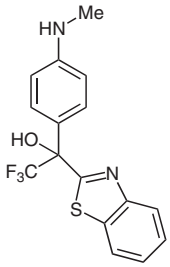
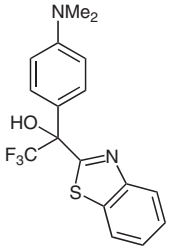
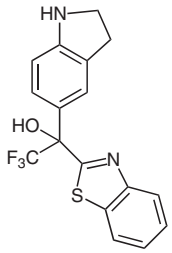
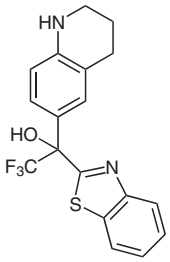
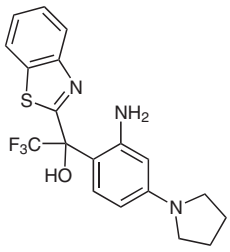
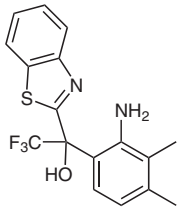
Ketone	Conditions	Product	Yield (%)
2	toluene, **1a** 100 °C, 2 h	 **2a**	25
3	toluene, **1a** 100 °C, 1 h	 **3a**	98
4	toluene, **1a** 60 °C, 0.5 h	 **4a**	81
5	toluene, **1a** 100 °C, 1 h	 **5a**	55
6	toluene, **1a** 100 °C, 4 h	 **6a**	30
7	toluene, **1a** 100 °C, 1 h	 **7a**	99
8	toluene, **1a** 100 °C, 1 h	 **8a**	36
9	toluene, **1a** 100 °C, 1 h	 **9a**	83
10	toluene, **1a** 100 °C, 1 h	 **10a**	93
11	toluene, **1a** 60 °C, 0.5 h	 **11a**	88
12	toluene, **1a** 100 °C, 2 h	 **12a**	55

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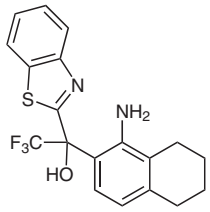
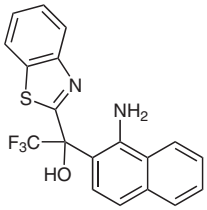
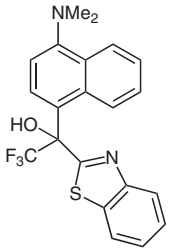
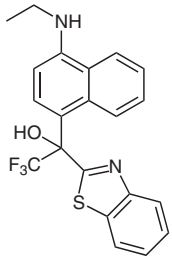
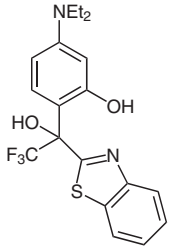
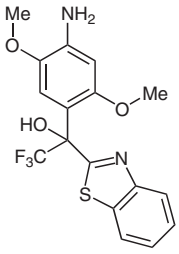
Table 1 CF_3-Substituted Alcohols **2a–18a** Prepared (continued)

Ketone	Conditions	Product	Yield (%)
13	toluene, **1a** 100 °C, 1 h	 **13a**	80
14	toluene, **1a** 100 °C, 3 h	 **14a**	63
15	toluene, **1a** 100 °C, 4 h	 **15a**	48
16	toluene, **1a** 100 °C, 1 h	 **16a**	88
17	toluene, **1a** 60 °C, 0.5 h	 **17a**	79
18	toluene, **1a** 100 °C, 1 h	 **18a**	46

Anilines **2–4** having the both *ortho*-positions blocked afforded the *para*-substituted products **2a–4a**. On the contrary, aniline **5**, with *ortho*/*para*-positions blocked gave the only possible *ortho*-isomer **5a**. However, although anilines **6–18** could theoretically react at the both *ortho*- and *para*-positions, all the products **6a–18a** were obtained as individual compounds and the formation of regioisomeric mixtures was not observed.

The reactions of hexafluoroacetone and trifluoropyruvates with anilines are widely known and well described in the literature.[7] According to the literature reports, an incorporation of the appropriate fluorine-containing substituents into aniline with the both *ortho*- and *para*-positions free usually affords *para*-substituted products.[7a–k] We, however, found that depending on the structure of the aniline both the *para*- and *ortho*-substitutions can take place. For example, anilines **6–10** reacted with **1a** to form, as expected, the products of *para*-substitution **6a–10a** (Table 1). The structures of the obtained compounds were determined by ^{1}H NMR and NOESY-experiments (see Supporting Information). However, anilines **11–14** with the both *ortho*/*para*-positions free rather unexpectedly gave the products of *ortho*-substitution **11a–14a**, in contrast to the previous literature data.[7a–k] We suggest, that the regioselectivity of **11–14** in the reaction with **1a** arises from the presence of *meta*-substituents in **11–14**, which disfavors the substitution at the *para*-position, leading thereby to the *ortho*-substituted products. Nevertheless, compounds **15–18** with *meta*-substituents and the both *ortho*/*para* positions free reacted with **1a** to provide again the products of *para*-substitution **15a–18a**. Presumably, the bulky *N*-alkyl groups in **15–17** protect the *ortho*-positions much more effectively than the *meta*-substituent does with the *para*-position. The corresponding favorable *ortho*-position is blocked in **18**.

In summary, we have developed a very simple and efficient one-step procedure to prepare CF_3-substituted tertiary alcohols from 2-trifluoroacetyl-1,3-benzothiazole and anilines. The reaction regioselectivity (*ortho*/*para*) was shown to depend strongly on the structure of the starting aniline. *meta*-Substituted anilines with free nonhindered *ortho*-positions tend to form *ortho*-substituted products rather than *para*-substituted ones.

Ketone **1a** was synthesized as reported previously.[6a] ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer at 499.9 MHz, 124.9 MHz, and 470.3 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

Oxyalkylation of Anilines 2–18 with 2-Trifluoroacetyl-1,3-benzothiazole (1a); General Procedure

A mixture of 2-trifluoroacetyl-1,3-benzothiazole (**1a**; 231 mg, 1 mmol) and the appropriate aniline **2–18** (1 mmol) was stirred in toluene (2 mL) under the conditions given in Table 1. The reaction mixture was cooled to r.t., and the formed crystalline solid was collected by filtration. The product was washed with CCl_4 (1 mL) on the filter and recrystallized from *i*-PrOH.

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1-(4-Amino-3,5-dimethylphenyl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (2a)
Yield: 25%; mp 222–223 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.05 (6 H, s), 4.77 (2 H, s), 7.10 (2 H, s), 7.46 (1 H, dd, *J* = 6.5 Hz), 7.53 (1 H, dd, *J* = 6.5 Hz), 8.08 (3 H, m).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.60, 78.34 (q, $^2J_{C,F}$ = 28.9 Hz), 120.35, 122.67, 123.27, 123.76, 124.99 (q, $^1J_{C,F}$ = 288.0 Hz), 126.09, 126.77, 126.78, 135.04, 145.54, 153.23, 173.03.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.88.

APSI MS: *m*/*z* = 353 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-(8-methyl-1,2,3,4-tetrahydroquinolin-6-yl)ethanol (3a)
Yield: 98%; mp 150–151 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.74 (2 H, m), 1.96 (3 H, s), 2.63 (2 H, m), 3.22 (2 H, m), 5.27 (1 H, br), 7.00 (1 H, s), 7.04 (1 H, s), 7.46 (1 H, dd, *J* = 8.0, 7.5 Hz), 7.53 (1 H, dd, *J* = 8.0, 7.5 Hz), 8.02–8.18 (3 H, m).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.05, 21.71, 27.81, 41.81, 78.35 (q, $^2J_{C,F}$ = 28.9 Hz), 119.22, 120.27, 122.35, 122.61, 123.70, 124.98 (q, $^1J_{C,F}$ = 288.0 Hz), 125.84, 126.01, 126.58, 126.70, 135.04, 144.14, 153.25, 173.06.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –74.68.

APSI MS: *m*/*z* = 379 (M^+ + 1).

9-[1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinolin-8-ol (4a)
Yield: 81%; mp 177–178 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.82 (4 H, m), 2.53 (4 H, m), 3.06 (4 H, m), 6.69 (1 H, s), 7.50 (1 H, dd, *J* = 8.0, 6.5 Hz), 7.56 (1 H, dd, *J* = 8.0, 6.5 Hz), 8.09 (1 H, d, *J* = 8.0 Hz), 8.13 (1 H, d, *J* = 8.0), 9.00 (2 H, br).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.45, 21.57, 22.15, 27.34, 49.01, 49.66, 79.79 (q, $^2J_{C,F}$ = 29.3 Hz), 108.40, 109.40, 112.66, 122.72, 123.75, 125.11 (q, $^1J_{C,F}$ = 288.0 Hz), 126.17, 126.22, 126.79, 135.33, 144.69, 152.08, 152.58, 172.60.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –74.73.

APSI MS: *m*/*z* = 421 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-(6-methyl-1,2,3,4-tetrahydroquinolin-8-yl)ethanol (5a)
Yield: 55%; mp 156–157 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.54–1.75 (2 H, m), 2.12 (3 H, s), 2.65 (2 H, m), 2.96 (1 H, m), 3.14 (1 H, m), 5.40 (1 H, s), 6.78 (1 H, s), 6.89 (1 H, s), 7.48 (1 H, dd, *J* = 7.5 Hz), 7.53 (1 H, dd, *J* = 8.0, 7.5 Hz), 8.04 (1 H, d, *J* = 8.0 Hz), 8.12 (1 H, d, *J* = 7.5 Hz), 8.89 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.70, 21.47, 27.73, 41.64, 80.35 (q, $^2J_{C,F}$ = 28.5 Hz), 119.42, 122.69, 123.50, 123.58, 123.79, 124.99 (q, $^1J_{C,F}$ = 288.0 Hz), 126.19, 126.36, 126.75, 131.36, 135.62, 142.36, 152.77, 171.61.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –72.87.

APSI MS: *m*/*z* = 379 (M^+ + 1).

1-(4-Aminophenyl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (6a)
Yield: 30%; mp 163–164 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.32 (2 H, br), 6.56 (2 H, d, *J* = 8.0 Hz), 7.34 (2 H, d, *J* = 8.0 Hz), 7.46 (1 H, m), 7.53 (1 H, m), 8.09 (2 H, m), 8.15 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 78.38 (q, $^2J_{C,F}$ = 28.5 Hz), 113.53, 122.65, 123.26, 123.72, 124.94 (q, $^1J_{C,F}$ = 288.4 Hz), 126.09, 126.78, 128.20, 135.02, 149.84, 153.27, 172.96.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.00.

APSI MS: *m*/*z* = 325 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-[4-(methylamino)phenyl]ethanol (7a)
Yield: 99%; mp 120–121 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.65 (3 H, d, *J* = 5.0 Hz), 5.87 (1 H, m), 6.53 (2 H, d, *J* = 8.5 Hz), 7.40 (2 H, d, *J* = 8.5 Hz), 7.48 (1 H, dd, *J* = 7.5, 6.5 Hz), 7.55 (1 H, dd, *J* = 8.0, 6.5 Hz), 8.09 (1 H, d, *J* = 8.0 Hz), 8.12 (1 H, d, *J* = 7.5 Hz), 8.17 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.98, 78.36 (q, $^2J_{C,F}$ = 28.9 Hz), 111.31, 122.70, 122.99, 123.74, 124.96 (q, $^1J_{C,F}$ = 288.0 Hz), 126.14, 126.82, 128.17, 135.01, 150.81, 153.26, 172.96.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.06.

APSI MS: *m*/*z* = 339 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-1-[4-(dimethylamino)phenyl]-2,2,2-trifluoroethanol (8a)
Yield: 36%; yellow oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.89 (6 H, s), 6.72 (2 H, d, *J* = 8.5 Hz), 7.44–7.52 (3 H, m), 7.56 (1 H, t, *J* = 7.5 Hz), 8.09 (1 H, d, *J* = 8.5 Hz), 8.12 (1 H, d, *J* = 8.0 Hz), 8.26 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 40.34, 78.27 (q, $^2J_{C,F}$ = 28.9 Hz), 79.66, 111.98, 122.70, 123.73, 124.89 (q, $^1J_{C,F}$ = 287.5 Hz), 126.15, 126.84, 128.09, 134.98, 150.96, 153.24, 172.79.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.09.

APSI MS: *m*/*z* = 353 (M^+ + 1) .

1-(1,3-Benzothiazol-2-yl)-1-(2,3-dihydro-1*H*-indol-5-yl)-2,2,2-trifluoroethanol (9a)
Yield: 83%; mp 153–154 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.89 (2 H, t, *J* = 8.5 Hz), 3.40 (2 H, t, *J* = 8.5 Hz), 5.72 (1 H, s), 6.46 (1 H, d, *J* = 8.0 Hz), 7.21 (1 H, d, *J* = 8.0 Hz), 7.31 (1 H, s), 7.48 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.55 (1 H, dd, *J* = 8.5, 7.0 Hz), 8.09 (1 H, d, *J* = 8.5 Hz), 8.12 (1 H, d, *J* = 8.0 Hz), 8.18 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.47, 47.01, 78.55 (q, $^2J_{C,F}$ = 28.9 Hz), 107.57, 122.68, 123.24, 123.76, 124.56, 124.94 (q, $^1J_{C,F}$ = 288.0 Hz), 126.13, 126.71, 126.80, 129.08, 135.03, 153.23, 153.76, 173.04.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –74.91.

APSI MS: *m*/*z* = 351 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-(1,2,3,4-tetrahydroquinolin-6-yl)ethanol (10a)
Yield: 93%; mp 101–102 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.74 (2 H, m), 2.61 (2 H, m), 3.15 (2 H, m), 5.89 (1 H, s), 6.40 (1 H, d, *J* = 8.0 Hz), 7.08–7.19 (2 H, m), 7.46 (1 H, dd, *J* = 8.0, 7.5 Hz), 7.53 (1 H, dd, *J* = 8.0, 7.0 Hz), 8.03–8.15 (3 H, m).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.73, 27.43, 41.13, 78.40 (q, $^2J_{C,F}$ = 28.5 Hz), 112.92, 119.49, 122.51, 122.67, 123.73, 124.99 (q, $^1J_{C,F}$ = 288.0 Hz), 125.82, 126.08, 126.78, 127.92, 135.04, 146.44, 153.28, 173.05.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –74.91.

APSI MS: *m*/*z* = 365 (M^+ + 1).

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1-(2-Amino-4-pyrrolidin-1-ylphenyl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (11a)
Yield: 88%; mp 173–174 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.91 (4 H, m), 3.15 (4 H, m), 5.00 (2 H, s), 5.83 (1 H, s), 5.86 (1 H, d, *J* = 9.0 Hz), 6.98 (1 H, d, *J* = 9.0 Hz), 7.47 (1 H, dd, *J* = 8.0, 7.5 Hz), 7.53 (1 H, dd, *J* = 7.5 Hz), 8.03 (1 H, d, *J* = 8.0 Hz), 8.10 (1 H, d, *J* = 7.5 Hz), 8.43 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.40, 47.58, 80.06 (q, $^2J_{C,F}$ = 28.9 Hz), 100.13, 101.56, 108.04, 122.64, 123.71, 125.32 (q, $^1J_{C,F}$ = 288.8 Hz), 126.11, 126.68, 128.98, 135.72, 148.43, 149.16, 152.73, 172.71.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –73.31.

APSI MS: *m*/*z* = 394 (M^+ + 1).

1-(4-Amino-2,3-dimethylphenyl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (12a)
Yield: 55%; mp 147–148 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.92 (3 H, s), 2.17 (3 H, s), 4.95 (2 H, br s), 6.50 (1 H, d, *J* = 8.5 Hz), 7.02 (1 H, d, *J* = 8.5 Hz), 7.47 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.52 (1 H, dd, *J* = 8.5, 7.0 Hz), 8.02 (1 H, d, *J* = 8.5 Hz), 8.11 (1 H, d, *J* = 8.0 Hz), 8.94 (1 H, br s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.56, 20.75, 80.33 (q, $^2J_{C,F}$ = 28.1 Hz), 118.10, 118.61, 122.69, 123.13, 123.80, 125.10 (q, $^1J_{C,F}$ = 289.2 Hz), 125.14, 126.23, 126.78, 135.65, 137.84, 145.18, 152.75, 171.87.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –72.97.

APSI MS: *m*/*z* = 353 (M^+ + 1) .

1-(1-Amino-5,6,7,8-tetrahydronaphthalen-2-yl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (13a)
Yield: 80%; mp 171–172 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.63 (2 H, m), 1.73 (2 H, m), 2.30 (2 H, m), 2.62 (2 H, m), 4.96 (2 H, br), 6.40 (1 H, d, *J* = 8.0 Hz), 7.03 (1 H, d, *J* = 8.0 Hz), 7.47 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.52 (1 H, dd, *J* = 8.0, 7.0 Hz), 8.04 (1 H, d, *J* = 8.0 Hz), 8.11 (1 H, d, *J* = 8.0 Hz), 8.84 (1 H, br).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.58, 23.13, 24.42, 29.91, 80.37 (q, $^2J_{C,F}$ = 28.5 Hz), 116.90, 117.36, 122.68, 123.52, 123.81, 125.04, 125.16 (q, $^1J_{C,F}$ = 288.0 Hz), 126.23, 126.78, 135.65, 138.67, 145.16, 152.75, 171.92.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –73.07.

APSI MS: *m*/*z* = 379 (M^+ + 1).

1-(1-Amino-2-naphthyl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (14a)
Yield: 63%; mp 195–196 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.07 (2 H, br s), 7.14 (1 H, d, *J* = 9.0 Hz), 7.35 (1 H, d, *J* = 9.0 Hz), 7.41 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.48 (2 H, m), 7.54 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.75 (1 H, d, *J* = 8.0 Hz), 8.06 (1 H, d, *J* = 8.0 Hz), 8.12 (2 H, m), 8.98 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 80.80 (q, $^2J_{C,F}$ = 28.5 Hz), 112.73, 115.71, 122.74, 122.94, 123.92, 124.49, 125.16, 125.43 (q, $^1J_{C,F}$ = 289.2 Hz), 125.89, 126.40, 126.90, 127.30, 128.14, 134.42, 135.68, 144.35, 152.65, 172.02.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –73.34.

APSI MS: *m*/*z* = 375 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-1-[4-(dimethylamino)-1-naphthyl]-2,2,2-trifluoroethanol (15a)
Yield: 48%; mp 155–156 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.85 (6 H, s), 7.17 (1 H, d, *J* = 8.0 Hz), 7.26 (1 H, dd, *J* = 8.0, 7.5 Hz), 7.39 (1 H, dd, *J* = 8.0, 7.5 Hz), 7.46 (2 H, m), 7.80 (1 H, d, *J* = 8.0 Hz), 7.90 (1 H, m), 8.14 (1 H, m), 8.18 (2 H, m), 8.57 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.16, 80.39 (q, $^2J_{C,F}$ = 28.1 Hz), 112.91, 122.80, 123.78, 125.10, 125.11 (q, $^1J_{C,F}$ = 289.2 Hz), 125.13, 126.25, 126.28, 126.49, 126.75, 126.82, 126.88, 129.50, 132.54, 135.69, 152.53, 152.77, 172.31.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –72.17.

APSI MS: *m*/*z* = 403 (M^+ + 1).

1-(1,3-Benzothiazol-2-yl)-1-[4-(ethylamino)-1-naphthyl]-2,2,2-trifluoroethanol (16a)
Yield: 88%; mp 186–187 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.30 (3 H, t, *J* = 7.0 Hz), 3.29 (3 H, q, *J* = 7.0 Hz), 6.43 (1 H, br s), 6.54 (1 H, d, *J* = 8.5 Hz), 7.20 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.28 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.45 (2 H, m), 7.66 (1 H, d, *J* = 8.0 Hz), 7.90 (1 H, d, *J* = 8.0 Hz), 8.08 (1 H, d, *J* = 8.5 Hz), 8.11 (1 H, d, *J* = 7.0 Hz), 8.18 (1 H, d, *J* = 8.0 Hz), 8.32 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.45, 38.06, 80.48 (q, $^2J_{C,F}$ = 28.1 Hz), 101.32, 119.25, 122.69, 122.69, 123.71, 123.90, 124.41, 125.31 (q, $^1J_{C,F}$ = 288.0 Hz), 126.04, 126.10, 126.52, 126.62, 127.71, 132.34, 135.85, 145.96, 152.81, 173.08.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –72.05.

APSI MS: *m*/*z* = 403 (M^+ + 1).

2-[1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]-5-(diethylamino)phenol (17a)
Yield: 79%; mp 202–203 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.05 (6 H, t, *J* = 6.8 Hz), 3.25 (4 H, q, *J* = 6.8 Hz), 6.06 (1 H, d, *J* = 1.2 Hz), 6.16 (1 H, dd, *J* = 9.2, 1.2 Hz), 7.23 (1 H, d, *J* = 9.2 Hz), 7.45 (1 H, dd, *J* = 7.5 Hz), 7.51 (1 H, dd, *J* = 7.5 Hz), 7.97 (1 H, s), 8.02 (1 H, d, *J* = 7.5 Hz), 8.08 (1 H, d, *J* = 7.5), 9.81 (1 H, s).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.96, 44.14, 78.80 (q, $^2J_{C,F}$ = 30.2 Hz), 99.30, 103.18, 108.41, 122.56, 123.62, 125.20 (q, $^1J_{C,F}$ = 288.0 Hz), 125.91, 126.53, 129.83, 135.47, 149.56, 152.92, 157.09, 173.14.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.72.

APSI MS: *m*/*z* = 397 (M^+ + 1).

1-(4-Amino-2,5-dimethoxyphenyl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (18a)
Yield: 46%; mp 135–136 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.24 (3 H, s), 3.71 (3 H, s), 5.09 (2 H, s), 6.32 (1 H, s), 7.08 (1 H, s), 7.43 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.49 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.69 (1 H, s), 7.99 (1 H, d, *J* = 8.0 Hz), 8.06 (1 H, d, *J* = 8.0 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 56.43, 56.56, 77.64 (q, $^2J_{C,F}$ = 28.9 Hz), 110.04, 111.70, 111.87, 122.45, 123.46, 125.12 (q, $^1J_{C,F}$ = 288.8 Hz), 125.76, 126.38, 135.49, 140.06, 140.87, 152.73, 153.13, 173.53.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –73.51.

APSI MS: *m*/*z* = 385 (M^+ + 1).

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