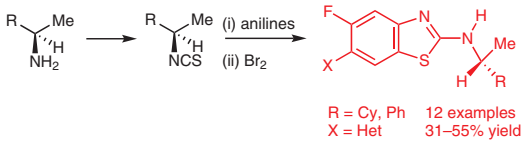
Synthesis of 5-Fluoroaminobenzothiazoles

Pooja Sharma[a]
Gurdial Singh*[a]
Bhoomendra A. Bhongade[a,b]
Malleshappa N. Noolvi[c]
Andanappa K. Gadad[d]

[a] Department of Chemistry, The University of The West Indies, St. Augustine, Trinidad and Tobago
gurdial.singh@sta.uwi.edu
[b] RAK College of Pharmaceutical Sciences, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE
[c] Shree Dhanvantary Pharmacy College, Surat, Gujarat, India
[d] School of Pharmacy, Faculty of Medical Sciences, The University of The West Indies, Mount Hope, Trinidad and Tobago



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Abstract A series of 5-fluoro-2-(N-substituted)aminobenzothiazoles were synthesized by intramolecular cyclisation of the corresponding thioureas, which were prepared by treatment of 4-substituted 3-fluoroanilines with appropriate isothiocyanates.

Key words synthetic methods, 2-aminobenzothiazoles, isothiocyanates, chiral, fluoro, heterocyclic

In 2018, the WHO reported that there were 10 million new cases of tuberculosis (TB) and it remains among the leading causes of the mortality and morbidity worldwide.[1] The discovery of several potent anti-TB agents was made about 65 years and, since then, a number of agents have been discovered.[2] The emergence of multi-drug resistant strains of TB bacillus to most of the currently used anti-TB drugs combined with their toxicity and side effects are of major concern in the treatment of TB.[3] Thus, successful treatment of TB demands the synthesis of new, safer and more effective agents.

Benzothiazoles are an important class of biodynamic heterocyclic compounds in medicinal chemistry because of their applications in drug discovery and development.[4] In particular, 2-aminobenzothiazole derivatives are reported to exhibit a wide range of biological activities such as antidiabetic,[5] antiepileptic,[6] analgesic,[7] antiinflammatory,[7c,8] anthelmintic,[9] antiviral,[10] antifungal,[11] anesthetic,[7c,12] antiproliferative,[13] antimicrobial,[14] anticancer[15] and antitubercular action.[16]

Similarly, several reports have described the anticancer[17] and anti-TB[17c,18] activities of various N-substituted thiourea derivatives. Of particular interest to us were the observations that 2-(N-substituted)aminobenzothiazole derivatives **1** (R = Cl, Br, Me, NO_2, NHAc) and thiourea derivative **2** (Figure 1) exhibited promising anti-TB[16c] and antitumor[17b] activities, respectively.

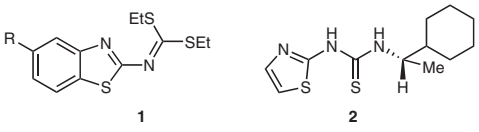


Figure 1

The discovery of the potent anti-TB drug bedaquiline[18] **3** (Figure 2) by Johnson & Johnson in 2005, provided new impetus for research in this area due to its effectiveness against both replicating and dormant multi-drug-resistant TB (MTB).[19]

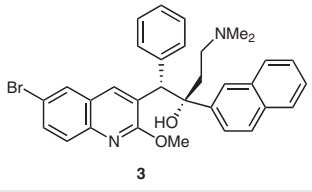


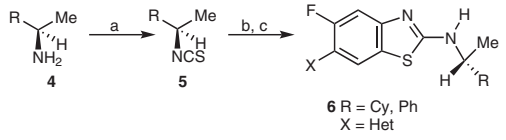
Figure 2

We have reported on some of our efforts in this area[20] with the findings that chiral thioureas exhibit promising activity against some tumour cell lines. In this paper we report on our endeavours on the synthesis of a range of chiral aminobenzothiazoles.

Molecules containing fluorine atoms are at the leading edge of many new developments in medicinal chemistry, resulting in an increased number of fluorinated organic molecules finding efficacy in the clinic.[19] Selective introduction of a fluorine atom into biomolecules often results in improved potency compared to their non-fluorinated analogues, primarily due to significant improvements in their physicochemical properties.[20] Over the last two decades, the development of enantiomerically pure drugs has become a major focus of most pharmaceutical companies because of their improved safety, efficacy and minimized side effects.[21–24]

In considerations of these findings, and in continuation of our research in the development of novel bioactive molecules,[25] we report the synthesis of optically active thiourea and N-substituted 5-fluoroaminobenzothiazoles derivatives and their preliminary in vitro evaluation as anti-TB agents.

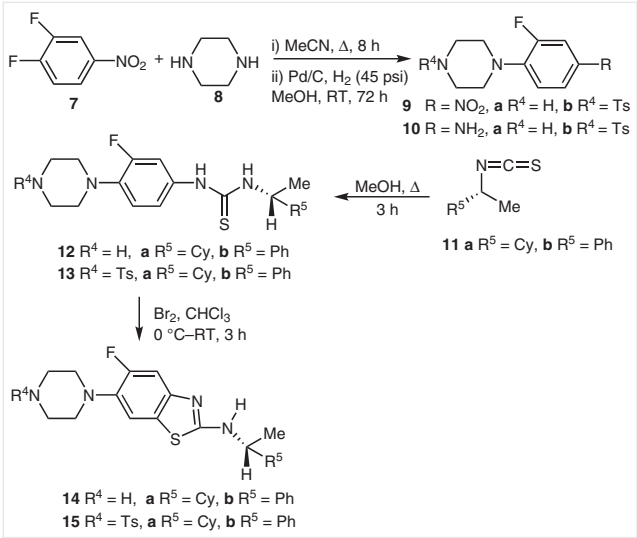
The general synthetic strategy employed for the synthesis of the optically active isothiocyanates **5** and 6-substituted 5-fluoro-2-(N-substituted)aminobenzothiazole derivatives **6** is summarised in Scheme 1. The optically active isothiocyanates **5** were prepared by the reaction of appropriate chiral amines **4** with thiophosgene in aqueous CH_2Cl_2 in the presence of $NaHCO_3$ at room temperature.[26] Treatment of the appropriate isothiocyanates **5** with 4-substituted-3-fluoroaniline in methanol under an inert atmosphere yielded the requisite thioureas. Intramolecular oxidative cyclisation of these using bromine in chloroform afforded the corresponding 5-fluoroaminobenzothiazoles **6** in 31–55% yields.



Scheme 1 *Reagents and conditions*: (a) $CSCl_2$, CH_2Cl_2, H_2O; $NaHCO_3$; (b) 4-substituted 3-fluoroaniline, MeOH, N_2, reflux; (c) Br_2, $CHCl_3$, r.t.

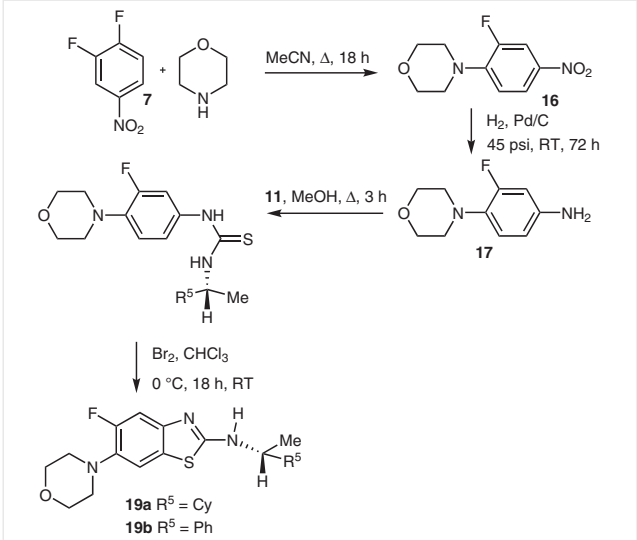
The ^1H NMR spectra for N-substituted 5-fluoroaminobenzothiazoles **6** showed corresponding resonances in the range of δ = 1.25–1.0 ppm for the methyl group, while the chiral proton was found to resonate in the range of δ = 4.85–4.60 ppm. In their ^{13}C NMR spectra, resonances in the range of δ = 60–49 and 25–22 ppm were observed for chiral and methyl carbons, respectively.[27]

The required N-substituted piperazine **10** was prepared as detailed in Scheme 2, in a two-step procedure from the commercially available 1,2-difluoro-4-nitrobenzene **7**. The resulting nitro derivative **9** was reduced to the corresponding aniline, which, on coupling with the chiral isothiocyanate **11**, afforded thiourea **12**. Oxidative cyclisation with bromine gave the target 5-fluoroaminobenzothiazole **14**. In our hands, this cyclisation was the most efficient procedure. We investigated the use of the Johnson and Johnson protocol[28] but this resulted in the formation of complex mixtures.



Scheme 2

Having prepared these compounds, we proceeded to synthesise piperidine, pyrrolidine, and morpholino analogues (Scheme 3 and Figure 3), by employing a similar protocol to that used for the preparation of **14** and **15**.



Scheme 3

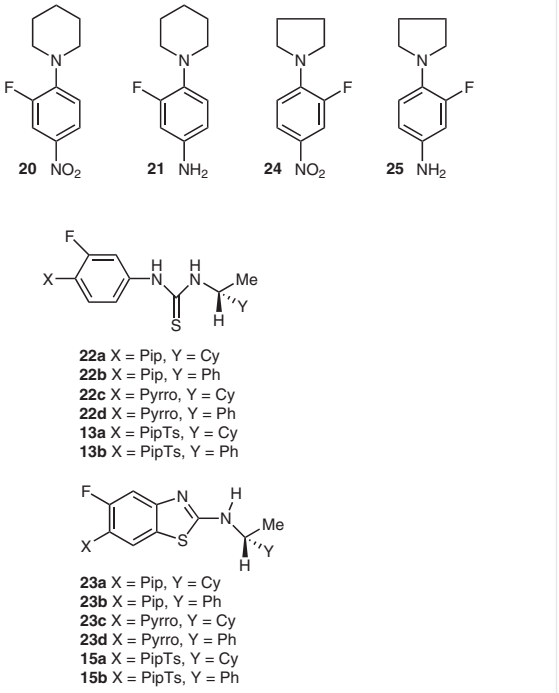


Figure 3

All of the prepared compounds were screened for anti-TB activity using a broth dilution assay using *M. tuberculosis* strain H37Rv. Benzothiazoles exhibited MIC values in the range of 5–100 μg/mL whilst the precursor thioureas did not show any inhibition at concentrations of 100 μg/mL.

In summary, we have prepared a series of chiral thioureas and 5-fluoroaminobenzothiazoles by employing a straightforward methodology.

Column chromatography was carried out using Merck 230–400 mesh silica gel. TLC was run on precoated silica gel 60 F254 plates. Specific rotations were measured with a Beltingham & Stanley Ltd. ADP 200 polarimeter at λ = 589 nm. All NMR spectra were recorded with a Bruker 600, 400 or 300 MHz spectrometer in the deuterated solvents stated. Anhydrous reactions were performed under argon or nitrogen atmospheres.

1-(2-Fluoro-4-nitrophenyl)piperazine (9)[29]

3,4-Difluoronitrobenzene **7** (1.43 g, 8.98 mmol) was dissolved in acetonitrile (30 mL). Piperazine **8** (2.00 g, 22.48 mmol) was then added and the mixture was heated to reflux for 8 h. The solution was cooled to ambient temperature and filtered. The filtrate was concentrated in vacuo to afford an orange solid, subsequent chromatographic purification with chloroform and MeOH (7:3) as eluents afforded **9**.

Yield: 1.97 g (98%); yellow solid; mp 68–69 °C [lit.[29] 68.5–71 °C].

IR (thin film): 3228 (NH), 2911, 2849, 1602 (Ar), 1497 (NO_2), 1453, 1389, 1323 (NO_2), 1263, 1237 (CF), 1203, 1155, 1144, 951, 936, 880, 846, 815, 802, 745, 709 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.9 (dd, *J* = 2.5, 9.0 Hz, 1 H), 7.9 (dd, *J* = 2.5, 13.2 Hz, 1 H), 6.9 (t, *J* = 8.8 Hz, 1 H), 3.3 (m, 4 H), 3.0 (m, 4 H), 1.9 (s, br, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0 (J_{C-F} = 249.3 Hz), 146.0 (J_{C-F} = 7.5 Hz), 140.4 (J_{C-F} = 9.4 Hz), 121.0 (J_{C-F} = 2.9 Hz), 117.0 (J_{C-F} = 4.0 Hz), 112.5 (J_{C-F} = 26.4 Hz), 50.8 (J_{C-F} = 5.0 Hz), 45.9.

UV: λ_{max} (MeOH): 368 (ε = 7648) nm.

HRMS: *m*/*z* calcd for $C_{10}H_{12}FN_3O_2Na$: 248.0811; found: 248.0806.

3-Fluoro-4-(piperazin-1-yl)aniline (10)

The nitro compound **9** (4.00 g, 17.80 mmol) was dissolved in anhydrous MeOH (40 mL). The resultant solution was hydrogenated at 45–50 psi using Pd/C (0.4 g) as catalyst at r.t., for 72 h. *Note*: *The addition of the catalyst was conducted under a nitrogen atmosphere and subsequently evacuated* (3×) *and replaced with a hydrogen atmosphere.* The reaction mixture was filtered through a plug of Celite and washed with MeOH (100 mL). Subsequent removal of the solvent in vacuo afforded **10**.

Yield: 3.00 g (86%); brown solid; mp 188–190 °C.

IR (thin film): 3337 (NH), 3190 (NH), 2948, 2832, 1656, 1629 (Ar), 1513, 1455, 1304, 1318, 1266, 1233 (CF), 1220, 1137, 1061, 969, 933, 871, 833, 821, 807, 743 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.8 (m, 1 H), 6.4 (dd, *J* = 2.2, 14.3 Hz, 1 H), 6.3 (dd, *J* = 2.3, 8.5 Hz, 1 H), 5.3 (NH, s, 2 H, br), 3.5 (m, 4 H), 2.8 (m, 4 H), 1.9 (s, br, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3 (J_{C-F} = 242.3 Hz), 145.2 (J_{C-F} = 37.6 Hz), 129.0 (J_{C-F} = 10.3 Hz), 121.3 (J_{C-F} = 4.2 Hz), 109.8, 102.0 (J_{C-F} = 23.3 Hz), 51.5 (J_{C-F} = 62.2 Hz), 45.3.

UV: λ_{max} (MeOH): 207 (ε = 11240) nm.

(*R*)-1-(1-Cyclohexylethyl)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)thiourea (12a)

The isothiocyanate **11a** (0.47 g, 2.80 mmol) was dissolved in anhydrous MeOH (20 mL) and an equimolar quantity of aromatic primary amine **10** (0.55 g, 2.80 mmol) was added with stirring. The reaction mixture was heated to reflux at 65 °C for 3 h. The reaction was monitored by TLC using petroleum ether and EtOAc (1:1) as eluent. The solvent was evaporated to afford a light-brown solid. Additional purification via silica gel chromatography using petroleum ether and EtOAc (1:1) gave **12a**.

Yield: 0.36 g (36%); buff coloured solid; mp 160–162 °C; $[\alpha]_D$ +13.8 (*c* 0.3, $CHCl_3$).

IR (thin film): 3292 (NH), 3197, 2936, 2854, 1729, 1626 (Ar), 1538, 1513, 1446, 1409, 1364, 1343, 1305 (CS), 1280, 1242 (CF) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.8 (t, *J* = 8.9 Hz, 1 H), 6.4 (dd, *J* = 2.41, 13.4 Hz, 1 H), 6.4 (dd, *J* = 2.4, 8.4 Hz, 1 H), 5.4 (d, *J* = 8.3 Hz, NH), 4.6 (m, *J* = 6.7, 7.7, 6.7 Hz, 1 H), 3.9 (m, 4 H), 3.6 (s, br, NH), 3.0 (m, 4 H),1.8 (s, br, 1 H), 1.6–1.1 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 181.8, 156.9 (J_{C-F} = 245.3 Hz), 143.3 (J_{C-F} = 10.5 Hz), 130.9 (J_{C-F} = 9.9 Hz), 120.8 (J_{C-F} = 4.1 Hz), 110.7 (J_{C-F} = 2.9 Hz), 103.8 (J_{C-F} = 23.7 Hz), 55.8, 50.9, 47.7, 43.1, 29.6, 26.5, 26.3, 17.5.

HRMS: *m*/*z* calcd for $C_{19}H_{30}FN_4S$: 365.2170; found: 365.2168.

(*R*)-*N*-(1-Cyclohexylethyl)-5-fluoro-6-(piperazin-1-yl)benzo[*d*]thiazol-2-amine (14a)

The thiourea **12a** (0.10 g, 0.27 mmol) was dissolved in chloroform (15 mL) and cooled to 0 °C. To this, an equimolar quantity of Br_2 (0.01 mL) was added. From this stock solution, 2 mL of solution was added to the reaction mixture. Following addition, the ice bath was removed and the reaction mixture was warmed to r.t. The mixture was stirred for a further 3 h and the resulting mixture was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $Na_2SO_4$and concentrated in vacuo. The resulting residue was purified by chromatography on silica, using petroleum ether and EtOAc (1:1) as eluent. Removal of the solvent in vacuo afforded the product **14a**.

Yield: 16 mg (16%); light-brown amorphous solid; $[\alpha]_D$ –29.6 (*c* 0.14, $CHCl_3$).

IR (thin film): 3342 (NH), 2924, 2852, 1708, 1625 (Ar), 1507, 1449 (CN thiazole), 1361 (CN thiazole), 1256 (CF), 1220, 1163, 999, 864, 745 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.0 (d, *J* = 8.5 Hz, 1 H), 6.5 (d, *J* = 12.9 Hz, 1 H), 4.2 (d, *J* = 8.4 Hz, 1 H, NH), 3.7 (m, *J* = 6.6, 8.0, 6.6 Hz, 1 H), 3.5 (m, 4 H), 2.9 (t, *J* = 5.0 Hz, 4 H), 1.75 (s, 1 H, br), 1.7–0.8 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0, 157.1 (J_{C-F} = 64.8 Hz), 140.3 (J_{C-F} = 10.2 Hz), 132.3 (J_{C-F} = 11.0 Hz), 127.0, 127.6, 103.9 (J_{C-F} = 25.2 Hz), 51.1, 50.6, 44.0, 43.4, 29.3, 28.9, 26.5, 18.5.

UV: λ_{max} (MeOH) = 210.9 (ε = 29368) nm.

(*R*)-(–)-(1-Isothiocyanatoethyl)benzene (11b)[30]

1,1′-Thiocarbonyldiimidazole (0.14 g, 0.82 mmol) was added to a rapidly stirring mixture of CH_2Cl_2 (18 mL) and water (18 mL) at r.t., then (*R*)-(+)-α-methylbenzylamine (0.10 g, 0.82 mmol) was added. $NaHCO_3$ (0.18 g, 2.2 mmol) was then added to the resultant mixture slowly over a period of 45 min, and stirring was continued at r.t. for 13 h. The two phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed in vacuo to afford the isothiocyanate as a light-brown semisolid, which was further purified by column chromatography using petroleum ether and EtOAc (10:1) to afford the title compound **11b**.

Yield: 0.06 g (45%); light-brown oil; $[\alpha]_D$ –13.2 (*c* 3.0, $CHCl_3$) {lit.[30a] $[\alpha]_D$ –4.3 (*c* 1.0, acetone); lit.[30b] $[\alpha]_D$ –17.3 ($CHCl_3$)}.

IR (thin film): 3033, 2985, 2933, 2085 (NCS), 1736, 1604 (Ar), 1494, 1454, 1374, 1345, 1326, 1308, 1278, 1242, 1203, 1182, 1158, 1103, 1067, 1045 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.3 (m, 2 H), 7.3 (t, *J* = 6.8 Hz, 3 H), 4.9 (q, *J* = 6.7, 6.7, 6.8 Hz, 1 H), 1.6 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 140.0, 132.1, 128.8, 128.1, 125.3, 56.9, 24.9.

UV: λ_{max} (MeOH) = 206 (ε = 15129) nm.

(*R*)-1-(3-Fluoro-4-(piperazin-1-yl)phenyl)-3-(1-phenylethyl)thiourea (12b)

The isothiocyanate **11b** (0.51 g, 3.00 mmol) was dissolved in anhydrous MeOH (15 mL) and an equimolar quantity of primary amine **10** was added with stirring. The reaction mixture was heated to reflux for 2 h at 65 °C. On completion of the reaction, the resultant mixture was concentrated in vacuo to afford a creamish white solid. Chromatographic purification (petroleum ether and EtOAc (1:1)) gave the product **12b**.

Yield: 0.30 g (28%); colorless solid; mp 126–128 °C; $[\alpha]_D$ –20.8 (*c* 0.8, $CHCl_3$).

IR (thin film): 3342 (NH), 2826, 1630 (Ar), 1513, 1339 (CS), 1280, 1219 (CF), 1014, 922, 808 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.3 (m, 5 H), 6.7 (t, *J* = 9.0 Hz, 1 H), 6.4 (m, 2 H), 5.8 (p, *J* = 6.9, 7.0, 7.0, 6.8 Hz, 1 H), 5.7 (d, *J* = 7.5 Hz, 1 H, NH), 3.1 (s, br, NH), 3.9 (m, 4 H), 2.0 (s, br, 1 H), 2.9 (m, 4 H), 1.6 (d, *J* = 6.8 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 181.4, 153.5 (JC–F = 43.5 Hz), 143.3 (JC–F = 10.4 Hz), 143.0, 130.8 (J_{C-F} = 10.2 Hz), 128.7, 127.4, 126.4, 120.8 (J_{C-F} = 4.1 Hz), 110.6 (J_{C-F} = 3.0 Hz), 103.8 (J_{C-F} = 23.6 Hz), 54.6, 50.8 (J_{C-F} = 2.0 Hz), 47.7, 21.5.

UV: λ_{max} (MeOH) = 206 (ε = 50716) nm.

HRMS: *m*/*z* calcd for $C_{19}H_{22}FN_4S$: 357.1544; found: 357.1510.

(*R*)-5-Fluoro-*N*-(1-phenylethyl)-6-(piperazin-1-yl)benzo[*d*]thiazol-2-amine (14b)

Thiourea **12b** (0.10 g, 0.28 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.014 mL) was added, the ice bath was removed, and the reaction mixture was brought to r.t. Stirring was continued for a further 15 h, then the mixture was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica eluting with petroleum ether and EtOAc (7:3) with 1% triethylamine as the eluent gave benzothiazole **14b**.

Yield: 22 mg (21%); brown amorphous solid; $[\alpha]_D$ –66.7 (*c* 0.2, $CHCl_3$).

IR (thin film): 3340, 1627 (Ar), 1508, 1451 (CN thiazole), 1418, 1386 (CN thiazole), 1257 (CF), 1222 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.3 (m, 5 H), 6.9 (d, *J* = 8.5 Hz, 1 H), 6.5 (d, *J* = 13.0 Hz, 1 H), 5.0 (q, *J* = 6.9, 6.9, 6.9 Hz, 1 H), 4.6 (d, *J* = 6.9 Hz, NH), 3.5 (m, 4 H), 2.9 (t, *J* = 5.0 Hz, 4 H),1.6 (s, br, NH), 1.5 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.9, 156.8, 144.2, 140.4 (J_{C-F} = 11.0 Hz), 132.2 (J_{C-F} = 37.3 Hz), 128.6, 127.7, 126.1, 123.7 (J_{C-F} = 3.9 Hz), 103.9 (J_{C-F} = 25.2 Hz), 103.1, 51.0, 50.2, 44.0, 22.5.

HRMS: *m*/*z* calcd for $C_{19}H_{23}FN_4S$: 357.1544; found: 357.1483.

1-(2-Fluoro-4-nitrophenyl)-4-tosylpiperazine (9b)

The piperazine substituted nitro aromatic **8** (2.10 g, 9.32 mmol) was dissolved in CH_2Cl_2 (20 mL). Triethylamine (1.30 mL, 9.32 mmol) and *p*-toluenesulfonyl chloride (1.95 g, 10.26 mmol) were added and the mixture was allowed to stir at r.t. for 3.5 h. The residue was filtered and the filtrate was evaporated in vacuo. The resulting residue was purified by chromatography using petroleum ether and EtOAc (3:1) as the eluent to afford **9b**.

Yield: 3.02 g (86%); pale-yellow solid; mp 164–166 °C.

IR (thin film): 3076, 2858, 1670, 1601, 1497 (NO_2), 1445, 1391, 1336 (NO_2), 1281, 1235 (CF), 1213, 1157 (SO_2), 1114, 1079, 945, 926, 885, 805 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.9 (dd, *J* = 2.4, 8.9 Hz, 1 H), 7.8 (dd, *J* = 2.5, 12.8 Hz, 1 H), 7.7 (d, *J* = 8.1 Hz, 2 H), 7.3 (d, *J* = 8.1 Hz, 2 H), 6.9 (t, *J* = 8.7 Hz, 1 H), 3.3 (m, 4 H), 3.2 (m, 4 H), 2.4 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.2 (J_{C-F} = 249.5 Hz), 144.8 (J_{C-F} = 8.0 Hz), 144.1, 141.4 (J_{C-F} = 8.8 Hz), 132.2, 129.9, 127.9, 120.9 (J_{C-F} = 3.2 Hz), 117.6 (J_{C-F} = 3.5 Hz), 112.6 (J_{C-F} = 26.3 Hz), 49.1 (J_{C-F} = 4.6 Hz), 45.8, 21.6.

UV: λ_{max} (MeOH) = 352 (ε = 20379) nm.

HRMS: *m*/*z* calcd for $C_{17}H_{17}FN_3O_4S$: 378.0918; found: 378.0876.

3-Fluoro-4-(4-tosylpiperazine-1-yl)aniline (10b)

The piperazine substituted nitro aromatic **9b** (4.00 g, 10.55 mmol) was dissolved in anhydrous MeOH (40 mL). The reaction flask was charged with 10% palladium on carbon and hydrogenated at 45–50 psi. for 72 h. The reaction mixture was filtered through a plug of Celite and washed with MeOH (100 mL). Subsequent removal of the solvent in vacuo afforded **10b**.

Yield: 3.52 g (96%); brownish solid; mp 181–184 °C.

IR (thin film): 3434 (NH), 3363 (NH), 2923, 1636, 1598, 1515, 1452, 1393, 1338, 1319 (SO_2), 1272, 1229 (CF), 1158 (SO_2), 1123, 1090, 1016, 948, 806, 726 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.2 Hz, 2 H), 7.3 (d, *J* = 7.9 Hz, 2 H), 6.7 (t, *J* = 8.8 Hz, 1 H), 6.4 (m, 2 H), 3.5 (NH, s, 2 H), 3.1 (m, 4 H), 3.0 (m, 4 H), 2.4 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.4 (J_{C-F} = 158.4 Hz), 143.8, 143.4, 143.3, 132.3, 129.7, 127.9, 120.9 (J_{C-F} = 4.0 Hz), 110.6 (J_{C-F} = 3.0 Hz), 103.7 (J_{C-F} = 23.7 Hz), 50.8 (J_{C-F} = 2.0 Hz), 46.4, 21.5.

UV: λ_{max} (MeOH) = 234 (ε = 13777) nm.

(*R*)-1-(1-Cyclohexylethyl)-3-(3-fluoro-4-(4-tosylpiperazin-1-yl))thiourea (13a)

The isothiocyanate **11a** (54.0 mg, 3.21 mmol) was dissolved in anhydrous MeOH (20 mL) and an equimolar quantity of **10b** (111.8 mg, 3.21 mmol) was added with stirring. The reaction mixture was heated at 70 °C for 2 h. On completion of the reaction, the solvent was evaporated in vacuo to gave a dark-brown solid that was purified by chromatography using petroleum ether and EtOAc (1:1) to give **13a**.

Yield: 0.14 g (85%); light-brown solid; mp 170–171 °C; $[\alpha]_D$ –11.9 (*c* 1.0, $CHCl_3$).

IR (thin film): 3396 (NH), 2925, 1726, 1598 (Ar), 1510, 1451, 1377, 1349 (SO_2), 1332, 1306 (CS), 1264 (CF), 1164, 1138 (SO_2), 1118, 1019, 947, 865, 730 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.2 Hz, 2 H), 7.3 (d, *J* = 8.0 Hz, 2 H), 6.7 (t, *J* = 8.8 Hz, 1 H), 6.4 (m, 2 H), 5.7 (s, NH), 4.1 (q, *J* = 7.2, 7.2, 7.2 Hz, 1 H), 3.6 (s, NH), 3.1 (m, 4 H), 3.0 (m, 4 H), 2.4 (s, 3 H), 0.8–1.8 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.0, 156.7 (J_{C-F} = 245.2 Hz), 143.8, 142.6, 132.3, 130.8, 129.7, 127.9, 120.8, 110.6 (J_{C-F} = 2.9 Hz), 103.7 (J_{C-F} = 23.8 Hz), 70.8, 50.7, 46.3, 42.1, 33.1, 32.8, 29.7, 27.1, 21.5.

UV: λ_{max} (MeOH) = 230 (ε = 25484) nm.

HRMS: *m*/*z* calcd for $C_{26}H_{35}FN_4NaO_2S_2$: 541.2083; found: 541.2099.

(*R*)-*N*-(1-Cyclohexylethyl)-5-fluoro-6-(4-tosylpiperazin-1-yl)benzo[*d*]thiazol-2-amine (15a)

The thiourea **13a** (0.17 g, 0.32 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.02 mL) in $CHCl_3$ (4 mL) was added, the ice bath was removed and the reaction mixture was brought to r.t. The mixture was stirred at r.t. for 3 h. On completion of the reaction, the resulting residue was concentrated in vacuo and was subjected to column chromatography (petroleum ether and EtOAc (7:3)). Subsequent in vacuo evaporation, afforded **15a**.

Yield: 0.07 g (41%); solid; $[\alpha]_D$ –114.3 (*c* 0.04, $CHCl_3$).

IR (thin film): 3365 (NH), 2981, 2099, 1600, 1474 (CN thiazole), 1393 (CN thiazole), 1329 (SO_2), 1217 (CF), 1158 (SO_2), 1035, 805, 726 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.2 Hz, 2 H), 7.3 (d, *J* = 8.0 Hz, 2 H), 6.9 (d, *J* = 8.5 Hz, 1 H), 6.4 (d, *J* = 13.0 Hz, 1 H), 3.9 (s, br, NH), 3.5 (m, *J* = 6.6, 7.5, 6.8 Hz, 1 H), 3.1 (m, 4 H), 3.0 (m, 4 H), 2.4 (s, 3 H), 1.8–0.8 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.4, 155.9 (J_{C-F} = 245.7 Hz), 143.8, 140.6 (J_{C-F} = 10.6 Hz), 132.3, 131.7, 131.6, 129.7, 127.9, 123.8, 103.8 (J_{C-F} = 25.4 Hz), 50.6 (J_{C-F} = 2.0 Hz), 50.5, 46.2, 43.7, 29.1, 28.9, 26.5, 26.3, 19.7.

UV: λ_{max} (MeOH) = 208 (ε = 35862) nm.

(*R*)-1-(3-Fluoro-4-(4-tosylpiperazin-1-yl)phenyl)-3-(1-phenylethyl)thiourea (13b)

The isothiocyanate **11b** (0.14 g, 0.86 mmol) was dissolved in anhydrous MeOH (10 mL) and an equimolar quantity of aromatic amine **10b** (0.30 g) was added with stirring. The reaction mixture was heated for 2 h then allowed to cool and poured into cold water, resulting in precipitation of the thiourea. The solid product was washed with water and purified by recrystallization from EtOAc and a small amount of EtOH to obtain **13b**.

Yield: 0.22 g (52%); brown solid; mp 89–92 °C; $[\alpha]_D$ –313.0 (*c* 0.2, $CHCl_3$).

IR (thin film): 3253 (NH), 3068, 3027, 2967, 1545, 1495, 1451, 1346 (SO_2), 1332, 1278, 1260 (CF), 1206, 1163 (SO_2), 1118, 1087, 1011, 949, 815, 759, 696 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.1 Hz, 2 H), 7.3 (d, *J* = 8.0 Hz, 2 H), 7.2–7.0 (m, 5 H), 6.7 (t, *J* = 8.9 Hz, 1 H), 6.4 (m, 2 H), 5.3 (s, br, NH), 4.8 (m, 1 H), 3.6 (br, NH), 3.1 (m, 4 H), 3.0 (m, 4 H), 2.4 (s, 3 H), 1.4 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.9, 156.7 (J_{C-F} = 245.0 Hz), 143.7 (2C), 143.3, 132.4, 130.9, 129.7, 127.9 (2C), 127.6, 125.6, 120.9 (J_{C-F} = 3.6 Hz), 110.6 (J_{C-F} = 2.8 Hz), 103.7 (J_{C-F} = 23.8 Hz), 54.2, 50.7, 46.3, 29.7, 21.5.

UV: λ_{max} (MeOH) = 231 (ε = 18750) nm.

HRMS: *m*/*z* calcd for $C_{26}H_{28}FN_4S_2O_2$: 511.1632; found: 511.1597.

(*R*)-5-Fluoro-*N*-(1-phenylethyl)-6-(4-tosylpiperazin-1-yl)benzo[*d*]thiazol-2-amine (15b)

The thiourea **13b** (0.10 g, 0.20 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.01 mL) in $CHCl_3$ (2 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t., and stirred at r.t. for 1 h. The resulting solution was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by chromatography with petroleum ether and EtOAc (1:1). The combined fractions, on evaporation, afforded **15b**.

Yield: 0.03 g (30%); light-brown solid; $[\alpha]_D$ +13.1 (*c* 0.3, $CHCl_3$).

IR (thin film): 3357 (NH), 2924, 2854, 1709, 1537, 1440, 1453 (CN thiazole), 1350 (CN thiazole), 1330, 1219 (CF), 1165, 1093, 948, 862, 731, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.2 Hz, 2 H), 7.3 (d, *J* = 7.2 Hz, 2 H), 7.3 (m, 5 H), 7.1 (d, *J* = 12.8 Hz, 1 H), 7.0 (d, *J* = 7.0 Hz, 1 H), 6.0 (s, br, NH), 4.7 (q, *J* = 6.6, 6.6, 6.7 Hz, 1 H), 3.1 (m, 4 H), 3.0 (d, *J* = 4.7 Hz, 4 H), 2.4 (s, 3 H), 1.6 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.5, 155.4 (J_{C-F} = 241.8 Hz), 143.9, 142.5, 134.7, 134.0, 133.7, 132.2, 129.8, 128.8, 127.9, 127.8, 127.7, 126.1, 125.9, 111.0 (J_{C-F} = 3.3 Hz), 106.5 (J_{C-F} = 23.9 Hz), 55.4, 50.7 (J_{C-F} = 2.3 Hz), 46.3, 23.6, 21.5.

UV: λ_{max} (MeOH) = 370 (ε = 66751) nm.

4-(2-Fluoro-4-nitrophenyl)morpholine (16)

3,4-Difluoronitrobenzene **7** (1.10 mL, 6.90 mmol) was dissolved in acetonitrile (30 mL). To the resultant mixture, morpholine (1.50 mL, 17.29 mmol) was added. The mixture was heated to reflux for 18 h, then the resultant mixture was poured into cold water and the residue was filtered. The residue was recrystallized with aqueous MeOH to afford **16**.

Yield: 1.09 g (70%); yellow solid; mp 110–112 °C [lit.[29] 111–112 °C].

IR (thin film): 3053, 2853, 1602 (Ar), 1516, 1493 (-NO_2), 1446, 1362, 1320 (NO_2), 1273, 1261, 1243 (CF), 1160, 1124, 1091, 1072, 1050, 1028, 949, 916, 859, 848, 815, 804, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.0 (m, 1 H), 7.9 (dd, *J* = 2.6, 13.1 Hz, 1 H), 6.9 (t, *J* = 8.7 Hz, 1 H), 3.9 (m, 4 H), 3.3 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.2 (J_{C-F} = 359.0 Hz), 145.5 (J_{C-F} = 6.0 Hz), 140.9 (J_{C-F} = 11.0 Hz), 121.0 (J_{C-F} = 4.0 Hz), 116.9, 112.7 (J_{C-F} = 28.0 Hz), 66.6, 49.9 (J_{C-F} = 5.0 Hz).

UV: λ_{max} (MeOH) = 360 (ε = 10535) nm.

HRMS: *m*/*z* calcd for $C_{10}H_{11}FN_2O_3Na$: 249.0646; found: 249.0595.

3-Fluoro-4-morpholinoaniline (17)[31]

The nitro compound **16** (1.00 g, 4.42 mmol) was dissolved in anhydrous MeOH (40 mL) and the reaction flask was charged with 10% palladium on carbon at 45–50 psi. The resultant mixture was shaken for 72 h at r.t. The reaction mixture was filtered through a plug of Celite and washed with MeOH (100 mL). Subsequent removal of the solvent in vacuo afforded **17**.

Yield: 0.80 g (92%); slightly pink solid; mp 116–117 °C.

IR (thin film): 3418 (NH), 3337 (NH), 3232, 2974, 2824, 1639, 1578, 1513, 1479, 1450, 1376, 1317, 1301, 1272, 1249 (CF), 1221, 1206, 1161, 1109, 815, 741 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.8 (t, *J* = 8.6 Hz, 1 H), 6.4 (dd, *J* = 2.5, 13.5 Hz, 1 H), 6.4 (dd, *J* = 7.9, 2.8 Hz, 1 H), 3.8 (m, 4 H), 3.6 (br, s, 2 H, NH), 2.9 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.0 (J_{C-F} = 245.0 Hz), 142.8 (J_{C-F} = 11.0 Hz), 131.8 (J_{C-F} = 9.0 Hz), 120.3 (J_{C-F} = 4.0 Hz), 110.6 (J_{C-F} = 3.0 Hz), 103.9 (J_{C-F} = 24.0 Hz), 67.3, 51.8 (J_{C-F} = 2.0 Hz).

UV: λ_{max} (MeOH) = 248 (ε = 24248) nm.

HRMS: *m*/*z* calcd for $C_{10}H_{13}FN_2ONa$: 219.0904; found: 219.0854.

(*R*)-1-(1-Cyclohexylethyl)-3-(3-fluoro-4-morpholinophenyl)thiourea (18a)

The isothiocyanate **11a** (0.09 g, 0.53 mmol) was dissolved in anhydrous MeOH (20 mL) and an equimolar quantity of aromatic amine **17** (0.10 g, 0.53 mmol) was added with stirring. The reaction mixture was then heated at 65 °C for 3 h. The reaction was monitored by TLC. On completion of the reaction, the solvent was evaporated to obtain the crude product, which was purified by column chromatography with petroleum ether and EtOAc (1:1) as the eluent. The eluents were then evaporated to afford **18a**.

Yield: 0.60 g (30%); off-white solid; mp 128–131 °C; $[\alpha]_D$ +57.2 (*c* 2.7, $CHCl_3$).

IR (thin film): 3172 (NH), 2924, 2853, 1579, 1514, 1449, 1378, 1303 (CS), 1254 (CF), 1223, 1209, 1162, 1047, 998, 892, 859, 817, 790, 727 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.6 (s, br, NH), 6.9 (d, *J* = 9.1 Hz, 1 H), 6.9 (m, 1 H), 6.9 (m, 1 H), 5.7 (NH), 4.4 (m, 1 H), 3.8 (m, 4 H), 3.1 (m, 4 H), 0.9–1.8 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.9, 155.7 (J_{C-F} = 249.0 Hz), 139.4 (J_{C-F} = 16.0 Hz), 130.0 (J_{C-F} = 8.0 Hz), 121.9, 119.5, 114.2 (J_{C-F} = 22.0 Hz), 66.9, 55.9, 50.7 (J_{C-F} = 3.0 Hz), 42.9, 29.3, 28.9, 26.4, 17.3.

UV: λ_{max} (MeOH) = 258 (ε = 65390) nm.

HRMS: *m*/*z* calcd for $C_{19}H_{27}FN_3OS$: 364.1859; found: 364.1850.

(*R*)-*N*-(1-Cyclohexylethyl)-5-fluoro-6-morpholinobenzo[*d*]thiazole-2-amine (19a)

Thiourea **18a** (0.20 g, 0.54 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath at 0 °C. Subsequently, an equimolar quantity of Br_2 (0.03 mL), dissolved in chloroform (6 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t. then stirred at r.t. for 18 h and the progress of the reaction was monitored by TLC. Chromatographic purification using petroleum ether and EtOAc (1:1), and removal of the eluents in vacuo gave **19a**.

Yield: 97.8 mg (49%); light-brown amorphous solid; $[\alpha]_D$ –16.0 (*c* 1.3, $CHCl_3$).

IR (thin film): 3376 (NH), 3046, 2926, 2855, 1609, 1509, 1479 (CN thiazole), 1450, 1364 (CN thiazole), 1292, 1265 (CF), 1179, 1123, 1049, 856, 823, 722, 669.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.1 (d, *J* = 12.8 Hz, 1 H), 7.1 (d, *J* = 8.0 Hz, 1 H), 4.6 (s, br, NH), 3.8 (m, 4 H), 3.4 (m, 1 H), 3.0 (m, 4 H), 1.0–1.9 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.2, 155.6 (J_{C-F} = 244.0 Hz), 146.9 (J_{C-F} = 12.0 Hz), 135.4 (J_{C-F} = 11.0 Hz), 124.6, 110.7, 105.9 (J_{C-F} = 24.0 Hz), 67.1, 57.7, 51.7 (J_{C-F} = 2.0 Hz), 43.6, 29.1, 26.2, 21.4, 18.0.

UV: λ_{max} (MeOH) = 225 (ε = 23953) nm.

HRMS: *m*/*z* calcd for $C_{19}H_{27}FN_3OS$: 364.1859; found: 364.1891.

(*R*)-1-(3-Fluoro-4-morpholinophenyl)-3-(1-phenylethyl)thiourea (18b)

Isothiocyanate **11b** (0.62 g, 3.80 mmol) was dissolved in anhydrous MeOH (10 mL) and an equimolar quantity of primary amine **17** (0.75 g, 3.80 mmol) was added with stirring. The reaction mixture was heated to reflux for 2 h at 65 °C, then cooled and poured into ice cold water, where thiourea was precipitated. The solid product was washed with water and was purified by column chromatography using petroleum ether and EtOAc (1:1) as the eluent. The eluents were then evaporated to afford **18b**.

Yield: 0.03 g (24%); white solid; mp 116–118 °C; $[\alpha]_D$ –87.3 (*c* 2.2, $CHCl_3$).

IR (thin film): 3240 (NH), 3010, 2857, 1581, 1514, 1449, 1375, 1343, 1305 (CS), 1254 (CF), 1223, 1212, 1155, 1113, 1069, 1023, 920, 859, 818, 792, 726.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.4 (s, br, NH), 7.3 (m, 2 H), 7.3 (m, 3 H), 6.9 (m, 3 H), 6.1 (s, br, NH), 5.6 (m, 1 H), 3.8 (m, 4 H), 3.0 (m, 4 H), 1.5 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.1, 155.5 (J_{C-F} = 250.9 Hz), 142.1, 141.6, 139.3, 128.8, 127.7, 126.2, 121.8, 119.4, 114.4 (J_{C-F} = 22.6 Hz), 66.9, 54.4, 50.6 (J_{C-F} = 2.6 Hz), 21.5.

UV: λ_{max} (MeOH) = 250 (ε = 20700) nm.

HRMS: *m*/*z* calcd for $C_{19}H_{21}FN_3OS$: 358.1389; found: 358.1377.

(*R*)-5-Fluoro-6-morpholino-*N*-(1-phenylethyl)benzo[*d*]thiazol-2-amine (19b)

Thiourea **18b** (0.08 g, 0.22 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.01 mL) in $CHCl_3$ (2 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t. The mixture was stirred at r.t. for 18 h, then the resulting solution was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by chromatography using petroleum ether and EtOAc (7:3). The combined eluents on evaporation afforded semi-solid **18b**.

Yield: 21 mg (29%); $[\alpha]_D$ +65.3 (*c* 0.3, $CHCl_3$).

IR (thin film): 3213 (NH), 2968, 2857, 2824, 1709, 1615, 1574, 1535, 1494, 1449 (CN thiazole), 1418, 1376, 1361 (CN thiazole), 1305, 1274, 1260 (CF), 1217, 1160, 1116, 1090, 1030, 999, 863, 700 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.3 (m, 2 H), 7.3 (m, 2 H), 7.2 (m, 1 H), 7.2 (d, *J* = 12.9 Hz, 1 H), 7.1 (d, *J* = 8.0 Hz, 1 H), 6.2 (s, br, NH), 4.7 (q, *J* = 6.6, 6.6, 6.7 Hz, 1 H), 3.8 (m, 4 H), 3.0 (m, 4 H), 1.6 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.4, 155.7 (J_{C-F} = 242.0 Hz), 147.6 (J_{C-F} = 13.0 Hz), 142.7, 135.5 (J_{C-F} = 11.1 Hz), 128.8, 127.7, 126.1, 125.9, 110.5 (J_{C-F} = 3.5 Hz), 106.6 (J_{C-F} = 2.4 Hz), 67.0, 55.4, 51.7 (J_{C-F} = 2.2 Hz), 23.6.

UV: λ_{max} (MeOH) = 225 (ε = 12599) nm.

HRMS: *m*/*z* calcd for $C_{19}H_{19}FN_3OS$: 356.1227; found: 356.1198.

1-(2-Fluoro-4-nitrophenyl)piperidine (20)[32]

3,4-Difluoronitrobenzene **7** (0.50 mL, 4.5 mmol) was dissolved in EtOH (20 mL), piperidine (1.15 mL, 11.6 mmol) was added and the mixture was heated to reflux for 8 h. The solvent was removed in vacuo and the residue was re-dissolved in EtOAc (20 mL) and washed with water (3 × 20 mL). The EtOAc layer was dried over Na_2SO_4, filtered and the solvent was removed in vacuo to afford **20**.

Yield: 0.64 g (64%); oil.

IR (thin film): 3088, 2937, 2854, 1601 (Ar), 1501 (NO_2), 1452, 1322 (NO_2), 1267, 1239 (CF), 1256, 1024, 946, 881, 803, 744 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.9 (dd, *J* = 2.5, 8.9 Hz, 1 H), 7.8 (dd, *J* = 2.5, 13.3 Hz, 1 H), 6.9 (t, *J* = 8.8 Hz, 1 H), 3.2 (m, 4 H), 1.7 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8 (J_{C-F} = 246.3 Hz), 146.5 (J_{C-F} = 7.9 Hz), 139.8, 121.0 (J_{C-F} = 2.8 Hz), 117.0 (J_{C-F} = 4.1 Hz), 112.5 (J_{C-F} = 26.5 Hz), 51.0 (J_{C-F} = 5.3 Hz), 25.8, 24.1.

UV: λ_{max} (MeOH) = 205 (ε = 16760) nm.

HRMS: *m*/*z* calcd for $C_{11}H_{13}FN_2NaO_2$: 247.0853; found: 247.0805.

3-Fluoro-4-(piperidin-1-yl)aniline (21)[32]

The nitro compound **20** (1.02 g, 4.5 mmol) was dissolved in anhydrous MeOH (40 mL) and the reaction flask was charged with 10% palladium on carbon and hydrogenated at 45–50 psi. The resultant mixture was shaken at r.t. for 72 h. The reaction mixture was filtered through a plug of Celite and washed with MeOH (100 mL). Subsequent removal of the solvent in vacuo afforded **21**.

Yield: 0.88 g (99%); brownish oil.

IR (thin film): 3420 (NH), 3341 (NH), 3220, 2932, 2851, 2803, 1629 (Ar), 1578, 1510, 1466, 1450, 1310, 1275, 1258 (CF), 1229, 1207, 1166, 1028, 962, 838, 721 cm^{-1}.

^1H NMR (300 MHz, MeOD): δ = 8.0 (t, *J* = 7.0 Hz, 1 H), 7.5 (d, *J* = 11.8 Hz, 1 H), 7.4 (d, *J* = 7.5 Hz, 1 H), 5.3 (s, br, 2 H, NH), 3.7 (s, 4 H), 2.1 (s, 4 H), 1.8 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3 (J_{C-F} = 253.0 Hz), 137.2 (J_{C-F} = 10.6 Hz), 127.5, 124.6, 119.3, 111.5 (J_{C-F} = 23.7 Hz), 56.4, 23.2, 20.8.

UV: λ_{max} (MeOH) = 206 (ε = 15606) nm.

(*R*)-1-(1-Cyclohexylethyl)-3-((3-fluoro-4-piperidin-1-yl)phenyl)thiourea (22a)

The isothiocyanate **11a** (0.08 g, 0.47 mmol) was dissolved in anhydrous MeOH (10 mL) and an equimolar quantity of aromatic amine **21** (0.09 g, 0.46 mmol) was added with stirring. The reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled and poured into ice cold water, where thiourea was precipitated. The solid product was washed with water and purified by column chromatography using petroleum ether and EtOAc (7:3) with 1% triethylamine as the eluent, which, on evaporation, afforded **22a**.

Yield: 0.05 g (28%); amorphous solid; $[\alpha]_D$ +32.0 (*c* 0.5, $CHCl_3$).

IR (thin film): 3268 (NH), 2928, 2852, 1509 (Ar), 1450, 1335 (CS), 1232, 1250 (CF), 1139, 919, 861, 700 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.2 Hz, NH), 6.9 (t, *J* = 9.0 Hz, 1 H), 6.9 (m, 2 H), 5.7 (s, br, NH), 4.4 (m, 1 H), 3.0 (m, 4 H), 1.8–1.0 (m, 20 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.9, 155.6 (J_{C-F} = 249.7.0 Hz), 140.8, 129.1, 121.9, 119.9, 114.0 (J_{C-F} = 22.4 Hz), 55.8, 51.9 (2C), 42.9, 29.7, 29.3, 28.9, 26.4, 26.0, 24.1, 17.3.

HRMS: *m*/*z* calcd for $C_{20}H_{29}FN_3S$: 362.2061; found: 362.2047.

(*R*)-*N*-(1-Cyclohexylethyl)-5-fluoro-6-(piperidin-1-yl)benzo[*d*]thiazol-2-amine (23a)

Thiourea **22a** (0.12 g, 0.33 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.017 mL), in $CHCl_3$ (3.4 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t. and stirred at r.t. for 18 h. The resulting solution was neutralized with saturated Na_2CO_3 and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by chromatography, eluting with petroleum ether and EtOAc (7:3) containing 1% triethylamine. The combined fractions were evaporated to afford **23a**.

Yield: 30 mg (29%); amorphous solid; $[\alpha]_D$ +35.5 (*c* 0.2, $CHCl_3$).

IR (thin film): 3219 (NH), 2928, 2852, 1615 (Ar), 1578, 1471 (CN thiazole), 1450, 1382 (CN), 1338, 1275, 1227 (CF), 1203, 924, 855, 742 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.2 (m, 2 H), 5.7 (s, br, NH), 3.5 (app p, *J* = 5.7, 5.7, 5.6, 5.6 Hz, 1 H), 2.9 (m, 4 H), 1.8–1.0 (m, 20 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.9, 155.7 (J_{C-F} = 243.3 Hz), 146.6, 136.7, 124.6, 111.0 (J_{C-F} = 3.6 Hz), 106.0 (J_{C-F} = 24.5 Hz), 57.3, 53.0 (J_{C-F} = 2.5 Hz), 43.5, 29.7, 29.4, 29.0, 26.1, 24.1, 18.0.

HRMS: *m*/*z* calcd for $C_{20}H_{28}FN_3NaS$: 384.1886; found: 384.1870.

(*R*)-1-(3-Fluoro-4-(piperidin-1-yl)phenyl)3-(1-phenyleth-yl)thiourea (22b)

Isothiocyanate **11b** (0.08 mL, 0.49 mmol) was dissolved in anhydrous MeOH (10 mL) and an equimolar quantity of aromatic amine **21** (90 mg, 0.46 mmol) was added with stirring. The reaction mixture was heated to reflux for 4 h at 65 °C, then concentrated in vacuo. The resultant mixture was redissolved in EtOAc (20 mL) and washed with water (3 × 20 mL). The EtOAc layer was dried over sodium sulphate and concentrated in vacuo. The resulting mixture was subjected to chromatography using petroleum ether and EtOAc (7:3) as the eluent. The eluents were then evaporated to afford **22b**.

Yield: 33 mg (22%); solid; $[\alpha]_D$ –59.3 (*c* 0.7, $CHCl_3$).

IR (thin film): 3253 (NH), 2934, 2853, 1509, 1451, 1332 (CS), 1250 (CF), 1232, 1136, 1121, 1025, 911, 861, 758, 725, 699 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.8 (s, br, NH), 7.3 (t, *J* = 7.5 Hz, 2 H), 7.2 (m, 3 H), 6.9 (t, *J* = 8.7 Hz, 1 H), 6.8 (m, 2 H), 6.1 (s, NH), 5.6 (m, 1 H), 3.0 (m, 4 H), 1.7 (m, 4 H), 1.6 (dt, *J* = 5.9, 5.9, 11.7 Hz, 2 H), 1.5 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.0, 155.5 (J_{C-F} = 49.7 Hz), 142.2, 140.7 (J_{C-F} = 9.3 Hz), 135.1, 128.8, 127.6, 126.1, 121.7 (J_{C-F} = 2.6 Hz), 119.8, 113.9 (J_{C-F} = 22.8 Hz), 54.3, 51.8 (J_{C-F} = 3.4 Hz), 26.0, 24.1, 17.6.

UV: λ_{max} (MeOH) = 253 (ε = 17954).

HRMS: *m*/*z* calcd for $C_{20}H_{24}FN_3NaS$: 380.1567; found: 380.1573.

(*R*)-5-Fluoro-*N*-(1-phenylethyl)-6-(piperidin-1-yl)benzo[*d*]thiazol-2-amine (23b)

Thiourea **22b** (0.14 g, 0.39 mmol) was dissolved in chloroform (15 mL) an the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.014 mL) in $CHCl_3$ (2.8 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t. and stirred at r.t. for 18 h. The mixture was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2CO_3 and concentrated in vacuo. The resulting residue was purified by chromatography using petroleum ether and EtOAc (7:3) containing 1% trimethylamine as the eluent. Evaporation of the solvents in vacuo afforded **23b**.

Yield: 0.05 g (36%); viscous oil; $[\alpha]_D$ +69.8 (*c* 0.8, $CHCl_3$).

IR (thin film): 3209 (NH), 2935, 2853, 1709, 1613 (Ar), 1574, 1534, 1466 (CN thiazole), 1450, 1356 (CN thiazole), 1276, 1226 (CF), 1144, 919, 855, 741 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.3 (m, 3 H), 7.3 (m, 2 H), 7.1 (d, *J* = 12.9 Hz, 1 H), 7.1 (d, *J* = 8.1 Hz, 1 H), 6.4 (s, br, NH), 4.7 (q, *J* = 6.7, 6.7, 6.6 Hz, 1 H), 2.9 (m, 4 H), 1.7 (m, 4 H), 1.6 (d, *J* = 6.8 Hz, 3 H), 1.5 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.4, 155.7 (J_{C-F} = 243.0 Hz), 146.7 (J_{C-F} = 12.1 Hz), 142.8, 136.9 (J_{C-F} = 11.3 Hz), 128.8, 127.7, 126.1, 125.5, 110.9 (J_{C-F} = 3.8 Hz), 106.3 (J_{C-F} = 24.6 Hz), 55.5, 52.9, 26.2, 24.1, 15.9.

HRMS: *m*/*z* calcd for $C_{20}H_{23}FN_3S$: 356.1591; found: 356.1555.

1-(2-Fluoro-4-nitrophenyl)pyrrolidine (24)

3,4-Difluoronitrobenzene **7** (2.86 g, 17.9 mmol) was dissolved in acetonitrile (30 mL), then pyrrolidine (3.32 g, 46.54 mmol) was added and the mixture was heated at 82 °C for 18 h. The resultant solution was concentrated in vacuo. The residue was recrystallized from aqueous MeOH to give desired product **24**.

Yield: 3.22 g (86%); yellow crystals; mp 134–137 °C [lit.[32] mp 137–138 °C].

IR (thin film): 3500, 2980, 2884, 1607 (Ar), 1525, 1487 (NO_2), 1460, 1481, 1300 (NO_2), 1285, 1258 (CF), 1207, 1160, 1077, 963, 880, 796, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.9 (dd, *J* = 2.5, 9.1 Hz, 1 H), 7.8 (dd, *J* = 2.5, 14.2 Hz, 1 H), 6.5 (t, *J* = 8.9 Hz, 1 H), 3.5 (m, 4 H), 2.0 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5 (J_{C-F} = 256.9 Hz), 147.3, 138.4 (J_{C-F} = 5.4 Hz), 121.9 (J_{C-F} = 1.6 Hz), 112.9 (J_{C-F} = 1.9 Hz), 112.7 (J_{C-F} = 17.9 Hz), 50.0 (J_{C-F} = 5.8 Hz), 25.4.

UV: λ_{max} (MeOH) = 206 (ε = 22213) nm.

HRMS: *m*/*z* calcd for $C_{10}H_{11}FN_2NaO_2$: 233.0697; found: 233.0227.

3-Fluoro-4-(pyrrolidin-1-yl)aniline (25)[32]

Nitro compound **24** (0.60 g, 2.85 mmol) was dissolved in anhydrous MeOH (40 mL) and the reaction flask was charged with 10% palladium on carbon and hydrogenated at 45–50 psi for 72 h. The reaction mixture was filtered through a plug of Celite and washed with MeOH (100 mL). Subsequent removal of the solvent in vacuo afforded **25**.

Yield: 0.51 g (99%); viscous oil.

IR (thin film): 3340 (NH), 3219 (NH), 2965, 2873, 1615 (Ar), 1512, 1460, 1359, 1299, 1235 (CF), 1143, 950, 851, 799, 754 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.3 (s, br, 2 H, NH), 6.6 (dd, *J* = 8.5, 9.7 Hz, 1 H), 6.4 (dd, *J* = 2.6, 14.3 Hz, 1 H), 6.4 (ddd, *J* = 0.8, 2.6, 8.5 Hz, 1 H), 3.2 (m, 4 H), 1.9 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.9 (J_{C-F} = 242.6 Hz), 139.1 (J_{C-F} = 10.0 Hz), 130.5 (J_{C-F} = 10.4 Hz), 117.0 (J_{C-F} = 5.8 Hz), 111.0, 104.5 (J_{C-F} = 24.0 Hz), 50.4, 45.4, 29.7, 24.6.

(*R*)-1-(1-Cyclohexylethyl)-3-(3-fluoro-4-(pyrrolidin-1-yl)phenyl)thiourea (22c)

Isothiocyanate **11a** (0.05 g, 0.29 mmol) was dissolved in anhydrous MeOH (10 mL) and an equimolar quantity of **25** (0.05 g, 0.27 mmol) was then added with stirring under N_2 atmosphere. The reaction mixture was heated to reflux for 3 h at 65 °C, then cooled and poured into ice cold water, in order to precipitate the thiourea. The solid product was washed with water and purified by column chromatography using petroleum ether and EtOAc (7:3) as the eluent, which, on evaporation, gave the desired product **22c**.

Yield: 10 mg (12%); brown amorphous solid; $[\alpha]_D$ +94.1 (*c* 0.3, $CHCl_3$).

IR (thin film): 3256 (NH), 2925, 2850, 1711, 1620 (Ar), 1510, 1487, 1363, 1298 (CS), 1248 (CF), 1139, 962, 865, 715 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.3 (s, br, NH), 6.8 (m, 2 H), 6.6 (m, 1 H), 5.7 (s, br, NH), 4.4 (m, 1 H), 3.4 (m, 4 H), 1.9 (m, 4 H), 1.8–0.9 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.4, 151.5 (J_{C-F} = 244.9 Hz), 137.1 (J_{C-F} = 9.4 Hz), 122.9 (J_{C-F} = 2.3 Hz), 115.4 (J_{C-F} = 6.5 Hz), 114.8, 102.4, 55.7, 49.7 (J_{C-F} = 5.1 Hz), 42.9, 29.3, 28.9, 26.4, 26.1, 26.0, 25.3, 17.3.

HRMS: *m*/*z* calcd For $C_{19}H_{28}FN_3NaS$: 372.1880; found: 372.1850.

(*R*)-*N*-(1-Cyclohexylethyl)-5-fluoro-6-(pyrrolidin-1-yl)benzo[*d*]thiazol-2-amine (23c)

Thiourea **22c** (0.07 g, 0.20 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.01 mL) in $CHCl_3$ (2 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t. and stirred at r.t. for 18 h. The resulting solution was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4

and concentrated in vacuo. The resulting residue was purified by chromatography with petroleum ether and EtOAc (7:3) as the eluents. Removal of the solvents in vacuo gave the desired product **23c**.

Yield: 0.06 g (86%); solid; $[\alpha]_D$ +28.1 (*c* 0.3, $CHCl_3$).

IR (thin film): 3216 (NH), 2924, 2852, 1702, 1615 (Ar), 1578, 1539, 1470 (CN thiazole), 1358 (CN thiazole), 1290, 1249 (CF), 1131, 850, 748, 700, 677 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.2 (d, *J* = 14.0 Hz, 1 H), 6.9 (d, *J* = 8.2 Hz, 1 H), 5.1 (s, br, NH), 3.5 (m, 1 H), 3.3 (m, 4 H), 1.9 (m, 4 H), 1.9–0.8 (m, 14 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.6, 152.9 (J_{C-F} = 240.0 Hz), 144.1, 133.6, 125.5, 106.6, 106.1, 56.9, 50.4, 43.6, 29.0, 26.4, 26.1, 24.9, 18.1.

HRMS: *m*/*z* calcd for $C_{19}H_{26}FN_3NaS$: 370.1729; found: 370.1734.

(*R*)-1-(3-Fluoro-4-(pyrrolidin-1-yl)phenyl)-3-(1-phenylethyl)thiourea (22d)

Isothiocyanate **11b** (0.21 g, 1.29 mmol) was dissolved in anhydrous MeOH (10 mL) and an equimolar quantity of **25** (0.23 g, 1.29 mmol) was added with stirring. The reaction mixture was heated for 3 h at 65 °C, then cooled and poured into ice-cold water, resulting in the thiourea being precipitated. The solid product was washed with water and purified by chromatography with petroleum ether and EtOAc (7:3) as the eluents. Subsequent evaporation of the solvents afforded **22d**.

Yield: 0.26 g (59%); amorphous solid; $[\alpha]_D$ +138.6 (*c* 1.9, $CHCl_3$).

IR (thin film): 3237 (NH), 2969, 2872, 1619 (Ar), 1514, 1486, 1364, 1303 (CS), 1232 (CF), 1179, 1147, 1022, 959, 864, 795, 757, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.7 (s, NH), 7.3 (t, *J* = 7.5 Hz, 2 H), 7.2 (m, 3 H), 6.8 (m, 2 H), 6.6 (t, *J* = 9.3 Hz, 1 H), 6.1 (br, NH), 5.7 (m, 1 H), 3.4 (m, 4 H), 1.9 (m, 4 H), 1.5 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.4, 151.3 (J_{C-F} = 244.7 Hz), 142.5, 137.0 (J_{C-F} = 9.7 Hz), 128.7, 127.4, 126.1, 125.7, 122.7, 115.4 (J_{C-F} = 6.0 Hz), 114.6, 54.1, 49.7 (J_{C-F} = 5.1 Hz), 25.3 (J_{C-F} = 1.7 Hz), 21.6.

HRMS: *m*/*z* calcd for $C_{19}H_{21}FN_3S$: 342.1435; found: 342.1422.

(*R*)-5-Fluoro-*N*-(1-phenylethyl)-6-(pyrrolidin-1-yl)benzo[*d*]thiazol-2-amine (23d)

Thiourea **22d** (0.16 g, 0.48 mmol) was dissolved in chloroform (15 mL) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br_2 (0.03 mL) in $CHCl_3$ (6 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was brought to r.t. and stirred at r.t. for 18 h. The resulting solution was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was subjected to column chromatography, eluting with toluene and EtOAc (9:1). Removal of the solvents in vacuo gave the desired product **23d**.

Yield: 0.03 g (21%); $[\alpha]_D$ +16.9 (*c* 0.7, $CHCl_3$).

IR (thin film): 3208 (NH), 2969, 2873, 1615 (Ar), 1536, 1469 (CN thiazole), 1356 (CN thiazole), 1249 (CF), 1128, 960, 851, 761, 699 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.4 (m, 2 H), 7.3 (m, 2 H), 7.2 (m, 1 H), 7.1 (d, *J* = 13.9 Hz, 1 H), 6.8 (d, *J* = 8.3 Hz, 1 H), 5.9 (s, br, NH), 4.7 (q, *J* = 6.7, 6.7, 6.7 Hz, 1 H), 3.3 (s, 4 H), 1.9 (m, 4 H), 1.6 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.8, 152.8 (J_{C-F} = 241.2 Hz), 142.9, 134.7, 128.8, 127.6, 127.5, 126.1, 106.6 (2C), 106.5 (J_{C-F} = 5.4 Hz), 55.3, 50.4 (J_{C-F} = 4.7 Hz), 24.9 (J_{C-F} = 1.3 Hz), 23.7.

HRMS: *m*/*z* calcd for $C_{19}H_{19}FN_3S$: 340.1284; found: 340.1293.

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Supporting Information

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