Synthesis of 5-Fluoroaminobenzothiazoles

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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. The discovery of several potent anti-TB agents was made about 65 years and, since then, a number of agents have been discovered. 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. 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. In particular, 2-aminobenzothiazole derivatives are reported to exhibit a wide range of biological activities such as anti-diabetic, antiepileptic, analgesic, antiinflammatory, antiallergic, antiviral, antifungal, anesthetic, antiproliferative, antimicrobial, anticancer and antitubercular action. Similarly, several reports have described the anticancer and anti-TB 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, NO2, NHAc) and thiourea derivative 2 (Figure 1) exhibited promising anti-TB and antitumor activities, respectively.

The discovery of the potent anti-TB drug bedaquiline 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). We have reported on some of our efforts in this area 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 CH2Cl2 in the presence of NaHCO3 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.

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 13C 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 correspond-
1-(2-Fluoro-4-nitrophenyl)piperazine (9)

Anhydrous reactions were performed under argon or nitrogen atmospheres. 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)

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 (NO2), 1453, 1389, 1323 (NO2), 1263, 1237 (CF), 1203, 1155, 1144, 951, 936, 880, 846, 815, 802, 745, 709 cm–1.

1H NMR (300 MHz, CDCl3): 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).

13C NMR (100 MHz, CDCl3): δ = 153.0 (JCF = 249.3 Hz), 146.0 (JCF = 7.5 Hz), 140.4 (JCF = 9.4 Hz), 121.0 (JCF = 2.9 Hz), 117.0 (JCF = 4.0 Hz), 112.5 (JCF = 26.4 Hz), 50.8 (JCF = 5.0 Hz), 45.9.

UV: λmax (MeOH): 368 (ε = 7648) nm.

HRMS: m/z calcld for C19H30FN4S: 365.2170; found: 365.2168.

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): 3292 (NH), 3197, 2936, 2854, 1729, 1626 (Ar), 1538, 1468, 1451, 1331, 1291, 1135, 1107, 1047, 997, 801 cm–1.

1H NMR (600 MHz, CDCl3): δ = 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).

13C NMR (150 MHz, CDCl3): δ = 156.3 (JCF = 242.3 Hz), 145.2 (JCF = 37.6 Hz), 129.0 (JCF = 10.3 Hz), 121.3 (JCF = 4.2 Hz), 109.8, 102.0 (JCF = 23.3 Hz), 51.5 (JCF = 62.2 Hz), 45.3.

UV: λmax (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; [α]D +13.8 (c 0.3, CHCl3).

IR (thin film): 3292 (NH), 3197, 2936, 2854, 1729, 1626 (Ar), 1538, 1513, 1455, 1304, 1318, 1266, 1233 (CF), 1220, 1137, 1061, 969, 933, 871, 833, 821, 807, 743 cm–1.

1H NMR (600 MHz, CDCl3): 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).

13C NMR (100 MHz, CDCl3): δ = 153.0 (JCF = 242.3 Hz), 145.2 (JCF = 37.6 Hz), 129.0 (JCF = 10.3 Hz), 121.3 (JCF = 4.2 Hz), 109.8, 102.0 (JCF = 23.3 Hz), 51.5 (JCF = 62.2 Hz), 45.3.

HRMS: m/z calcld for C19H30FN4S: 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 Br₂ (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 NaHCO₃ and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried over Na₂SO₄ 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; [α]₀ = 29.6 (c 0.14, CHCl₃).

IR (thin film): 3033, 2985, 2933, 2085 (NCS), 1736, 1604 (Ar), 1494, 1511, 1381, 1339 (CS), 1280, 1219 (CF), 1014, 922, 808 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.3 (m, 5 H), 6.7 (d, 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 (J= 43.5 Hz), 143.3 (J= F = 10.4 Hz), 143.0, 130.8 (J CF = 10.2 Hz), 128.7, 127.4, 126.4, 120.8 (J CF = 4.1 Hz), 110.6 (J CF = 3.0 Hz), 103.8 (J CF = 23.6 Hz), 54.6, 50.8 (J CF = 2.0 Hz), 47.7, 21.5.

UV: λmax (MeOH) = 206 (ε = 50716) nm.

HRMS: m/z calcd for C₁₉H₂₂FN₄S: 357.1544; found: 357.1510.

(R)-(−)-(1-Isothiocyanatoethyl)benzene (11b)³⁰

1,1'-Thiocarbonyldimidazole (0.14 g, 0.82 mmol) was added to a rapidly stirring mixture of CH₂Cl₂ (18 mL) and water (18 mL) at r.t., then (R)-(−)-α-methylbenzylamine (0.10 g, 0.82 mmol) was added. NaHCO₃ (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 Na₂SO₄. 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; [α]₀ = 132 (c 3.0, CHCl₃) [lit. ³⁰α [α]₀ = 4.3 (c 1.0, acetone); lit. ³⁰α [α]₀ = −17.3 (CHCl₃)].

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, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): δ = 140.0, 132.1, 128.8, 128.1, 125.3, 56.9, 24.9.

UV: λmax (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; [α]₀ = −20.8 (c 0.8, CHCl₃).

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

1H NMR (400 MHz, CDCl₃): 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 (J= 43.5 Hz), 143.3 (J= F = 10.4 Hz), 143.0, 130.8 (J CF = 10.2 Hz), 128.7, 127.4, 126.4, 120.8 (J CF = 4.1 Hz), 110.6 (J CF = 3.0 Hz), 103.8 (J CF = 23.6 Hz), 54.6, 50.8 (J CF = 2.0 Hz), 47.7, 21.5.

UV: λmax (MeOH) = 206 (ε = 50716) nm.

HRMS: m/z calcd for C₁₉H₂₂FN₄S: 357.1544; found: 357.1510.

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

The piperazine substituted nitro aromatic 8 (2.10 g, 9.32 mmol) was dissolved in CH₂Cl₂ (20 mL). Triethylamine (1.30 mL, 9.32 mmol) and the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br₂ (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 NaHCO₃ and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried over Na₂SO₄ 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; [α]₀ = −66.7 (c 0.2, CHCl₃).

IR (thin film): 3340, 1627 (Ar), 1418, 1386 (CN thiazole), 1257 (CF), 1222 cm⁻¹.

1H NMR (600 MHz, CDCl₃): 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).

13C NMR (100 MHz, CDCl₃): δ = 174.9, 156.8, 144.2, 140.4 (J CF = 11.0 Hz), 132.2 (J CF = 37.3 Hz), 128.6, 127.7, 126.1, 123.7 (J CF = 3.9 Hz), 103.9 (J CF = 25.2 Hz), 103.1, 51.0, 50.2, 44.0, 22.5.

HRMS: m/z calcd for C₁₉H₁₂FN₄S: 357.1544; found: 357.1483.
UV: $\lambda_{\text{max}}$ (MeOH) = 352 (ε = 20379) nm.
HRMS: m/z calcd for C$_{17}$H$_{27}$FN$_{4}$O$_{2}$S: 578.0918; found: 578.0876.

3-Fluoro-4-(4-tosylpiperazin-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 2 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$_3$): $\delta$ = 7.6 (d, $J = 8.2$ Hz, 2 H), 7.3 (d, $J = 8.1$ Hz, 2 H), 6.7 (l, $J = 8.8$ 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).

13C NMR (150 MHz, CDCl$_3$): $\delta$ = 155.4 ($J_{C,F}$ = 158.4 Hz), 143.8, 143.4, 143.3, 132.3, 125.7, 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: $\lambda_{\text{max}}$ (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, 0.32 mmol) was dissolved in anhydrous MeOH (20 mL) and an equimolar quantity of 10b (111.8 mg, 0.32 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 give 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$_3$): $\delta$ = 7.6 (d, $J = 8.2$ Hz, 2 H), 7.3 (d, $J = 8.0$ Hz, 2 H), 6.7 (l, $J = 8.8$ Hz, 1 H), 6.4 (m, 2 H), 5.7 (s, NH), 4.1 (q, $J = 7.2$, 2.2 Hz, 2 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).

13C NMR (150 MHz, CDCl$_3$): $\delta$ = 176.0, 165.7 ($J_{C,F}$ = 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: $\lambda_{\text{max}}$ (MeOH) = 230 (ε = 25484) nm.
HRMS: m/z calcd for C$_{26}$H$_{35}$FN$_{4}$NaO$_{2}$S: 541.2083; found: 541.2099.

(R)-5-Fluoro-6-(1-phenylethyl)-6-(4-tosylpiperazin-1-yl)benzod[1]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$_2$Cl$_2$ (3 × 10 mL). The combined organic phases were dried over Na$_2$SO$_4$ 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), 2981, 2099, 1600, 1474 (CN thiazole), 1393 (CN thiazole), 1329 (SO$_2$), 1217 (CF), 1158 (SO$_2$), 1035, 805, 726 cm$^{-1}$.

HRMS: m/z calcd for C$_{26}$H$_{35}$FN$_{4}$NaO$_{2}$S: 541.2083; found: 541.2099.
1H NMR (300 MHz, CDCl3): δ = 8.0 (m, 1 H), 7.9 (dd, J = 2.6, 13.1 Hz, 1 H), 6.9 (J = 8.7 Hz, 1 H), 3.9 (m, 3.3 H, 4 H).

3-Fluoro-4-morpholinophenol (17)  

The nitro compound 16 (1.00 g, 4.4 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 rt. 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: 0.89 g (92%); slightly pink solid; mp 116–117 °C.

HRMS: m/z calcd for C19H27FN3OS: 364.1859; found: 364.1850.

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: 0.60 g (30%); off-white solid; mp 128–131 °C; [α]D 16.0 (c 2.7, CHCl3).

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.

1H NMR (600 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): δ = 179.9, 155.7 (JCF = 249.0 Hz), 139.4 (JCF = 160.0 Hz), 130.0 (JCF = 8.0 Hz), 121.9, 119.5, 114.2 (JCF = 22.0 Hz), 66.9, 55.9, 50.7 (JCF = 3.0 Hz), 42.9, 29.3, 28.9, 26.4, 17.3.

UV: λmax (MeOH) = 360 (ε = 66571) nm.

HRMS: m/z calcd for C19H27FN3OS: 364.1859; found: 364.1850.
an equimolar quantity of Br₂ (0.01 mL) in CHCl₃ (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 NaHCO₃ and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄ 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%); amorphous solid; [α]₀ +65.3 (c 0.3, CHCl₃).

IR (thin film): 3088, 2937, 2854, 1601 (Ar), 1501 (NO₂), 1452, 1322 (C–NO₂), 1260 (CF), 1217, 1166, 1028, 962, 838, 721 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 8.0 (d, 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).

13C NMR (150 MHz, CDCl₃): δ = 155.3 (J₋₋₋ = 253.0 Hz), 137.2 (J₋₋₋ = 10.6 Hz), 127.5, 124.6, 119.3, 111.5 (J₋₋₋ = 23.7 Hz), 56.4, 23.2, 20.8.

UV: λ_max (MeOH) = 206 (c = 15600) nm.

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

The isothiocynate 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; [α]₀ +32.0 (c 0.5, CHCl₃).

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, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): δ = 179.9, 155.6 (J₋₋₋ = 249.7 Hz), 140.8, 129.1, 121.9, 119.9, 114.0 (J₋₋₋ = 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 C₁₉H₂₁FN₃O₂S: 362.2061; found: 362.2047.

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

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, 2038, 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).

13C NMR (75 MHz, CDCl₃): δ = 155.3 (J₋₋₋ = 253.0 Hz), 137.2 (J₋₋₋ = 10.6 Hz), 127.5, 124.6, 119.3, 111.5 (J₋₋₋ = 23.7 Hz), 56.4, 23.2, 20.8.

UV: λ_max (MeOH) = 360 (c = 15600) nm.

HRMS: m/z calcd for C₁₉H₂₀FN₃O₂S: 384.1886; found: 384.1870.
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**Paper**

(R)-1-{(3-Fluoro-4-(piperidin-1-yl)phenyl)3-(1-phenylethyl)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 resulting 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 residue was recrystallized from petroleum ether and EtOAc (7:3) as the eluent. The eluents were then evaporated to afford 22b.

Yield: 33 mg (22%); solid; [α]_D+59.3 (c 0.7, CHCl₃).

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

HRMS: m/z calcd for C₂₀H₂₄FN₃NaS: 380.1567; found: 380.1573.

UV: λ_max (MeOH) = 253 (ε = 17954).

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): δ = 167.4, 155.7 (J_C-F = 243.0 Hz), 146.7 (J_C-F = 121.2 Hz), 142.8, 136.9 (J_C-F = 11.3 Hz), 128.8, 127.7, 126.1, 125.5, 110.3 (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 C₁₀H₁₁FN₂O₂: 233.0697; found: 233.0697.

23b

Thiourea (0.07 g, 0.20 mmol) was dissolved in chloroform (15 mL) an the reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br₂ (0.01 mL) in CHCl₃ (3 × 10 mL) was added with stirring under N₂ atmosphere. The reaction mixture was cooled and the reaction mixture was brought to r.t. and stirred at r.t. for 18 h. The reaction mixture was cooled in an ice bath. Subsequently, an equimolar quantity of Br₂ (0.014 mL) in CHCl₃ (2.8 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was 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; [α]_D+59.3 (c 0.7, CHCl₃).

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

HRMS: m/z calcd for C₁₀H₁₁FN₂O₂: 233.0697; found: 233.0697.

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

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, 1487, 1460, 1359, 1299, 1235 (CF), 1143, 950, 851, 799, 754 cm⁻¹.

HRMS: m/z calcd for C₁₉H₂₈FN₃NaS: 372.1880; found: 372.1850.

UV: λ_max (MeOH) = 253 (ε = 17954).

(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 N₂ 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; [α]_D+94.1 (c 0.3, CHCl₃).

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

HRMS: m/z calcd for C₁₉H₂₈FN₃Na₂O₂: 380.1567; found: 380.1573.

IR (thin film): 3500, 2980, 2884, 1607 (Ar), 1525, 1487 (NO₂), 1460, 1481, 1300 (NO₂), 1285, 1258 (CF), 1207, 1160, 1077, 963, 880, 796, 742 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): 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 C₁₉H₁₉FN₃O₂: 323.0697; found: 323.0227.

3-Fluoro-4-(pyrrolidin-1-yl)aniline (25)

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.

HRMS: m/z calcd for C₁₉H₂₈FN₃NaS: 372.1880; found: 372.1850.

UV: λ_max (MeOH) = 253 (ε = 17954).

HRMS: m/z calcd for C₁₉H₂₈FN₃Na₂O₂: 380.1567; found: 380.1573.
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): 3237 (NH), 2969, 2872, 1619 (Ar), 1514, 1486, 1364, 1249, 1229, 1128, 1061, 960, 851, 761, 699 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 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), 1.9–2.0 (m, 14 H).

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 116.6, 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$_{10}$H$_{12}$FN$_3$: 370.1729; found: 370.1732.

(R)-1-(3-Fluoro-4-(pyrrolidin-1-yl)-phenyl)-3-(1-phenylethyl)-thiourea (23d)

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 ºC, 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: 0.07 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, 1127, 1022, 959, 864, 795, 757, 698 cm$^{-1}$.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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, 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$_{19}$FN$_3$: 340.1284; found: 340.1293.

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Supporting Information

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