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 antidiabetic, antiepileptic, analgesic, antiinflammatory, anthelmintic, 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.

![Figure 1](image1.png)

The discovery of the potent anti-TB drug bedaquiline 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).

![Figure 2](image2.png)

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. 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. 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.

In considerations of these findings, and in continuation of our research in the development of novel bioactive molecules, 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 and 6-substituted 5-fluoro-2-(N-substituted)aminobenzothiazole derivatives is summarised in Scheme 1. The optically active isothiocyanates were prepared by the reaction of appropriate chiral amines with thiophosgene in aqueous CH$_2$Cl$_2$ in the presence of NaHCO$_3$ at room temperature. Treatment of the appropriate isothiocyanates 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 in 31–55% yields.

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

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

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.
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1-(2-Fluoro-4-nitrophenyl)piperazine (9)

atmospheres. Anhydrous reactions were performed under argon or nitrogen using the Bruker 600, 400 or 300 MHz spectrometer in the deuterated solvents DMSO-d6 and CDCl3. The IR spectra were recorded in chloroform and MeOH (1:1). All 1H NMR spectra were recorded with a Bruker 600 MHz spectrometer in CDCl3 with TMS as an internal reference and with DMSO-d6 as the internal standard. The 13C NMR spectra were recorded with a Bruker 150 MHz spectrometer. The UV spectra were recorded in MeOH with a Varian Cary 300 spectrophotometer. 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 polarimeter at λ = 589 nm. All NMR spectra were recorded with a Bruker 600 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 (1.43 g, 8.98 mmol) was dissolved in acetonitrile (30 mL). Piperazine (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), 1455, 1304, 1318, 1263, 1233 (CF), 1220, 1137, 1061, 969, 933, 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 = 29.3 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 calc for C10H12FN3O2Na: 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): 3228 (NH), 2911, 2849, 1602 (Ar), 1497 (NO2), 1455, 1304, 1318, 1263, 1233 (CF), 1220, 1137, 1061, 969, 933, 871, 833, 821, 807, 743 cm⁻¹.

1H NMR (600 MHz, CDCl3): 1.9 (s, br, 1 H), 1.6–1.1 (m, 14 H), 3.9 (m, 4 H), 3.3 (m, 4 H), 1.8 (s, br, 1 H). 13C NMR (150 MHz, CDCl3): 129.0 (JCF = 249.3 Hz), 146.0 (JCF = 7.5 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): 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): 3228 (NH), 2911, 2849, 1729, 1626 (Ar), 1538, 1513, 1446, 1409, 1364, 1343, 1305 (CS), 1280, 1242 (CF) 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 (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)-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: 0.06 g (45%); light-brown amorphous solid; [α]₂⁰ –29.6 (c 0.14, CHCl₃).

IR (thin film): 3342 (NH), 2924, 2852, 1708, 1625 (Ar), 1507, 1449 cm⁻¹.

UV: max (MeOH) = 206 (ε 50716) nm.

HRMS: m/z calcd for C₁₉H₂₂FN₄S: 357.1544; found: 357.1483.

(R')-(+)-(1-Isothiocyanatoethyl)benzene (11b)

1.1'-Thiocarbonylindimidazole (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')-(+)-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]₂⁰ –13.2 (c 0.30, CHCl₃) [lit.30a [α]₂⁰ –4.3 (c 1.0, acetone); lit.30b [α]₂⁰ +66.7 (c 0.2, 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]₂⁰ –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 (JC–F = 43.5 Hz), 143.3 (JC–F = 10.4 Hz), 143.0, 130.8 (JC–F = 10.2 Hz), 128.7, 127.4, 126.4, 120.8 (JC–F = 4.1 Hz), 110.6 (JC–F = 3.0 Hz), 103.8 (JC–F = 23.6 Hz), 54.6, 50.8 (JC–F = 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.

(12b) 2.10 g, 9.32 mmol) was dissolved in CH₂Cl₂ (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 (NO₂), 1445, 1391, 1336 (NO₂), 1281, 1235 (CF), 1213, 1157 (SO₂), 1114, 1079, 945, 926, 885, 805 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): δ = 153.2 (JC–F = 249.5 Hz), 144.8 (JC–F = 8.0 Hz), 144.1, 141.4 (JC–F = 8.8 Hz), 132.2, 129.9, 127.9, 120.9 (JC–F = 3.2 Hz), 117.6 (JC–F = 3.5 Hz), 112.6 (JC–F = 26.3 Hz), 49.1 (JC–F = 4.6 Hz), 45.8, 21.6.

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UV: $\lambda_{\text{max}}$ (MeOH) = 352 (ε = 20379) nm.
HRMS: m/z calcd for C$_7$H$_7$F$_2$NO$_3$: 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 vacuum afforded 10b.

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

IR (thin film): 3434 (NH), 3363 (NH), 2923, 1638, 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, $J$ = 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).

13C NMR (150 MHz, CDCl$_3$): $\delta$ = 155.4 ($J_{C,F}$ = 158.4 Hz), 143.8, 143.4, 143.3, 132.5, 129.7, 129.9, 129 (J$_{C,F}$ = 4.0 Hz), 110.6 ($J_{C,F}$ = 3.0 Hz). 1037.4 ($J_{C,F}$ = 23.7 Hz), 50.8 ($J_{C,F}$ = 2.0 Hz). 46, 21.5.

UV: $\lambda_{\text{max}}$ (MeOH) = 234 (ε = 13777) nm.

IR (thin film): 3253 (NH), 3069, 3027, 2967, 1545, 1495, 1451, 1346 (SO$_2$), 1332, 1278, 1260 (CF), 1206, 1163 (SO$_3$), 1118, 1087, 1011, 949, 815, 759, 696 cm$^{-1}$.

1H NMR (600 MHz, CDCl$_3$): $\delta$ = 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).

13C NMR (150 MHz, CDCl$_3$): $\delta$ = 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, 50.7, 46.3, 29.7, 21.5.

UV: $\lambda_{\text{max}}$ (MeOH) = 231 (ε = 18750) nm.
HRMS: m/z calcd for C$_{26}$H$_{35}$F$_{2}$N$_{4}$O$_{2}$S$_{2}$: 541.2083; found: 541.2099.

(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, 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 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$_3$), 1118, 1019, 987, 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 (t, $J$ = 8.8 Hz, 1 H), 6.4 (m, 2 H), 5.7 (s, NH), 4.1 (q, $J$ = 7.2, 7.2 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, 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: $\lambda_{\text{max}}$ (MeOH) = 230 (ε = 25484) nm.
HRMS: m/z calcd for C$_{26}$H$_{35}$FN$_{4}$NaO$_{2}$S$_{2}$: 541.2083; found: 541.2099.

(R)-5-Fluoro-N-(1-phenylethyl)-6-(4-tosylpiperazin-1-yl)benz[d]thiazol-2-amine (15b)
The thioamide 13a (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 mmol) 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), 2924, 2854, 1709, 1537, 1440, 1453 (CN thiazole), 1350 (CN thiazone), 1330, 1219 (CF), 1165, 1093, 984, 862, 731, 701 cm$^{-1}$.

1H NMR (600 MHz, CDCl$_3$): $\delta$ = 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).
(R)-N-(1-Cyclohexylethyl)-5-fluoro-6-morpholinobenzothiazole-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 Br2 (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; [α]D −16.0 (c 1.3, CHCl3).

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.

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

13C NMR (150 MHz, CDCl3): δ = 176.2, 155.6 (JCF = 244.0 Hz), 146.9 (JCF = 12.0 Hz), 135.4 (JCF = 11.0 Hz), 124.6, 110.7, 105.9 (JCF = 24.0 Hz), 67.1, 57.7, 51.7 (JCF = 2.0 Hz), 43.6, 29.1, 26.2, 21.4, 18.0.

UV: λmax (MeOH) = 225 (ε = 1800) nm.

HRMS: m/z calcd for C19H27F2N5O5S: 364.1859; found: 364.1891.

(R)-1-(3-Fluoro-4-morpholinophenyl)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; [α]D −87.3 (c 2.2, CHCl3).

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.

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

13C NMR (150 MHz, CDCl3): δ = 180.1, 155.5 (JCF = 250.9 Hz), 142.1, 141.6, 139.3, 128.8, 127.7, 126.2, 121.8, 119.4, 114.4 (JCF = 22.6 Hz), 66.9, 54.4, 50.6 (JCF = 2.6 Hz), 21.5.

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UV: \( \lambda_{\text{max}} \) (MeOH) = 250 (\( \varepsilon = 20700 \)) nm.

HRMS: \( m/z \) calcd for \( \text{C}_{10}\text{H}_{13}\text{FN}_{2}\text{NaO}_{2} \): 247.0853; found: 247.0805.

1-(5-Fluoro-6-(piperidin-1-yl)benzo[d][1,3]thiazol-2-amine (23a))

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 23a.

Yield: 0.05 g (28%); amorphous solid; \([\alpha]_{D}^{20} +32.0^\circ \) (c 0.5, CHCl\(_3\)).

IR (thin film): 3213 (NH), 2968, 2857, 2824, 1709, 1615, 1574, 1535, 1471 (CN thiourea), 1338, 1275, 1258, 1090, 863, 744 cm\(^{-1}\).

HRMS: \( m/z \) calcd for \( \text{C}_{20}\text{H}_{28}\text{FN}_{3}\text{NaS} \): 384.1886; found: 384.1870.

(5)-1-(1-Cyclohexylethyl)-5-fluoro-6-(piperidin-1-yl)phenyl thiourea (22a)

Thiourea 22a (0.012 g, 0.02 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\(_2\)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 using petroleum ether and EtOAc (7:3). The combined eluents on evaporation afforded semi-solid 22b.

Yield: 0.21 mg (29%); [\( \alpha \)]\(_{D}^{20} \) +65.3\(^\circ \) (c 0.3, CHCl\(_3\)).

IR (thin film): 3420 (NH), 3341 (NH), 3220, 2928, 2852, 1509 (Ar), 1450, 1335 (CS), 1232, 1250 (CF), 1139, 919, 861, 700 cm\(^{-1}\).

UV: \( \lambda_{\text{max}} \) (MeOH) = 20700 nm.

HRMS: \( m/z \) calcd for \( \text{C}_{19}\text{H}_{19}\text{FN}_{3}\text{S} \): 356.1227; found: 356.1198.

3-Fluoro-4-(piperidin-1-yl)aniline (21)

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 resulting 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\(^{-1}\).

1\(^H\) NMR (300 MHz, MeOD): \( \delta = 8.0 \) (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).

1\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 155.3 \) (\( J_{C-F} = 253.0 \) 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: \( \lambda_{\text{max}} \) (MeOH) = 206 (\( \varepsilon = 15600 \)) nm.
(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 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: 3.22 g (86%); yellow crystals; mp 134–137 °C [lit.32 mp 137–138 °C].

(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, 1481, 1460, 1363, 1298 (CS), 1248 (CF), 1139, 962, 865, 715 cm–1.

UV: \( \lambda_{\text{max}} (\text{MeOH}) = 253 \) (\( \lambda_{\text{max}} (\text{MeOH}) = 253 \) nm).

HRMS: \( m/z \) calcd for C_{19}H_{28}FN_{3}NaS: 372.1880; found: 372.1850.

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Yield: 0.26 g (59%); amorphous solid; as the eluents. Subsequent evaporation of the solvents afforded thiourea being precipitated. The solid product was washed with water and concentrated in vacuo, then cooled and poured into ice-cold water, resulting in the reaction mixture was heated for 3 h at 65 °C, then cooled and poured into ice-cold water, resulting in the isothiocyanate (0.16 g, 0.48 mmol) was dissolved in chloroform (15 mL) and an equimolar quantity of Br2 (0.03 mL) in CHCl3 (6 mL) was added to the reaction mixture. The ice bath was removed and the reaction mixture was subjected to column chromatography with petroleum ether and EtOAc (7:3) as the eluents. Removal of the solvents in vacuo gave the desired product 22d.

Yield: 0.06 g (86%); solid; [α]D +28.1 (c 0.3, CHCl3).

HRMS: m/z calcd for C19H21FN3S: 342.1435; found: 342.1422.


