Synthesis of 3-Aryl-3-Sulfanyl Azetidines by Iron Catalyzed Thiol Alkylation with N-Cbz Azetidinols

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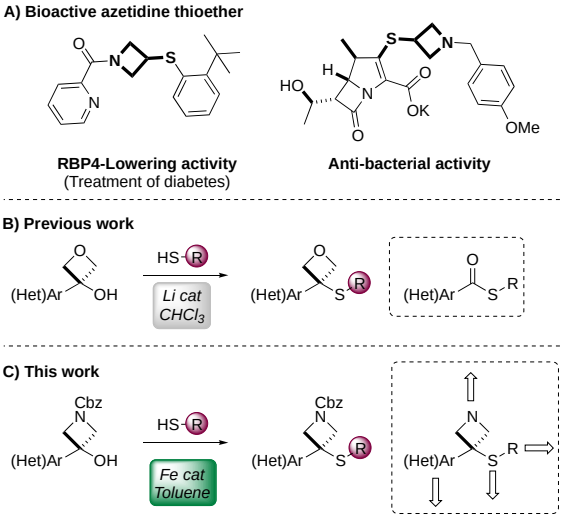
ABSTRACT: New small ring derivatives can provide valuable motifs in new chemical space for drug design. 3-Aryl-3-sulfanyl azetidines are synthesized directly from azetidine-3-ols in excellent yield by a mild Fe-catalyzed thiol alkylation. A broad range of thiols and azetidinols bearing electron donating aromatics are successful, proceeding via an azetidine carbocation. The *N*-Cbz group is a requirement for good reactivity, and enables the NH-azetidine to be revealed. Further reactions of the azetidine sulfides demonstrate their potential for incorporation in drug discovery programs.

New chemical motifs with appropriate physicochemical properties offer valuable opportunities in drug design.[1,2] As a result, there has been significant recent attention on the synthesis of new modules that may be readily incorporated in medicinal chemistry, as fragments, building blocks or isosteres.[3] Small heterocyclic rings are attractive in this context due to low molecular weight and defined exit vectors.[4,5] Small rings readily access new chemical and IP space, particularly when combined with medicinally relevant substituents, which is partly due to their limited synthetic accessibility preventing their investigation. Sulfur functional groups are prevalent in pharmaceuticals and agrochemicals,[6] with thioethers being important in their own right and as intermediates to access sulfoxide, sulfone and sulfoximine moieties. There are examples of azetidine thioethers in biologically active compounds in the literature with the majority 3-monosubstituted, including compounds having RBP4-lowering activity and antibacterial activity (Figure 1A).[7,8] 3,3-Disubstituted azetidine sulfides, without additional C2 or C4

substituents, are largely unexplored.[9,10] Synthetic reports include the addition of thiols to azetidine Michael-acceptors,[10a,3d] ring expansion of aziridines,[10b,c] or trifluoromethylthiolation of an azetidine nitrile anion.[10d] As part of our interests in the preparation of 4-membered rings substituted with sulfur groups, as fragments[11] and bioisosteres,[12] we became interested in 3-aryl-3-sulfanylazetidines as novel achiral architectures for incorporation in medicinal chemistry programs.

Figure 1. Bioactive azetidine thioethers and targeted 3-aryl-3-azetidine sulfides.

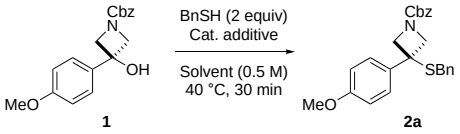


Catalytic functionalization of π-activated alcohols provides an attractive synthetic approach as it avoids pre-activation, and generates only water as a by-product.[13,14] We recently reported the synthesis of 3,3-diaryloxetanes[15] and 3,3-diarylazetidines[16] by a catalytic Friedel-Crafts alkylation with tertiary benzylic oxetan-3-ols and azetidin-3-ols. Relatively few examples of thioetherification of functionalized activated alcohols can be found in the literature, often requiring higher loadings of expensive metal catalyst or harsher conditions.[17] We previously used Li(NTf_2) as a catalyst for thiol alkylation with secondary and tertiary benzylic alcohols including oxetanols (Figure 1B).[12] Notably, iron catalysis for alcohol activation remains under developed,[18] but offers a more sustainable approach than many other catalyst systems, compatible with greener reaction conditions. Samec has reported limited examples of thiol etherification with alcohols using $FeCl_3$, in a comparison of nucleophile reactivity across different catalysts and substrates.[19]

Here, the preparation of azetidine sulfides is reported through an iron-catalyzed alkylation of thiols with readily available 3-arylazetidin-3-ols (Figure 1C). The use of inexpensive $FeCl_3$ is suitable as a catalyst and is sufficiently mild to be compatible with the azetidine, despite the additional demands on forming a carbocationic intermediate on the strained ring. The functionalization of 3-aryl-3-sulfanylazetidines through a range of chemical transformations demonstrates the applicability of this method to prepare drug-like molecules for medical chemistry.

Building on our prior studies,[12,16] the alkylation of benzylmercaptan was investigated with azetidinol **1** (Table 1). Pleasingly, applying the conditions previously successful for oxetanes using 2 equiv BnSH, lithium triflimide and an ammonium salt as a catalyst, in chloroform at 40 °C for 30 min, gave sulfanyl azetidine **2a** in 88% yield (Table 1, entry 1). Calcium triflimide[14c,d] and iron chloride increased the yield of azetidine **2a** (entry 2 and 3), whereas they were less reactive for oxetanols. Iron chloride was chosen as the preferred catalyst as it is more abundant and over 100 times less expensive than calcium triflimide.[20] Various solvents were well tolerated (entries 4-6), and toluene was selected as an environmentally benign option with excellent yield.[21] Decreasing the catalyst loading from 20 to 5 mol% resulted in reduced yield of 90% (entry 7). A catalyst loading of 7.5 mol % $FeCl_3$ was chosen as optimal with a yield of 98% in just 30 min for these reactants (entry 8). Boc protected azetidinol (**Boc-1**) gave no product under these conditions (entry 9), consistent with the Cbz protecting group enhancing the reactivity of the azetidinols as previously reported. However, a 14% yield of **Boc 2a** was achieved using $Ca(NTf_2)_2$ (5 mol %), nBu_4NPF_6 (5 mol %), and 3 equiv benzylmercaptan in toluene (0.5 M) at 40 °C for 15 h.[22] Finally, in absence of catalyst the starting material was recovered unreacted.

Table 1. Selected optimization studies for thioalkylation of azetidinol 1 with benzylmercaptan.

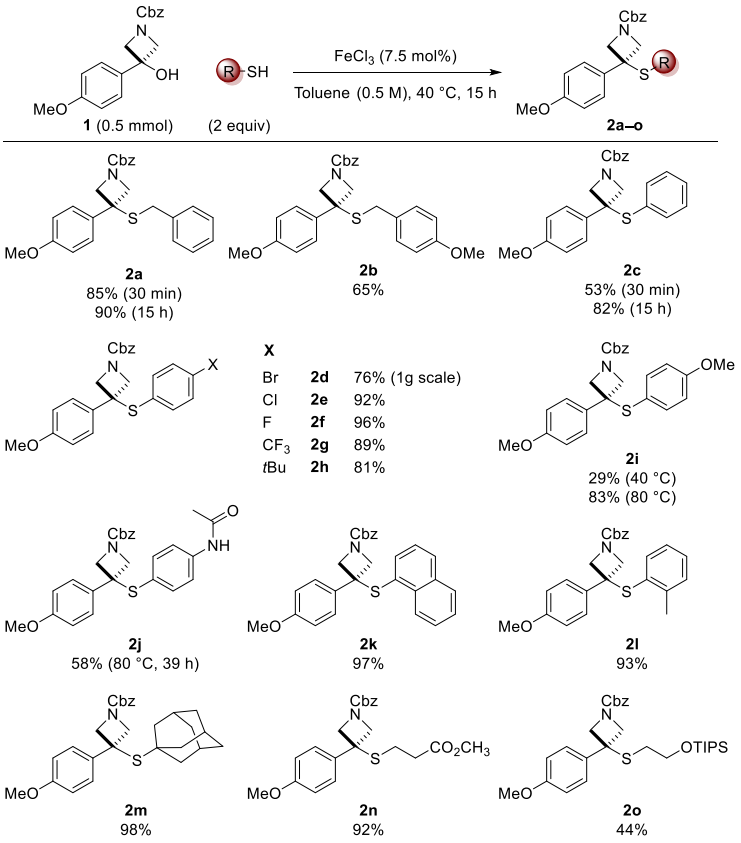


Entry[a]	Cat/additive (mol%)	Solvents	Yield[b] **2a** (%)
1	$Li(NTf_2)/Bu_4NPF_6$ (11/5.5)	$CHCl_3$	88
2	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5)	$CHCl_3$	99
3	$FeCl_3$ (20)	$CHCl_3$	97
4	$FeCl_3$ (20)	CH_2Cl_2	100
5	$FeCl_3$ (20)	EtOAc	73
6	$FeCl_3$ (20)	Toluene	100
7	$FeCl_3$ (5)	Toluene	90
8	$FeCl_3$ (7.5)	Toluene	98
9[c]	$FeCl_3$ (7.5)	Toluene	0
10[c]	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5)	Toluene	14
11	No catalyst	Toluene	0[d]

[a] Using 0.25 mmol of **1**. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Using 0.25 mmol of *N*-Boc protected azetidinol **Boc-1**. [d] 98% Starting material **1** returned.

Different thiols were examined under the standard conditions using azetidinol **1** (Scheme 1). Benzyl mercaptan successfully afforded **2a** in excellent yield in 30 min. 4-Methoxybenzyl mercaptan and aromatic thiols required longer reaction times and leaving the reaction for 15 h gave **2b** in good yield and increased the yield of **2c** to 82%. Pleasingly, thiophenols bearing electron-withdrawing or donating groups such as Br, Cl, F, CF_3 and *t*Bu gave **2d**–**2h** all in excellent yields. The reaction was readily scaled to prepare >1 g of **2d** using bromothiophenol. Methoxybenzenethiol and an acetamide derivative required higher temperature to overcome catalyst coordination and solubility issues, giving **2i** in 83% yield and **2j** in 58% yield. 1-Naphthalenethiol and *ortho*-methylbenzenethiol were also well tolerated to give **2k** and **2l** in 97% and 93% yield respectively. Alkyl thiols were similarly successful, including bulky adamantane-thiol (**2m**), ester (**2n**) and TIPS-protected alcohol (**2o**) derivatives.

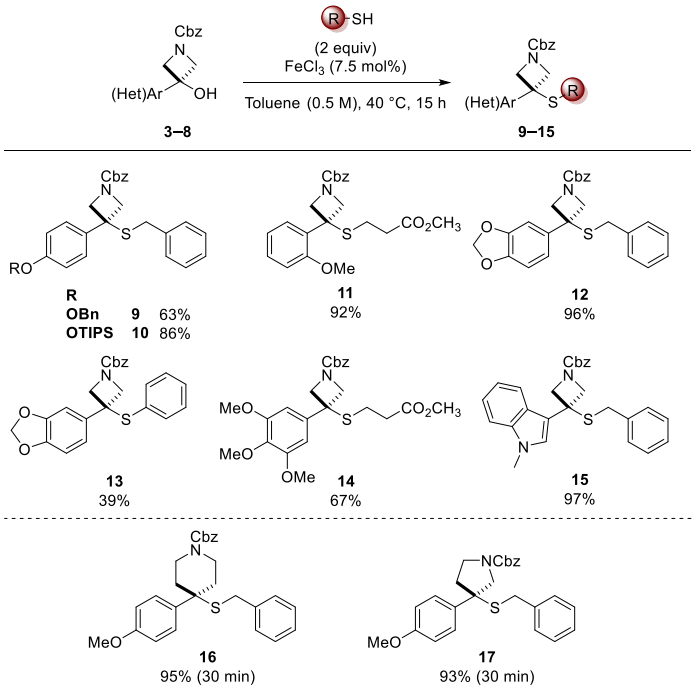
Scheme 1. Scope of thiols using azetidinol 1.[a]



[a] Isolated yields quoted.

Alternative 3-aryl-azetidin-3-ol substrates (**3**-**8**) were prepared by the addition of Grignard reagents to commercially available *N*-Cbz azetidine-3-one (Scheme 2).[16] Preinstalled benzyl- and TIPS-protected phenols were tolerated under the reaction conditions producing **9** and **10** in excellent yield. Increasing the steric demands of the azetidinol with *ortho*-substituted aromatics gave azetidine **11** in 92% yield. Benzodioxole and trimethoxybenzene azetidinols reacted similarly well giving products **12** to **14** in good yield using benzylic, aryl or alkyl thiols respectively as nucleophiles. Importantly, indole containing sulfanylazetidine **15** was formed in 97% yield. As such, a range of 3-sulfanyl azetidines can be readily prepared with appealing functionalities of interest to medicinal chemists, varying both the thiol and preinstalled aryl group. 3-Phenylazetidin-3-ol returned starting material, even increasing the temperature to 80 °C, indicating the need for electron-rich aromatics to stabilize the postulated azetidine carbocation intermediate. The reaction could be extended to the 5 and 6-membered *N*-heterocycles giving piperidine **16** and pyrrolidine **17** in 95% and 93% yield respectively using benzylmercaptan.

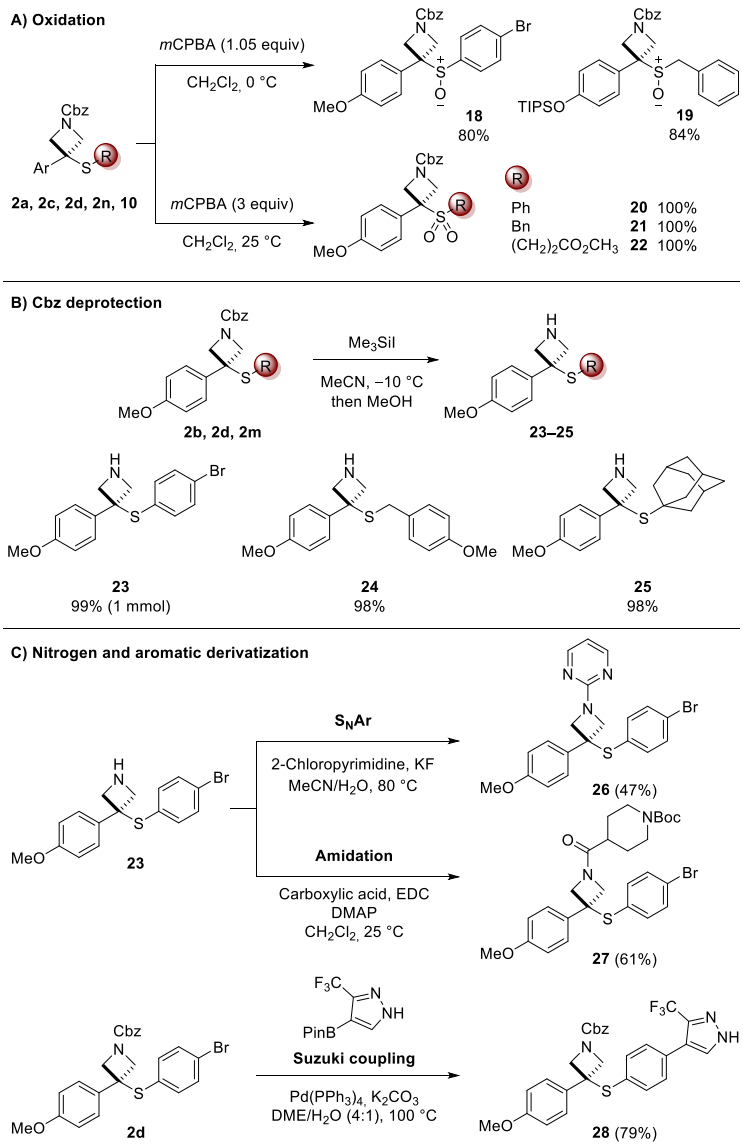
Scheme 2. Scope of azetidinols.[a]



[a] Isolated yields quoted.

The derivatization of various 3-sulfanyl azetidines was undertaken to demonstrate the applicability of this method to access drug-like compounds. Oxidation of the azetidine sulfides with *m*CPBA selectively formed 3-sulfinylazetidines **18** and **19** or 3-sulfonylazetidines **20**–**22** in excellent yields (Scheme 3A).[23] To exploit the amine functionality, removal of the Cbz protecting group was investigated on azetidine sulfide **2d** (Scheme 3B). Typical conditions employing H_2 and Pd/C, Brønsted acid, or $LiAlH_4$ were unsuccessful. Instead, subjecting azetidine **2d** to Me_3SiI followed by addition of methanol revealed the amine functionality **23** in 99% yield.[24] In addition, benzylic and alkyl azetidine sulfides **2b** and **2m** were also tolerated under these conditions affording amines **24** and **25** in quantitative yields, and provided building blocks for further reactions. Amine **23** was derivatized through an S_NAr reaction with 2-chloropyrimidine to give azetidine **26** in 47% yield, and piperidine amide **27** could be installed in 61% yield (Scheme 3C). Finally, Suzuki-Miyaura cross-coupling of the bromide functionality afforded pyrazole **28** in 79% yield, also demonstrating the stability of the 3-sulfanylazetidine to high temperature.

Scheme 3. Derivatization of azetidinyl sulfides.[a]



[a] Isolated yields quoted

In summary, thiol alkylation with readily available azetidinols has been developed using an $FeCl_3$ catalyst to access 3-aryl-3-sulfanyl azetidines as a new design scaffold for medicinal chemistry. A variety of benzylic, alkyl and aromatic thiols, bearing electron donating or withdrawing groups, were tolerated providing a wide range of 3-aryl-3-sulfanyl azetidines in high yields. Additionally, different aryl moieties could be preinstalled, including indoles. The azetidine sulfides were converted to sulfoxide and sulfone derivatives; themselves providing new classes of 3,3-disubstituted azetidines. Removal of the Cbz group with Me_3SiI revealed the free amine functionality, providing an additional vector for functionalization

through the nitrogen atom. Good reactivity and high stability of the products was demonstrated in S_NAr, amidation and transition metal-catalyzed cross-coupling reactions. These versatile building blocks contain attractive functionality for incorporation into medicinal chemistry programs.

EXPERIMENTAL SECTION

General Experimental Considerations

All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried or oven-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (DMF, THF, CH_2Cl_2) or used directly from commercial sources (toluene, MeCN, EtOAc, $CHCl_3$) without drying. Lithium triflimide (99.95 % trace metal basis) was purchased from Sigma Aldrich, calcium bistriflimide (95%) was purchased from TCI, iron(III) chloride (98%) was purchased from Acros Organics, stored in a desiccator, and used directly without further treatment. Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glassbacked silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate or *p*-anisaldehyde stains. Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the residual protic solvent resonance as the internal standard (chloroform: δ = 7.27 ppm, DMSO-d_6: δ = 2.50 ppm, MeOD-d_4: δ = 3.31 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet and br = broad), coupling constant in Hz, integration, assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ = 77.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm, $^{13}CD_3OD$: δ = 49.0 ppm). *J* values are reported in Hz. Assignments of $^1H/^{13}C$ spectra were made by the analysis of δ/J values, and COSY, HSQC, and HMBC experiments as appropriate. Melting points are uncorrected. Heating blocks were used for reactions above room temperature.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary. Azetidinols **1**, **Boc-1**, and **3–8** were prepared as previously reported.[15]

Synthesis of 3-aryl-3-sulfanyl azetidines 2a–2o (Scheme 1).

Benzyl 3-(benzylthio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2a)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and benzyl mercaptan (124 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded the azetidine **2a** (189 mg, 90%) as a white solid. R_f = 0.55 (40% Et_2O/pentane); mp = 76–78 °C; IR (film)/cm^{-1} 3025, 2945, 2875, 2834, 1701 (C=O), 1610, 1513, 1494, 1455, 1405, 1355, 1298, 1256, 1172, 1113, 1030, 998, 949, 831, 762, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 12 H, 12 × Ar-CH), 6.98–6.95 (m, 2 H, 2 × Ar-CH), 5.14 (s, 2 H, OCH_2Ph), 4.51 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.27 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.86 (s, 3 H, OCH_3), 3.56 (s, 2 H, SCH_2Ph); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.0 (C=O), 136.9 (Ar-C_q-CH_2), 136.3 (Ar-C_q-CH_2), 134.0 (Ar-C_q-C_q), 128.8 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.3 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.0 (Ar-CH), 113.8 (2 × Ar-CH), 66.7 (OCH_2Ph), 62.4 and 61.7 (CH_2NCH_2), 55.2 (OCH_3), 47.6 (C_q), 35.1 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{25}H_{26}NO_3S^+$ $[M+H]^+$: 420.1633; Found: 420.1627.

tert-Butyl 3-(benzylthio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(Boc-2a)**. Calcium (II) bis(trifluoromethanesulfonimide) (7.5 mg, 0.0125 mmol) and tetrabutylammonium hexafluorophosphate (4.8 mg, 0.0125 mmol) were added to a solution of *tert*-butyl 3-hydroxy-3-(4-methoxyphenyl) azetidine-1-carboxylate **Boc-1** (70.0 mg, 0.25 mmol) and benzyl mercaptan (62.0 mg, 0.50 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **Boc-2a** (13.0 mg, 14%) as a white paste. R_f = 0.50 (40% Et_2O/pentane); IR (film)/cm^{-1} 2964, 2933, 1699 (C=O), 1610, 1512, 1390, 1365, 1248, 1132, 1032, 831, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.20 (m, 7 H, 7 × Ar-CH), 6.93–6.91 (m, 2 H, 2 × Ar-CH), 4.39 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.15 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 3.54 (s, 2 H, SCH_2Ph), 1.43 (s, 9 H, 3 × CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.1 (C=O), 137.1 (Ar-C_q-CH_2), 134.5 (Ar-C_q-C_q), 129.0 (2 × Ar-CH), 128.5 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.1 (Ar-CH), 113.8 (2 × Ar-

CH), 79.8 ($C_q(CH_3)_3$), 62.6 and 61.5 (CH_2NCH_2), 55.4 (OCH_3), 47.2 (C_q), 35.1 (SCH_2Ph), 28.3 (3 × CH_3); HRMS (ESI) *m/z* Calcd for $C_{22}H_{28}NO_3S^+$ $[M+H]^+$: 386.1793; Found: 386.1790.

Benzyl 3-((4-methoxybenzyl)thio)-3-(4-methoxyphenyl) azetidine-1-carboxylate **(2b)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 4-methoxy-α-toluenethiol (154 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded azetidine **2b** (146 mg, 65%) as a white solid. R_f = 0.32 (40% Et_2O/pentane); mp = 88 °C; IR (film)/cm^{-1} 2953, 2825, 1708 (C=O), 1610, 1511, 1415, 1354, 1248, 1178, 1129, 1033, 831, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 5 H, 5 × Ar-CH), 7.22–7.18 (m, 2 H, 2 × Ar-CH), 7.13–7.10 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 6.81–6.78 (d, *J* = 7.8 Hz, 2 H, 2 × Ar-CH), 5,10 (s, 2 H, OCH_2Ph), 4.46 (d, *J* =7.6 Hz, 2 H, C*H*HNC*H*H), 4.23 (d, *J* = 7.6 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.49 (s, 2 H, SCH_2Ph); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.72 (Ar-C_q-OCH_3), 158.67 (Ar-C_q-OCH_3), 156.2 (C=O), 136.4 (Ar-C_q-CH_2), 134.3 (Ar-C_q-C_q), 130.0 (2 × Ar-CH), 128.8 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.8 (2 × Ar-CH), 113.95 (2 × Ar-CH), 113.89 (2 × Ar-CH), 66.8 (OCH_2Ph), 62.6 and 61.8 (CH_2NCH_2), 55.4 (OCH_3), 55.2 (OCH_3), 47.6 (C_q), 34.6 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{26}H_{28}NO_4S^+$ $[M+H]^+$: 450.1739; Found: 450.1746.

Benzyl 3-(4-methoxyphenyl)-3-(phenylthio)azetidine-1-carboxylate **(2c)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and thiophenol (110 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2c** (166 mg, 82%) as a white solid. R_f = 0.33 (40% Et_2O/pentane); mp = 109–110 °C; IR (film)/cm^{-1} 3033, 2952, 2879, 2836, 1705 (C=O), 1610, 1512, 1409 1351, 1299, 1246, 1123, 1032, 830, 749, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 6 H, 6 × Ar-CH), 7.28–7.20 (m, 4 H, 4 × Ar-CH), 6.97 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 6.83 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.52 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.45 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 156.0 (C=O), 136.3 (Ar-C_q-CH_2), 135.5 (2 × Ar-CH), 134.4 (Ar-C_q-C_q), 131.5 (S-C_q-Ar), 128.9 (Ar-CH), 128.6 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.9 (Ar-CH), 127.8 (2 × Ar-

CH), 127.7 (2 × Ar-CH), 113.4 (2 × Ar-CH), 66.7 (OCH_2Ph), 62.1 and 61.4 (CH_2NCH_2), 55.1 (OCH_3), 50.0 (C_q); HRMS (ESI) *m/z* Calcd for $C_{24}H_{24}NO_3S^+$ $[M+H]^+$: 406.1477; Found: 406.1477.

Benzyl 3-((4-bromophenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2d)**. Azetidinol **1** (940 mg, 3.00 mmol) was added to a solution of $FeCl_3$ (36.5 mg, 0.225 mmol) and 4-bromothiophenol (1.10 g, 6.00 mmol) in toluene (6.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (40 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2d** (1.10 g, 76%) as a white solid. R_f = 0.23 (20% Et_2O/pentane); mp = 121–122 °C; IR (film)/cm^{-1} 2952, 2885, 1710 (C=O), 1610, 1513, 1415, 1354, 1250, 1180, 1129, 1009, 819, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 7 H, 7 × Ar-CH), 7.00 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 6.93 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 6.82 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 5.09 (s, 2 H, OCH_2Ph), 4.48 (d, *J* = 9.0 Hz, 2 H, *CH*HN*CH*H), 4.37 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_q-OCH_3), 156.2 (C=O), 137.0 (2 × Ar-CH), 136.4 (Ar-C_q-CH_2), 134.2 (Ar-C_q-C_q), 131.9 (2 × Ar-CH), 130.7 (S-C_q-Ar), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.8 (2 × Ar-CH), 123.9 (Ar-C_q-Br), 113.7 (2 × Ar-CH), 66.9 (OCH_2Ph), 61.6 and 61.5 (CH_2NCH_2), 55.3 (OCH_3), 50.4 (C_q); HRMS (ESI) *m/z* Calcd for $C_{24}H_{23}{}^{79}BrNO_3S^+$ $[M+H]^+$: 484.0582; Found: 484.0605.

Benzyl 3-((4-chlorophenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2e)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 4-chlorothiophenol (145 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2e** (202 mg, 92%) as a white solid. R_f = 0.40 (40% Et_2O/pentane); mp = 124–125 °C; IR (film)/cm^{-1} 3070, 2949, 2870, 1708 (C=O), 1608, 1512, 1447, 1417, 1370, 1247, 1174, 1128, 1091, 1102, 1011, 965, 822, 762, 735, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (m, 5 H, 5 × Ar-CH), 7.21–7.18 (m, 2 H, 2 × Ar-CH), 7.10–7.06 (m, 2 H, 2 × Ar-CH), 6.94–6.91 (m, 2 H, 2 × Ar-CH), 6.84–6.81 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.49 (d, *J* = 9.1 Hz, 2 H, C*H*HNC*H*H), 4.39 (d, *J* = 9.1 Hz, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.0 (C=O), 136.8 (2 × Ar-CH), 136.2 (Ar-C_q-CH_2), 135.5 (Ar-C_q-Cl), 134.0 (Ar-C_q-C_q), 129.9 (S-C_q-Ar), 128.8 (2 × Ar-CH), 128.3 (2 × Ar-CH), 128.0 (Ar-CH), 127.8 (2 × Ar-CH), 127.7

(2 × Ar-CH), 113.5 (2 × Ar-CH), 66.7 (OCH_2Ph), 62.0 and 61.4 (CH_2NCH_2), 55.1 (OCH_3), 50.3 (C_q); HRMS (ESI) *m/z* Calcd for $C_{24}H_{23}{}^{35}ClNO_3S^+$ $[M+H]^+$: 440.1087; Found: 440.1078.

Benzyl 3-((4-fluorophenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2f)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 4-fluorothiophenol (178 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/hexane) afforded azetidine **2f** (203 mg, 96%) as a white solid. R_f = 0.48 (40% Et_2O/pentane); mp = 134–137 °C; IR (film)/cm^{-1} 2948, 2832, 1709 (C=O), 1609, 1584,1511, 1446, 1420, 1371, 1247, 1177, 1132, 1001, 819, 757, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5 H, 5 × Ar-CH), 7.17–7.13 (m, 2 H, 2 × Ar-CH), 6.95–6.86 (m, 4 H, 4 × Ar-CH), 6.81 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.49 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.40 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.4 (d, J_{CF} = 250.2 Hz, Ar-C_q-F), 158.5 (Ar-C_q-OCH_3), 156.0 (C=O), 138.0 (d, J_{CF} = 8.4 Hz, 2 × Ar-CH), 136.2 (Ar-C_q-CH_2), 134.1 (Ar-C_q-C_q), 128.3 (2 × Ar-CH), 127.9 (Ar-CH), 127.8 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.7 (d, J_{CF} = 3.4 Hz, S-C_q-Ar), 115.7 (d, J_{CF} = 21.6 Hz, 2 × Ar-CH), 113.4 (2 × Ar-CH), 66.7 (OCH_2Ph), 61.8 and 61.1 (CH_2NCH_2), 55.1 (OCH_3), 50.3 (C_q); ^{19}F NMR (377 MHz, $CDCl_3$) δ –111.0; HRMS (ESI) *m/z* Calcd for $C_{24}H_{23}FNO_3S^+$ $[M+H]^+$: 424.1383; Found: 424.1387.

Benzyl 3-(4-methoxyphenyl)-3-((4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxylate **(2g)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 4-fluorothiophenol (178 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2g** (211 mg, 89%) as a white solid. R_f = 0.42 (40% Et_2O/pentane); mp = 119–121 °C; IR (film)/cm^{-1} 3034, 3010, 2962, 2840, 1704 (C=O), 1606, 1511, 1420, 1362, 1322, 1246, 1166, 1125, 1061, 948, 829, 730, 751, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 7.41–7.31 (m, 5 H, 5 × Ar-CH), 7.22 (d, *J* = 8.0 Hz, 2 H, 2 × Ar-CH), 7.06–7.02 (m, 2 H, 2 × Ar-CH), 6.86–6.82 (m, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, OCH_2Ph), 4.53 (d, *J* = 9.1 Hz, 2 H, C*H*HNC*H*H), 4.42 (d, *J* = 9.1 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_q-OCH_3), 156.1 (C=O), 136.9 (Ar-C_q-C_q), 136.2 (Ar-C_q-CH_2), 134.0 (2 ×

Ar-CH), 133.7 (S-C_q-Ar), 130.3 (q, J_{CF3} = 32.5 Hz, Ar-C_q-CF_3), 128.4 (2 × Ar-CH), 128.1 (Ar-CH), 127.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 125.4 (q, J_{CF3} = 3.9 Hz, 2 × Ar-CH) 123.8 (q, J_{CF3} = 272 Hz, CF_3), 113.7 (2 × Ar-CH), 66.9 (OCH_2Ph), 62.5 and 61.9 (CH_2NCH_2), 55.2 (OCH_3), 50.1 (C_q); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.7; HRMS (ESI) *m/z* Calcd for $C_{25}H_{23}F_3NO_3S^+$ $[M+H]^+$: 474.135; Found: 474.1346.

Benzyl 3-((4-(tert-butyl)phenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2h)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 4-(*tert*-butyl)benzethiol (166 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2h** (187 mg, 81%) as a white solid. R_f = 0.27 (20% Et_2O/pentane); mp = 109–111 °C; IR (film)/cm^{-1} 2958, 2878, 1711 (C=O), 1611, 1513, 1455, 1413, 1353, 1249, 1180, 1128, 1034, 829, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 5 H, 5 × Ar-CH), 7.29–7.25 (m, 2 H, 2 × Ar-CH), 7.17–7.13 (m, 2 H, 2 × Ar-CH), 6.98–6.95 (m, 2 H, 2 × Ar-CH), 6.85–6.81 (m, 2 H, 2 × Ar-CH), 5.10 (s, 2 H, OCH_2Ph), 4.52–4.42 (m, 4 H, CH_2NCH_2), 3.82 (s, 3 H, OCH_3), 1.32 (s, 9 H, 3 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.2 (C=O), 152.4 (Ar-C_q-$C(CH_3)_3$), 136.4 (Ar-C_q-CH_2), 135.4 (2 × Ar-CH), 134.8 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.2 (S-C_q-Ar), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.8 (2 × Ar-CH), 125.8 (2 × Ar-CH), 113.5 (2 × Ar-CH), 66.8 (OCH_2Ph), 62.2 and 61.5 (CH_2NCH_2), 55.3 (OCH_3), 50.1 (C_q), 34.6 ($C_q(CH_3)_3$), 31.2 ($C_q(CH_3)_3$); HRMS (ESI) *m/z* Calcd for $C_{28}H_{32}NO_3S^+$ $[M+H]^+$: 462.2103; Found: 462.2091.

Benzyl 3-(4-methoxyphenyl)-3-((4-methoxyphenyl)thio)azetidine-1-carboxylate **(2i)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and methoxythiophenol (123 µL, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 80 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2i** (180 mg, 83%) as a white solid. R_f = 0.14 (20% Et_2O/pentane); mp = 122–123 °C; IR (film)/cm^{-1} 3027, 2938, 2841, 1707 (C=O), 1587, 1454, 1421, 1371, 1247, 1131, 1029, 823, 760, 738, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H, 5 × Ar-CH), 7.14–7.11 (m, 2 H, 2 × Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 6.82–6.80 (m, 2 H, 2 × Ar-CH), 6.78–6.75 (m, 2 H, 2 × Ar-CH), 5.07 (s, 2 H, OCH_2Ph), 4.46 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.39 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.80

(s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.7 (Ar-C_q-OCH_3), 158.5 (Ar-C_q-OCH_3), 156.2 (C=O), 137.9 (2 × Ar-CH), 136.4 (Ar-C_q-CH_2), 134.7 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.01 (Ar-CH), 127.95 (2 × Ar-CH), 127.8 (2 × Ar-CH), 122.1 (S-C_q-Ar), 114.2 (2 × Ar-CH), 113.5 (2 × Ar-CH), 66.8 (OCH_2Ph), 61.8 and 61.4 (CH_2NCH_2), 55.3 (OCH_3), 55.2 (OCH_3), 50.2 (C_q); HRMS (ESI) *m/z* Calcd for $C_{25}H_{26}NO_4S^+$ $[M+H]^+$: 436.1583; Found: 436.1587.

Benzyl 3-((4-acetamidophenyl)thio)-3-(4-methoxyphenyl) azetidine-1-carboxylate **(2j)**. Azetidinol **1** (78.0 mg, 0.25 mmol) was added to a solution of $FeCl_3$ (3.0 mg, 0.01875 mmol) and *N*-4-sulfanylphenyl-acetamide (84.0 mg, 0.50 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 80 °C for 39 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc/pentane) afforded azetidine **2j** (67 mg, 58%) as a colorless oil. R_f = 0.22 (50% EtOAc/pentane); IR (film)/cm^{-1} 3320, 2956, 1677 (C=O), 1589, 1513, 1418, 1308, 1247, 1178, 1129, 1033, 908, 829, 728, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1 H, NH), 7.41 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 7.37–7.29 (m, 5 H, 5 × Ar-CH), 7.11 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 6.90 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 6.79 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 5.07 (s, 2 H, OCH_2Ph), 4.45 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.38 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.79 (s, 3 H, OCH_3), 2.14 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.5 (NH-*C*O-CH_3), 158.6 (Ar-C_q-OCH_3), 156.3 (C=O), 139.3 (N-C_q-Ar) 136.8 (2 × Ar-CH), 136.3 (Ar-C_q-CH_2), 134.5 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.1 (Ar-CH), 127.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.0 (S-C_q-Ar), 119.5 (2 × Ar-CH), 113.6 (2 × Ar-CH), 66.9 (OCH_2Ph), 62.1 and 61.3 (CH_2NCH_2), 55.3 (OCH_3), 50.3 (C_q), 24.6 (CH_3); HRMS (ESI) *m/z* Calcd for $C_{26}H_{27}N_2O_4S^+$ $[M+H]^+$: 463.1692; Found: 463.1683.

Benzyl 3-(4-methoxyphenyl)-3-(naphthalenyl-1-thio)azetidine-1-carboxylate **(2k)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 1-naphthalenethiol (160 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2k** (220 mg, 97%) as a white solid. R_f = 0.37 (40% Et_2O/pentane); mp = 103–105 °C; IR (film)/cm^{-1} 3030, 2952, 2834, 1688 (C=O), 1610, 1511, 1453, 1424, 1353, 1244, 1176, 1130, 1031, 998, 823, 811, 796, 769, 758, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 7.84 (dd, *J* = 11.7, 8.1 Hz, 2 H, 2 × Ar-CH), 7.50–7.32 (m, 9 H, 9 × Ar-CH), 6.89–6.85

(m, 2 H, 2 × Ar-CH), 6.73–6.70 (m, 2 H, 2 × Ar-CH), 5.13 (s, 2 H, OCH_2Ph), 4.58–4.50 (m, 4 H, CH_2NCH_2), 3.75 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 156.0 (C=O), 136.2 (Ar-C_q-CH_2), 135.4 (Ar-C_q-C_q), 135.3 (Ar-CH), 134.2 (C_q-napht.), 133.7 (C_q-napht.), 129.9 (Ar-CH), 129.1 (S-C_q-Ar), 128.3 (2 × Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 127.7 (2 × Ar-CH), 127.4 (2 × Ar-CH), 126.5 (Ar-CH), 125.9 (Ar-CH), 125.6 (Ar-CH), 125.0 (Ar-CH), 113.3 (2 × Ar-CH), 66.6 (OCH_2Ph), 62.0 and 61.5 (CH_2NCH_2), 55.1 (OCH_3), 50.9 (C_q); HRMS (ESI) *m/z* Calcd for $C_{28}H_{26}NO_3S^+$ $[M+H]^+$: 456.1633; Found: 456.1639.

Benzyl 3-(4-methoxyphenyl)-3-(o-tolylthio)azetidine-1-carboxylate **(2l)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 2-methylbenzenethiol (124 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2l** (205 mg, 93%) as a white solid. R_f = 0.46 (40% Et_2O/pentane); mp = 92–94 °C; IR (film)/cm^{-1} 3061, 2958, 2842, 1711 (C=O), 1607, 1513, 1448, 1413, 1368, 1252, 1180, 1131, 1028, 815, 755, 726, 692; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 5 H, 5 × Ar-CH), 7.23–7.14 (m, 3 H, 3 × Ar-CH), 7.10–7.05 (m, 1 H, Ar-CH), 6.98–6.94 (m, 2 H, 2 × Ar-CH), 6.82–6.78 (m, 2 H, 2 × Ar-CH), 5.13 (s, 2 H, OCH_2Ph), 4.52–4.46 (m, 4 H, CH_2NCH_2), 3.80 (s, 3 H, OCH_3), 2.09 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.2 (C=O), 142.4 (Ar-C_q-CH_3), 136.4 (Ar-C_q-CH_2), 135.4 (Ar-CH), 134.6 (Ar-C_q-C_q), 131.2 (S-C_q-Ar), 130.4 (Ar-CH), 128.8 (Ar-CH), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.5 (2 × Ar-CH), 126.1 (Ar-CH), 113.5 (2 × Ar-CH), 66.8 (OCH_2Ph), 62.5 and 61.9 (CH_2NCH_2), 55.2 (OCH_3), 50.2 (C_q), 20.6 (CH_3); HRMS (ESI) *m/z* Calcd for $C_{25}H_{26}NO_3S^+$ $[M+H]^+$: 420.1633; Found: 420.1617.

Benzyl 3-(1-adamantanethiol)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2m)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 1-adamantanethiol (168 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2m** (227 mg, 98%) as a yellow solid. R_f = 0.26 (20% Et_2O/pentane); mp = 135–136 °C, IR (film)/cm^{-1} 2911, 2848, 1702 (C=O), 1611, 1509, 1421, 1350, 1299, 1244, 1180, 1131, 1031, 996, 827, 758, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 7 H, 7 × Ar-CH), 6.88 (d, *J* = 8.3 Hz, 2 H, 2 ×

Ar-CH), 5.10 (s, 2 H, OCH_2Ph), 4.55 (s, br, 2 H, C*H*HNC*H*H), 4.37 (d, *J* = 8.3 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3), 1.86 (s, 3 H, 3 × CH), 1.60–1.48 (m, 12 H, 6 × CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar-C_q-OCH_3), 156.5 (C=O), 136.37 (Ar-C_q-CH_2), 136.36 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.94 (Ar-CH), 127.89 (2 × Ar-CH), 113.5 (2 × Ar-CH), 66.7 (OCH_2Ph), 64.4 and 63.4 (CH_2NCH_2), 55.2 (OCH_3), 49.0 (C_q), 46.7 (S-$C_{q(adamantane)}$), 43.5 (3 × CH_2), 35.9 (3 × CH_2), 29.4 (3 × CH); HRMS (ESI) *m/z* Calcd for $C_{28}H_{34}NO_3S^+$ $[M+H]^+$: 464.2272; Found: 464.2259.

Benzyl 3-((3-methoxy-3-oxopropyl)thio)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(2n)**. Azetidinol **1** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and methyl 3-mercaptoproprionate (120 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded azetidine **2n** (193 mg, 92%) as a colorless oil. R_f = 0.34 (40% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2885, 2837, 1705 (C=O), 1512, 1412, 1152, 1177, 1123, 1031, 831, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5 H, 5 × Ar-CH), 7.18–7.14 (m, 2 H, 2 × Ar-CH), 6.91–6.87 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.54 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.31 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3), 3.65 (s, 3 H, CO_2CH_3), 2.59 (t, *J* = 7.4 Hz, 2 H, S$CH_2$$CH_2CO_2CH_3$), 2.37 (t, *J* = 7.4 Hz, 2 H, $SCH_2CH_2CO_2CH_3$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.8 (CO_2CH_3), 158.6 (Ar-C_q-OCH_3), 156.1 (C=O), 136.3 (Ar-C_q-CH_2), 134.0 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 66.8 (OCH_2Ph), 62.7 and 62.0 (CH_2NCH_2), 55.2 (OCH_3), 51.7 (CO_2CH_3), 47.2 (C_q), 33.6 ($SCH_2CH_2CO_2CH_3$), 25.1 ($SCH_2CH_2CO_2CH_3$); HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}NO_5S^+$ $[M+H]^+$: 416.1532; Found: 416.1538.

2-((Triisopropylsilyl)oxy)ethane-1-thiol. Triisopropylsilyl chloride (470 µL, 2.20 mmol) was added to a solution of 2-mercaptoethanol (140 µL, 2.00 mmol) in CH_2Cl_2 (4.0 mL). The reaction mixture was stirred at 40 °C for 4 h, then quenched with water (30 mL). The layers were separated and the aqueous portion was extracted with pentane (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through a plug of silica and concentrated under reduced pressure to afford TIPS-protected thiol **S1** (453 mg, 97%) as a colorless oil. R_f = 0.50 (100% pentane); IR (film)/cm^{-1} 2940, 2866, 1461, 1107, 1069, 995, 879, 801, 715, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (t, *J* = 6.4 Hz, 2 H, $SHCH_2CH_2O$), 2.67 (dt, *J* = 8.2, 6.4 Hz, 2 H, $SHCH_2CH_2O$), 1.61 (t, *J* = 8.2 Hz, 1 H, SH), 1.16–1.00 (m, 21 H, 3 × CH, 6 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 65.3 ($SHCH_2CH_2O$), 27.5 ($SHCH_2CH_2O$), 18.0 (6 × CH_3), 12.0 (3

× CH); HRMS (ESI) *m/z* Calcd for $C_{12}H_{27}O_3SSi^-$ $[M\text{-}H+HCO_2H]^-$: 279.1450; Found: 279.1443. Compound previously reported without characterization data.[25]

Benzyl 3-(4-methoxyphenyl)-3-((2-((triisopropylsilyl)oxy)ethyl)thio)azetidine-1-carboxylate **(2o)**. Azetidinol **1** (157 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and 2-((triisopropylsilyl)oxy)ethane-1-thiol (235 mg, 1.0 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **2o** (117 mg, 44%) as a colorless oil. R_f = 0.18 (20% Et_2O/pentane); IR (film)/cm^{-1} 2940, 2862, 1710 (C=O), 1513, 1463, 1412, 1353, 1297, 1248, 1177, 1114, 1032, 995, 879, 831, 730, 678; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5 H, 5 × Ar-CH), 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.53 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.30 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3), 3.56 (t, *J* = 7.2 Hz, 2 H, OC$H_2$$CH_2$S), 2.53 (t, *J* = 7.2 Hz, 2 H, $OCH_2C$$H_2$S), 1.04–0.97 (m, 21 H, 3 × CH, 6 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_q-OCH_3), 156.2 (C=O), 136.4 (Ar-C_q-CH_2), 134.7 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.6 (2 × Ar-CH), 113.9 (2 × Ar-CH), 66.9 (OCH_2Ph), 62.6 (CH_2NCH_2), 55.3 (OCH_3), 47.0 (C_q), 32.9 (OCH_2CH_2S), 17.9 (6 × CH_3), 17.7 (OCH_2CH_2S), 11.9 (3 × CH); HRMS (ESI) *m/z* Calcd for $C_{29}H_{44}NO_4SSi^+$ $[M+H]^+$: 530.2760; Found: 530.2770.

Synthesis of 3-aryl-3-sulfanyl azetidines 9–17 (Scheme 2).

Benzyl 3-(4-(benzyloxy)phenyl)-3-(benzylthio)azetidine-1-carboxylate **(9)**. Azetidinol **3** (195 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and benzyl mercaptan (124 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **9** (156 mg, 63%) as yellow oil. R_f = 0.55 (40% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2889, 1703 (C=O), 1608, 1512, 1453, 1406, 1356, 1252, 1128, 1002, 831, 731, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.19 (m, 17 H, 17 × Ar-CH), 7.02–6.98 (m, 2 H, 2 × Ar-CH), 5.10 (s, 4 H, 2 × OCH_2Ph), 4.47 (d, *J* = 8.9 Hz, 2 H, C*H*HNC*H*H), 4.23 (dd, *J* = 8.9, 1.5 Hz, 2 H, CH*H*NCH*H*), 3.53 (s, 2 H, SCH_2Ph); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.9 (Ar-C_q-OBn), 156.2 (C=O), 137.0 (Ar-C_q-CH_2), 136.7 (Ar-C_q-CH_2),

136.4 (Ar-C_q-CH_2), 134.4 (Ar-C_q-C_q), 128.9 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.53 (2 × Ar-CH), 128.46 (2 × Ar-CH), 128.1 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.5 (2 × Ar-CH), 127.2 (Ar-CH), 114.9 (2 × Ar-CH), 70.1 (OCH_2Ph), 66.8 (OCH_2Ph), 61.7 (CH_2NCH_2), 47.7 (C_q), 35.2 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{31}H_{30}NO_3S^+$ $[M+H]^+$: 496.194; Found: 496.1952.

Benzyl 3-(benzylthio)-3-(4-((triisopropylsilyl)oxy)phenyl)azetidine-1-carboxylate **(10)**. $FeCl_3$ (6.1 mg, 0.0375 mmol) was added to a solution of azetidinol **4** (228 mg, 0.50 mmol) and methyl 3-mercaptoproprionate (117 µL, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/pentane) afforded azetidine **10** (249 mg, 86%) as a colorless oil. R_f = 0.15 (10% Et_2O/pentane); IR (film)/cm^{-1} 2944, 2866, 1710 (C=O), 1602, 1509, 1453, 1408, 1350, 1259, 1177, 1125, 998, 909, 834, 752, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 7.29–7.22 (m, 3 H, 3 × Ar-CH), 7.19–7.17 (m, 2 H, 2 × Ar-CH), 7.14–7.11 (m, 2 H, 2 × Ar-CH), 6.92–6.89 (m, 2 H, 2 × Ar-CH), 5.10 (s, 2 H, OCH_2Ph), 4.47 (d, *J* = 8.9 Hz, 2 H, C*H*HNC*H*H), 4.22 (d, *J* = 8.9 Hz, 2 H, CH*H*NCH*H*), 3.50 (s, 2 H, SCH_2Ph), 1.32–1.23 (m, 3 H, 3 × CH), 1.12 (d, *J* = 7.2 Hz, 18 H, 6 × CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.5 (Ar-C_q-OTIPS), 155.3 (C=O), 137.0 (Ar-C_q-CH_2), 136.4 (Ar-C_q-CH_2), 134.4 (Ar-C_q-C_q), 128.9 (2 × Ar-CH), 128.52 (2 × Ar-CH), 128.46 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.2 (Ar-CH), 119.9 (2 × Ar-CH), 66.8 (OCH_2Ph), 62.5 (CH_2NCH_2), 47.7 (C_q), 35.2 (SCH_2Ph), 17.9 (3 × CH), 12.6 (6 × CH_3); HRMS (ESI) *m/z* Calcd for $C_{33}H_{44}NO_3SSi^+$ $[M+H]^+$: 562.2809; Found: 562.2811.

Benzyl 3-((3-methoxy-3-oxopropyl)thio)-3-(2-methoxyphenyl)azetidine-1-carboxylate **(11)**. Azetidinol **5** (78.3 mg, 0.25 mmol) was added to a solution of $FeCl_3$ (3.1 mg, 0.019 mmol) and methyl 3-mercaptoproprionate (55.2 µL, 0.50 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded azetidine **11** (96.8 mg, 92%) as a yellow oil. R_f = 0.23 (40% Et_2O/pentane); IR (film)/cm^{-1} 2952, 1703 (C=O), 1490, 1408, 1349, 1248, 1174, 1125, 1025, 995, 752, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 6 H, 6 × Ar-CH), 7.00–6.93 (m, 2 H, 2 × Ar-CH), 6.90 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.57 (d, *J* = 9.3 Hz, 2 H, C*H*HNC*H*H), 4.28 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 3.64 (s, 3 H, CO_2CH_3), 2.66 (t, *J* = 7.6 Hz, 2 H, $SCH_2CH_2CO_2Me$),

2.35 (t, *J* = 7.6 Hz, 2 H, $SCH_2CH_2CO_2Me$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1 (CO_2CH_3), 156.5 (C=O, Ar-C_q-OCH_3), 136.5 (Ar-C_q-CH_2), 129.6 (Ar-C_q-C_q), 129.1 (Ar-CH), 128.4 (2 × Ar-CH), 128.03 (Ar-CH), 128.02 (2 × Ar-CH), 127.2 (Ar-CH), 120.3 (Ar-CH), 111.5 (Ar-CH), 66.8 (OCH_2Ph), 62.2 (br, CH_2NCH_2), 55.4 (OCH_3), 51.7 (CO_2CH_3), 46.4 (C_q), 33.8 ($SCH_2CH_2CO_2CH_3$), 25.1 ($SCH_2CH_2CO_2CH_3$); HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}NO_5S^+$ $[M+H]^+$: 416.1532; Found: 416.1533.

Benzyl 3-(1,3-benzodioxol-5-yl)-3-(benzylthio)azetidine-1-carboxylate **(12)**. Azetidinol **6** (164 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and benzyl mercaptan (124 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **12** (208 mg, 96%) as a white solid. R_f = 0.39 (40% Et_2O/pentane); mp = 93–95 °C; IR (film)/cm^{-1} 3030, 2952, 2883, 1704 (C=O), 1490, 1410, 1352, 1220, 1122, 1037, 931, 809, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.21 (m, 10 H 10 × Ar-CH), 6.81 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.77 (d, *J* = 1.9 Hz, 1 H, Ar-CH), 6.70 (dd, *J* = 8.0, 1.9 Hz, 1 H, Ar-CH), 6.00 (s, 2 H, OCH_2O), 5.10 (s, 2 H, OCH_2Ph), 4.43 (d, *J* = 8.9 Hz, 2 H, C*H*HNC*H*H), 4.20 (d, *J* = 8.9 Hz, 2 H, CH*H*NCH*H*), 3.55 (s, 2 H, SCH_2Ph); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 148.0 (Ar-C_q-O), 146.8 (Ar-C_q-O), 136.9 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 136.0 (Ar-C_q-CH_2), 128.9 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.2 (Ar-CH), 119.9 (Ar-CH), 107.7 (Ar-CH), 107.2 (Ar-CH), 101.3 (OCH_2O), 66.8 (OCH_2Ph), 62.5 and 61.7 (CH_2NCH_2), 48.1 (C_q), 35.2 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{25}H_{24}NO_4S^+$ $[M+H]^+$: 434.1426; Found: 434.1432.

Benzyl 3-(1,3-benzodioxol-5-yl)-3-(phenylthio)azetidine-1-carboxylate **(13)**. Azetidinol **6** (164 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and thiophenol (110 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **13** (82 mg, 39%) as a white solid. R_f = 0.36 (40% Et_2O/pentane); mp = 94–95 °C; IR (film)/cm^{-1} 3059, 2934, 2879, 1694 (C=O), 1492, 1445, 1419, 1371, 1253, 1217, 1128, 1104, 1031, 927, 805, 763, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 6 H, 6 × Ar-CH), 7.27–7.21 (m, 4 H, 4 × Ar-CH), 6.67 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.59 (d, *J* = 1.9 Hz, 1 H, Ar-CH), 6.38 (dd, *J* = 8.1, 1.9 Hz, 1 H, Ar-CH), 5.96 (s, 2 H, OCH_2O), 5.08 (s, 2 H, OCH_2Ph), 4.46–4.38 (m, 4 H, CH_2NCH_2); $^{13}C\{^1H\}$ NMR (101 MHz,

$CDCl_3$) δ 156.1 (C=O), 147.6 (Ar-C_q-O), 146.6 (Ar-C_q-O), 136.33 (Ar-C_q-C_q), 136.31 (Ar-C_q-CH_2), 135.6 (2 × Ar-CH), 131.4 (S-C_q-Ar), 129.1 (Ar-CH), 128.7 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 120.0 (Ar-CH), 107.5 (Ar-CH), 107.1 (Ar-CH), 101.2 (OCH_2O), 66.8 (OCH_2Ph), 62.1 and 61.5 (CH_2NCH_2), 50.5 (C_q); HRMS (ESI) *m/z* Calcd for $C_{24}H_{22}NO_4S^+$ $[M+H]^+$: 420.1270; Found: 420.1255.

Benzyl 3-((3-methoxy-3-oxopropyl)thio)-3-(3,4,5-trimethoxyphenyl)azetidine-1-carboxylate **(14)**. Azetidinol **7** (93.4 mg, 0.25 mmol) was added to a solution of $FeCl_3$ (3.1 mg, 0.019 mmol) and methyl 3-mercaptoproprionate (55.2 µL, 0.50 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% Et_2O/pentane) afforded azetidine **14** (80 mg, 67%) as a white solid. R_f = 0.40 (80% Et_2O/pentane); mp = 79–83 °C; IR (film)/cm^{-1} 2948, 1707 (C=O), 1587, 1505, 1453, 1408, 1353, 1241, 1215, 1174, 1121, 1002, 764, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 6.44 (s, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.55 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.30 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.86–3.85 (m, 9 H, 3 × OCH_3), 3.66 (s, 3 H, CO_2CH_3), 2.65 (t, *J* = 7.4 Hz, 2 H, SC*H*$_2$CH$_2$CO$_2$CH$_3$), 2.39 (t, *J* = 7.4 Hz, 2 H, SCH$_2$C*H*$_2$CO$_2$CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.9 (*C*O_2CH_3), 156.2 (C=O), 153.2 (3 × Ar-C_q-OCH_3), 137.8 (Ar-C_q-C_q), 136.3 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 103.7 (2 × Ar-CH), 67.0 (OCH_2Ph), 62.8 (br, CH_2NCH_2), 60.9 (OCH_3), 56.3 (2 × OCH_3), 51.9 (CO_2CH_3), 48.0 (C_q), 33.7 (SCH$_2$*C*H$_2$CO$_2$CH$_3$), 25.4 (S*C*H$_2$CH$_2$CO$_2$CH$_3$); HRMS (ESI) *m/z* Calcd for $C_{24}H_{30}NO_7S^+$ $[M+H]^+$: 476.1743; Found: 476.1734.

Benzyl 3-(benzylthio)-3-(1-methylindolin-3-yl)azetidine-1-carboxylate **(15)**. Azetidinol **8** (168 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and benzyl mercaptan (124 mg, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **15** (215 mg, 97%) as yellow oil. R_f = 0.36 (40% Et_2O/pentane); IR (film)/cm^{-1} 3029, 2947, 2879, 1702 (C=O), 1412, 1352, 1123, 737, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1 H, $Ar_{(indole)}$-CH), 7.43–7.33 (m, 7 H, 7 × Ar-CH), 7.31–7.19 (m, 6 H, 6 × Ar-CH), 6.99 (s, 1 H, N-CH-C_q), 5.15 (s, 2 H, OCH_2Ph), 4.55 (d, *J* = 8.7 Hz, 2 H, C*H*HNC*H*H), 4.38 (d, *J* = 8.7 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, NCH_3), 3.55 (s, 2 H, SCH_2Ph); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 137.7 ($Ar_{(indole)}$-

C_q), 137.6 (Ar-C_q-CH_2), 136.4 (Ar-C_q-CH_2), 128.8 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.95 (Ar-CH),127.86 (2 × Ar-CH), 127.3 (Ar-CH), 126.9 ($Ar_{(indole)}$-C_q), 125.2 (N-*C*H-C_q), 122.3 ($Ar_{(indole)}$-CH), 120.3 ($Ar_{(indole)}$-CH), 119.3 ($Ar_{(indole)}$-CH), 115.2 (N-CH-C_q), 109.5 ($Ar_{(indole)}$-CH), 66.7 (OCH_2Ph), 63.1 and 62.5 (CH_2NCH_2), 43.5 (C_q), 35.4 (SCH_2Ph), 32.8 (NCH_3); HRMS (ESI) *m/z* Calcd for $C_{27}H_{26}N_2O_2NaS^+$ $[M+Na]^+$: 465.1613; Found: 465.1623.

Benzyl 4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carboxylate **(29)**. *n*-BuLi (2.19 M solution in hexanes, 5.9 mL, 13.0 mmol) was added dropwise over 5 min to a solution of 4-bromoanisole (1.63 mL, 13.0 mmol) in THF (40 mL) at –78 °C. The reaction mixture was stirred at –78 °C for a further 30 min. Benzyl 4-oxopiperidine-1-carboxylate (2.33 g, 10.0 mmol) in THF (5 mL) was added dropwise to the reaction mixture. Following a further 10 min at –78 °C the reaction mixture was warmed to rt then quenched with water (30 mL). The layers were separated and the aqueous portion extracted with Et_2O (3 × 30 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) afforded piperidin-4-ol **29** (1.83 g, 54%) as a white solid. R_f = 0.34 (30% EtOAc/hexane); mp = 103–104 °C [Lit. mp = 102–104 °C][26]; IR (film)/cm^{-1} 3447 (OH), 2956, 1669 (C=O), 1513, 1471, 1427, 1275, 1246, 1216, 1176, 1072, 1022, 923, 825, 730, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 7 H, 7 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2-Ph), 4.10 (br s, 2 H, C*H*HNC*H*H), 3.81 (s, 3 H, OCH_3), 3.34 (br s, 2 H, CH*H*NCH*H*), 1.98 (br s, 2 H, C*H*HCC*H*H), 1.76 (br d, *J* = 13.2 Hz, 2 H, CH*H*CCH*H*), 1.68 (s, 1 H, OH); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_q-OCH_3), 155.3 (C=O), 140.0 (Ar-C_q), 136.8 (Ar-C_q), 128.5 (2 × Ar-CH), 127.9 (Ar-CH), 127.9 (2 × Ar-CH), 125.6 (2 × Ar-CH), 113.7 (2 × Ar-CH), 71.0 (C_q), 67.1 (CH_2-Ph), 55.3 (OCH_3), 40.2 (2 × NCH_2), 38.0 (2 × NCH_2CH_2); HRMS (ESI) *m/z* Calcd for $C_{20}H_{23}NO_4$ [M+H]: 324.1594; Found: 324.1596. Compound previously reported as a mixture.

Benzyl 4-(benzylthio)-4-(4-methoxyphenyl)piperidine-1-carboxylate **(16)**. Piperidin-4-ol **29** (171 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and benzylmercaptan (120 µL, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 30 min, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded piperidine **16** (214 mg, 95%) as a colorless oil. R_f = 0.19 (20% Et_2O/pentane); IR (film)/cm^{-1} 2937, 1692 (C=O), 1509, 1423, 1349, 1278, 1233, 1177, 1110, 1069, 1021, 805, 760, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.43–7.38 (m, 2 H, 2 × Ar-CH), 7.40–7.28 (m, 5 H, 5 × Ar-CH), 7.27–7.13 (m, 3 H, 3 × Ar-CH), 7.12–7.07 (m, 2 H, 2 × Ar-CH), 6.95–6.89 (m, 2 H, 2 × Ar-CH), 5.13 (d, J = 1.6 Hz, 2 H, OCH_2Ph), 3.85 (s, 3 H, OCH_3), 3.82–3.75 (m, 2 H, 2 × $NCHHCH_2$), 3.62–3.55 (m, 2 H, 2 × $NCHHCH_2$), 3.25 (d, J = 3.9 Hz, 2 H, SCH_2Ph), 2.07 (br s, 4 H, 2 × NCH_2CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 155.2 (C=O), 137.8 (Ar-C_q-C_q), 136.8 (Ar-C_q-CH_2), 136.3 (Ar-C_q-CH_2), 128.8 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.9 (Ar-CH), 127.82 (2 × Ar-CH), 127.79 (2 × Ar-CH), 126.8 (Ar-CH), 113.6 (2 × Ar-CH), 67.0 (OCH_2Ph), 55.3 (OCH_3), 51.0 (C_q), 40.5 (2 × NCH_2), 36.3 and 35.9 (2 × NCH_2CH_2), 33.3 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{27}H_{29}NO_3SNa^+$ $[M+Na]^+$: 470.1766; Found: 470.1754.

Benzyl 3-hydroxy-3-(4-methoxyphenyl)pyrrolidine-1-carboxylate **(30)**. *n*-BuLi (2.40 M in hexanes, 5.42 mL, 13.0 mmol) was added dropwise over 10 min to a solution of 4-bromoanisole (1.63 mL, 13.0 mmol) in THF (35 mL) at –78 ºC. The reaction mixture was stirred at –78 ºC for a further 30 min. A solution of benzyl 3-oxopyrrolidine-1-carboxylate (2.19 g, 10.0 mmol) in THF (5 mL) was added dropwise over 15 min to the reaction mixture. Following a further 15 min at –78 ºC the reaction mixture was warmed to rt, stirred for 1 h and then quenched with H_2O (40 mL). The layers were separated and the aqueous portion was extracted with diethylether (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (10% to 20% Et_2O/CH_2Cl_2) afforded pyrrolidin-3-ol **30** (1.58 g, 48%) as a brown solid. R_f = 0.28 (20% Et_2O/CH_2Cl_2); mp = 94–96 ºC; IR (film)/cm^{-1} 3418 (br, OH), 2895, 1677 (C=O carbamate), 1514, 1423, 1360, 1249, 1179, 1104, 1132, 831, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 7 H, 7 × Ar-CH), 6.93–9.87 (m, 2 H, 2 × Ar-CH), 5.30–5.08 (m, 2 H, CH_2Ph), 3.87–3.58 (m, 7 H, OCH_3 and 2 × NCH_2), 2.40–2.14 (m, 3 H, OH and NCH_2CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar-C_q-OMe), 155.1 and 154.9 (C=O), 136.8 and 136.7 (Ar-C_q), 134.73 and 134.65 (Ar-C_q), 128.4 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.8 (Ar-CH), 126.5 and 126.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 80.2 and 79.3 (C_qOH), 66.8 (OCH_2Ph), 59.0 (NCH_2COH), 55.3 (OCH_3), 45.1 and 44.9 (NCH_2), 39.2 and 38.5 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calcd for $C_{19}H_{22}NO_4$ [M+H] 328.1549; Found 328.1549.

Benzyl 3-(benzylthio)-3-(4-methoxyphenyl)pyrrolidine-1-carboxylate **(17)**. Pyrrolidin-3-ol **30** (194 mg, 0.59 mmol) was added to a solution of $FeCl_3$ (7.2 mg, 0.044 mmol) and benzylmercaptan (140 µL, 1.19 mmol) in toluene (1.2 mL). The reaction mixture was stirred at 40 °C for 30 min, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% to 30% Et_2O/pentane) afforded

pyrrolidine **17** (240 mg, 93%) as a colorless oil. R_f = 0.11 (20% Et_2O/pentane); IR (film)/cm^{-1} 2948, 1699 (C=O), 1610, 1513, 1449, 1412, 1252, 1211, 1177, 1133, 1107, 1028, 827, 764, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.13 (m, 10 H, 10 × Ar-CH), 7.12–7.10 (m, 2 H, 2 × Ar-CH), 6.94–6.86 (m, 2 H, 2 × Ar-CH), 5.22–5.10 (m, 2 H, OCH_2Ph), 4.04 (d, *J* = 11.7 Hz, 0.5 H, NC*H*HC_q), 3.89 (dd, *J* = 11.7 Hz, 0.5 H, NC*H*HC_q), 3.84 (m, 3 H, OCH_3), 3.80 (d, *J* = 11.7 Hz, 0.5 H, NCH*H*C_q), 3.77–3.69 (m, 1.5 H, NCH*H*C_q and NC*H*HCH_2), 3.58–3.48 (m, 1 H, NCH*H*CH_2), 3.47–3.34 (m, 2 H, SCH_2Ph), 2.37–2.23 (m, 2 H, NCH_2CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 154.9 and 154.7 (C=O), 137.7 (Ar-C_q-CH_2), 137.4 (Ar-C_q-CH_2), 134.4 and 134.3 (Ar-C_q-C_q), 128.9 and 128.8 (2 × Ar-CH), 128.45 and 128.44 (2 × Ar-CH), 128.37 and 128.36 (2 × Ar-CH), 128.1 (2 × Ar-CH), 127.93 and 127.88 (Ar-CH), 127.89 and 127.8 (Ar-CH), 126.9 (2 × Ar-CH), 113.7 (2 × Ar-CH), 66.85 and 66.81 (OCH_2Ph), 57.5 and 56.7 (C_q), 57.0 and 56.9 (NCH_2C_q), 55.3 (OCH_3), 44.9 and 44.5 (2 × NCH_2CH_2), 37.2 and 36.2 (2 × NCH_2CH_2), 34.7 and 34.6 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{26}H_{27}NO_3SNa^+$ $[M+Na]^+$: 456.1609; Found: 456.1600.

Synthesis of 3-aryl-3-sulfinyl- and sulfonyl-azetidines 18–22 (Scheme 3A).

Benzyl 3-((4-bromophenyl)sulfinyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(18)**. *m*CPBA (45.3 mg, 0.26 mmol) was added in 3 portions over 30 minutes to a solution of azetidine **2d** (121 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at 0 ºC for 2.5 h then 1 M aq. K_2CO_3 (10 mL) and CH_2Cl_2 (15 mL) were added. The phases were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% Et_2O/pentane) afforded sulfoxide **18** (100 mg, 80%) as a white solid. R_f = 0.30 (70% Et_2O/pentane); mp = 65–70 °C, IR (film)/cm^{-1} 2937, 1707 (C=O), 1610, 1513, 1408, 1353, 1252, 1181, 1129, 1084, 1051, 820, 764, 723; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2 H, 2 × Ar-CH), 7.37–7.32 (m, 5 H, 5 × Ar-CH), 6.84 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-CH), 6.83 (d, *J* = 8.3 Hz, 2 H, 2 × Ar-CH), 6.68 (d, *J* = 8.3 Hz, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.76–4.68 (m, 2 H, C*HH*NCHH), 4.34 (d, *J* = 9.3 Hz, 1 H, CHHNC*H*H), 4.16 (d, *J* = 9.3 Hz, 1 H, CHHNCH*H*), 3.83 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.9 (Ar-C_q-OCH_3), 155.9 (C=O), 137.6 (Ar-C_q-C_q), 136.2 (Ar-C_q-CH_2), 131.4 (2 × Ar-CH), 129.2 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.4 (Ar-C_q-Br), 125.5 (Ar-C_q-SO), 113.9 (2 × Ar-CH), 67.1 (C_q, OCH_2Ph), 62.6 (CH_2NCH_2), 55.4 (OCH_3); HRMS (ESI) *m/z* Calcd for $C_{24}H_{23}NO_4S^{79}Br^+$ $[M+H]^+$: 500.0531; Found: 500.0541.

Benzyl 3-(benzylsulfinyl)-3-(4-((triisopropylsilyl)oxy)phenyl)azetidine-1-carboxylate **(19)**. *m*CPBA (45.3 mg, 0.26 mmol) was added in 3 portions over 30 minutes to a solution of azetidine **10** (141 mg,

0.25 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at 0 ºC for 2.5 h then 1 M aq. K_2CO_3 (10 mL) and CH_2Cl_2 (15 mL) were added. The phases were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (60% Et_2O/pentane) afforded sulfoxide **19** (122 mg, 84%) as a colorless oil. R_f = 0.06 (50% Et_2O/pentane); IR (film)/cm^{-1} 2944, 2866, 1707 (C=O), 1602, 1509, 1453, 1408, 1353, 1267, 1125, 1073, 905, 838, 752, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 8 H, 8 × Ar-CH), 7.14–7.10 (m, 4 H, 4 × Ar-CH), 7.02–6.98 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.83 (d, *J* = 9.4 Hz, 1 H, C*H*HNCHH), 4.62–4.48 (m, 2 H, CH*H*NC*H*H), 4.36 (d, *J* = 9.3 Hz, 1 H, CHHNCH*H*), 3.43 (d, *J* = 12.7 Hz, 1 H, SC*H*HPh), 3.26 (s, 1 H, SCH*H*Ph), 1.34–1.25 (m, 3 H, 3 × CH), 1.13 (d, *J* = 7.4 Hz, 18 H, 6 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.6 (Ar-C_q-OTIPS), 155.9 (C=O), 136.1 (Ar-C_q-OCH_2), 130.0 (Ar-C_q-C_q), 130.3 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.4 (4 × Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 126.3 (Ar-C_q-CH_2), 120.6 (2 × Ar-CH), 67.0 (OCH_2Ph), 59.9 (C_q), 57.3 and 56.1 (CH_2NCH_2), 53.1 (br, $SOCH_2Ph$), 51.6 (CH_2NCH_2), 17.8 (3 × CH), 12.6 (6 × CH_3); HRMS (ESI) *m/z* Calcd for $C_{33}H_{44}NO_4SSi^+$ $[M+H]^+$: 578.2760; Found: 578.2770.

Benzyl 3-(4-methoxyphenyl)-3-(phenylsulfonyl)azetidine-1-carboxylate **(20)**. *m*CPBA (129 mg, 0.75 mmol) was added to a solution of azetidine **2c** (101 mg, 0.25 mmol) in CH_2Cl_2 (12.5 mL). The reaction mixture was stirred at 25 °C for 3 h, then quenched with aq. KOH (3 M, 5.0 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 5 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The sulfone **20** (109 mg, 100%) was obtained as a yellow solid. R_f = 0.31 (80% Et_2O/pentane); mp = 156–159 °C; IR (film)/cm^{-1} 3021, 2979, 2849, 1715 (C=O), 1610, 1515, 1448, 1418, 1303, 1259, 1172, 1141, 829, 762, 727, 691, 621, 578, 526; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 1 H, Ar-CH), 7.41–7.30 (m, 9 H, 9 × Ar-CH), 6.82–6.76 (m, 4 H, 4 × Ar-CH), 5.11 (s, 2 H, OCH_2Ph), 4.94 (s, br, 2 H, C*H*HNC*H*H), 4.38 (d, *J* = 9.4 Hz, 2 H, CH*H*NCH*H*), 3.79 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.0 (Ar-C_q-OCH_3), 155.8 (C=O), 136.1 (Ar-C_q-CH_2), 134.2 (Ar-CH, Ar-C_q-SO_2), 130.0 (2 × Ar-CH), 129.9 (2 × Ar-CH), 128.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 125.9 (Ar-C_q-C_q), 113.6 (2 × Ar-CH), 67.2 (OCH_2Ph), 64.4 (C_q), 56.7 and 56.1 (CH_2NCH_2), 55.4 (OCH_3); HRMS (ESI) *m/z* Calcd for $C_{24}H_{24}NO_5S^+$ $[M+H]^+$: 438.1375; Found: 438.1381.

Benzyl 3-(benzylsulfonyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate **(21)**. *m*CPBA (129 mg, 0.75 mmol) was added to a solution of azetidine **2a** (105 mg, 0.25 mmol) in CH_2Cl_2 (12.5 mL). The reaction mixture was stirred at 25 °C for 3 h, then quenched with aq. KOH (3 M, 5.0 mL). The layers were

separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 5 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The sulfone **21** (113 mg, 100%) was obtained as a white solid. R_f = 0.32 (80% Et_2O/pentane); mp = 81 °C; IR (film)/cm^{-1} 2956, 2258, 1705 (C=O), 1704, 1611, 1514, 1411,1354, 1302, 153, 1124, 1031, 910, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 12 H, 12 × Ar-CH), 7.01 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 5.10 (s, 2 H, OCH_2Ph), 4.78 (s, br, 2 H, C*H*HNC*H*H), 4.40 (d, *J* = 9.5 Hz, 2 H, CH*H*NCH*H*), 3.92–3.87 (m, 5 H, OCH_3, SCH_2Ph); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.3 (Ar-C_q-OCH_3), 155.7 (C=O), 136.0 (Ar-C_q-CH_2), 131.0 (2 × Ar-CH), 129.9 (2 × Ar-CH), 129.0 (Ar-CH), 128.7 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 126.0 (Ar-C_q-CH_2), 125.5 (Ar-C_q-C_q), 114.4 (2 × Ar-CH), 67.1 (OCH_2Ph), 63.3 (C_q), 56.5 and 55.9 (CH_2NCH_2), 55.4 (SO_2CH_2Ph), 53.6 (OCH_3); HRMS (ESI) *m/z* Calcd for $C_{25}H_{25}NO_5SNa^+$ $[M+Na]^+$: 474.135; Found: 474.1352.

Benzyl 3-((3-methoxy-3-oxopropyl)sulfonyl)-3-(4-methoxyphenyl) azetidine-1-carboxylate **(22)**. *m*CPBA (129 mg, 0.75 mmol) was added to a solution of azetidine **2n** (104 mg, 0.25 mmol) in CH_2Cl_2 (12.5 mL). The reaction mixture was stirred at 25 °C for 3 h, then quenched with aq. KOH (3 M, 5.0 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 5 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The sulfone **22** (112 mg, 100%) was obtained as a white solid. R_f = 0.13 (100% Et_2O); mp = 136–137 °C; IR (film)/cm^{-1} 2997, 2968, 1736, 1710 (C=O), 1611, 1518, 1466, 1415, 1355, 1299, 1253, 1179, 1122, 816, 752, 695, 609, 540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 7 H, 7 × Ar-CH), 6.97 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, OCH_2Ph), 4.86 (d, *J* = 9.4 Hz, 2 H, C*H*HNC*H*H), 4.48 (d, *J* = 9.4 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 3.69 (s, 3 H, CO_2CH_3), 3.05–3.01 (m, 2 H, $SCH_2CH_2CO_2Me$), 2.69–2.65 (m, 2 H, $SCH_2CH_2CO_2Me$); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6 (CO_2CH_3), 160.4 (Ar-C_q-OCH_3), 155.8 (C=O), 136.0 (Ar-C_q-CH_2), 129.6 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.0 (2 × Ar-CH), 125.1 (Ar-C_q-C_q), 114.5 (2 × Ar-CH), 67.2 (C_q), 63.2 (OCH_2Ph), 56.3 and 55.8 (CH_2NCH_2), 55.4 (OCH_3), 52.4 (CO_2CH_3), 42.8 ($SO_2CH_2CH_2CO_2Me$), 25.7 ($SO_2CH_2CH_2CO_2CH_3$); HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}NO_7S^+$ $[M+H]^+$: 448.1430; Found: 448.1440.

Cbz removal. Synthesis of NH-azetidines 23–25 (Scheme 3B).

3-((4-Bromophenyl)thio)-3-(4-methoxyphenyl)azetidine **(23)**. Me_3SiI (1.20 mL, 8.50 mmol) was added to a solution of azetidine **2d** (484 mg, 1.00 mmol) in MeCN (5.0 mL) at −10 °C. The reaction mixture was stirred for 4 h 30 min at −5 °C then quenched with MeOH (1.0 mL). After stirring for a further 10 min, the solvent was removed under reduced pressure. Purification by flash column chromatography (4% MeOH/CH_2Cl_2) afforded amine **23** (301 mg, 99 %) as a yellow solid. R_f = 0.23 (5% MeOH/CH_2Cl_2);

mp = 142–146 °C; IR (film)/cm^{-1} 2896 (br, NH), 1610, 1513, 1468, 1438, 1297, 1244, 1177, 1036, 1006, 816, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2 H, 2 × Ar-CH), 7.07–7.04 (m, 2 H, 2 × Ar-CH), 6.79 (s, 4 H, 4 × Ar-CH), 5.70 (s, br, 1 H, NH), 4.59–4.56 (m, 2 H, C*H*HNC*H*H), 4.37–4.34 (m, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_q-OCH_3), 137.9 (2 × Ar-CH), 132.30 (2 × Ar-CH), 132.25 (Ar-C_q-C_q), 128.8 (S-C_q-Ar), 127.2 (2 × Ar-CH), 124.9 (Ar-C_q-Br), 114.0 (2 × Ar-CH), 56.4 (CH_2NCH_2), 55.4 (OCH_3), 52.5 (C_q); HRMS (ESI) *m/z* Calcd for $C_{16}H_{17}NOS^{79}Br^{+}$ $[M+H]^{+}$: 350.0214; Found: 350.0208.

3-((4-Methoxybenzyl)thio)-3-(4-methoxyphenyl)azetidine **(24)**. Me_3SiI (75 µL, 0.53 mmol) was added in three portions over 30 min to a solution of azetidine **2b** (90 mg, 0.20 mmol) in MeCN (1.2 mL) at −10 °C. The reaction mixture was stirred for 1 h then quenched with MeOH (50 µL). After stirring for a further 10 min, the solvent was removed under reduced pressure. Purification by flash column chromatography (2 to 8% MeOH/CH_2Cl_2) afforded amine **24** (62.0 mg, 98 %) as a pale yellow solid. R_f = 0.10 (5% MeOH/CH_2Cl_2); mp = 149–151 °C; IR (film)/cm^{-1} 3004 (br, NH), 2926, 2840, 1606, 1509, 1461, 1300, 1237, 1177, 1118, 1073, 1032, 808, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.11 (m, 4 H, 4 × Ar-CH), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 6.83–6.80 (m, 2 H, 2 × Ar-CH), 4.45–4.42 (m, 2 H, C*H*HNC*H*H), 4.06–4.03 (m, 2 H, CH*H*NCH*H*), 3.85 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.48 (s, 2 H, SCH_2Ph); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q-OCH_3), 159.0 (Ar-C_q-OCH_3), 131.3 (Ar-C_q-C_q), 130.3 (2 × Ar-CH), 127.8 (Ar-C_q-CH_2), 127.4 (2 × Ar-CH), 114.4 (2 × Ar-CH), 114.2 (2 × Ar-CH), 56.8 (CH_2NCH_2), 55.4 (OCH_3), 55.3 (OCH_3), 50.0 (C_q), 34.8 (SCH_2Ph); HRMS (ESI) *m/z* Calcd for $C_{18}H_{22}NO_2S^{+}$ $[M+H]^{+}$: 316.1371; Found: 316.1380.

3-(((3s,5s,7s)-Adamantan-1-yl)thio)-3-(4-methoxyphenyl)azetidine **(25)**. Me_3SiI (114 µL, 0.80 mmol) was added in three portions over 30 min to a solution of azetidine **2m** (92.7 mg, 0.2 mmol) in MeCN (1.2 mL) at −10 °C. The reaction mixture was stirred for 1 h then quenched with MeOH (50 µL). After stirring for a further 10 min, the solvent was removed under reduced pressure. Purification by flash column chromatography (2 to 4% MeOH/CH_2Cl_2) afforded amine **25** (64.6 mg, 98 %) as a pale yellow solid. R_f = 0.15 (5% MeOH/CH_2Cl_2); mp = 197 °C (decomposition at 184 °C to black amorphous solid); IR (film)/cm^{-1} 2903 (br, NH), 2847, 1610, 1513, 1449, 1300, 1241, 1185, 1099, 1036, 916, 831, 775, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2 H, 2 × Ar-CH), 6.91–6.87 (m, 2 H, 2 × Ar-CH), 6.30 (s, br, 1 H, NH), 4.63–4.60 (m, 2 H, C*H*HNC*H*H), 4.34–4.31 (m, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 1.86 (s, 3 H, 3 × CH), 1.58–1.47 (m, 12 H, 6 × CH_2); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.0 (Ar-C_q-OCH_3), 133.6 (Ar-C_q-C_q), 127.6 (2 × Ar-CH), 114.0 (2 × Ar-CH), 56.6 (CH_2NCH_2), 55.3 (OCH_3), 50.1

(C_q), 49.1 (S-$C_{q(adamantane)}$), 43.4 (3 × CH_2), 35.8 (3 × CH_2), 29.4 (3 × CH); HRMS (ESI) *m/z* Calcd for $C_{20}H_{28}NOS^+$ $[M+H]^+$: 330.1892; Found: 330.1896.

Derivatization. Synthesis of azetidines 26–28 (Scheme 3C).

2-(3-((4-Bromophenyl)thio)-3-(4-methoxyphenyl)azetidin-1-yl)pyrimidine **(26)**. A solution of amine **23** (75.3 mg, 0.25 mmol), 2-chloropyrimidine (34.4 mg, 0.30 mmol) and KF (19.1 mg, 0.33 mmol) in water/MeCN (2/1, 1.0 mL) was stirred at 80 °C for 22 h. The reaction mixture was then cooled to rt and water (20 mL) was added. The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/pentane) afforded azetidine **26** (50.8 mg, 47%) as an off white solid. R_f = 0.13 (40% Et_2O/pentane); mp = 113–116 °C; IR (film)/cm^{-1} 2969, 2914, 2870, 1576, 1543, 1490, 1446, 1379, 1293, 1244, 1174, 1006, 820, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.8 Hz, 2 H, 2 × $Ar_{(pyrimidine)}$-CH), 7.34–7.31 (m, 2 H, 2 × Ar-CH), 7.07–7.04 (m, 2 H, 2 × Ar-CH), 7.03–6.99 (m, 2 H, 2 × Ar-CH), 6.85–6.81 (m, 2 H, 2 × Ar-CH), 6.57 (t, *J* = 4.8 Hz, 1 H, $Ar_{(pyrimidine)}$-CH), 4.61 (d, *J* = 9.4 Hz, 2 H, C*H*HNC*H*H), 4.55 (d, *J* = 9.4 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5 (N-$C_{q(pyrimidine)}$), 158.6 (Ar-C_q-OCH_3), 157.8 (2 × $Ar_{(pyrimidine)}$-CH), 137.1 (2 × Ar-CH), 134.7 (Ar-C_q-C_q), 131.8 (2 × Ar-CH), 131.0 (S-C_q-Ar), 127.9 (2 × Ar-CH), 123.7 (Ar-C_q-Br), 113.6 (2 × Ar-CH), 110.8 ($Ar_{(pyrimidine)}$-CH), 62.6 (CH_2NCH_2), 55.3 (OCH_3), 50.6 (C_q); HRMS (ESI) *m/z* Calcd for $C_{20}H_{19}N_3OS^{79}Br^+$ $[M+H]^+$: 428.0432; Found: 428.0422.

tert-Butyl 4-(3-((4-bromophenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carbonyl)piperidine-1-carboxylate **(27)**. DMAP (30.5 mg, 0.25 mmol) followed by EDC·HCl (57.5 mg, 0.30 mmol) was added to a solution of amine **23** (75.3 mg, 0.25 mmol) and boc-Inp-OH (64.2 mg, 0.28 mmol) in CH_2Cl_2 (1.25 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (80% Et_2O/pentane) afforded azetidine **27** (85.8 mg, 61%) as a white solid. R_f = 0.12 (70% Et_2O/pentane); mp = 146–148 °C; IR (film)/cm^{-1} 2955, 2878, 1692 (C=O), 1636 (C=O), 1517, 1453, 1423, 1394, 1364, 1304, 1244, 1166, 1066, 1006, 931, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2 H, 2 × Ar-CH), 7.04–7.01 (m, 2 H, 2 × Ar-CH), 6.95–6.92 (m, 2 H, 2 × Ar-CH), 6.85–6.82 (m, 2 H, 2 × Ar-CH), 4.60 (d, *J* = 8.6 Hz, 1 H, C*H*HNCHH), 4.48–4.44 (m, 2 H, CH*H*NCH*H*), 4.39 (d, *J* = 9.8 Hz, 1 H, CHHNC*H*H), 4.12 (s, br, 2 H, $CH_2CHHNCHHCH_2$), 3.81 (s, 3 H, OCH_3), 2.76–2.72 (m, 2 H, $CH_2CHHNCHHCH_2$), 2.24 (tt, *J* = 10.5, 5.0 Hz, 1 H, COC*H*), 1.68–1.57

(m, 4 H, C*H*$_2$CH$_2$NCH$_2$C*H*$_2$), 1.46 (s, 9 H, 3 × CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.3 (C=O), 158.8 (Ar-*C*$_q$-OCH$_3$), 154.6 (C=O), 137.1 (2 × Ar-CH), 133.8 (Ar-*C*$_q$-C$_q$), 132.0 (2 × Ar-CH), 130.4 (S-C$_q$-Ar), 127.8 (2 × Ar-CH), 124.1 (Ar-C$_q$-Br), 113.8 (2 × Ar-CH), 79.6 (*C*$_q$(CH$_3$)$_3$), 62.6 (*C*H$_2$NCH$_2$), 60.3 (CH$_2$N*C*H$_2$), 55.3 (OCH$_3$), 49.7 (C$_q$), 42.7 (br, CH$_2$*C*H$_2$N*C*H$_2$CH$_2$), 38.0 (CO*C*H), 28.4 (3 × CH$_3$), 27.6 (*C*H$_2$CH$_2$NCH$_2$CH$_2$), 27.5 (CH$_2$CH$_2$NCH$_2$*C*H$_2$); HRMS (ESI) *m/z* Calcd. for C$_{27}$H$_{34}$N$_2$O$_4$S^{79}Br$^+$ [M+H]$^+$: 561.1423; Found: 561.1417.

Benzyl 3-(4-methoxyphenyl)-3-((4-(3-(trifluoromethyl)-1H-pyrazol-4-yl)phenyl)thio)azetidine-1-carboxylate **(28)**. Azetidine **2d** (121 mg, 0.25 mmol), pyrazole pinacol ester (83.9 mg, 0.32 mmol), Pd(PPh$_3$)$_4$ (28.9 mg, 0.025 mmol) and K$_2$CO$_3$ (69.1 mg, 0.50 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. DME/water (88:22, 2.5 mL) was added *via* syringe into the vial. The reaction mixture was stirred at 100 °C for 18 h then cooled to rt. Diethylether (15 mL) was added and the crude mixture was filtered through celite and then concentrated under reduced pressure. Purification by flash column chromatography (8% Et$_2$O/pentane) afforded azetidine **28** (107 mg, 79%) as a white solid. R$_f$ = 0.25 (8% Et$_2$O/pentane); mp = 67–72 °C; IR (film)/cm^{-1} 3172 (br, NH), 2952, 1684 (C=O), 1513, 1453, 1420, 1356, 1248, 1114, 1032, 976, 827, 730, 697; ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.71 (s, 1 H, NH), 7.66 (d, *J* = 1.1 Hz, 1 H, N-Ar-CH), 7.29–7.19 (m, 7 H, 7 × Ar-CH), 7.13–7.10 (m, 2 H, 2 × Ar-CH), 6.88–6.85 (m, 2 H, 2 × Ar-CH), 6.75–6.71 (m, 2 H, 2 × Ar-CH), 5.02 (s, 2 H, OCH$_2$Ph), 4.44 (d, *J* = 9.1 Hz, 2 H, C*H*HNC*H*H), 4.37 (d, *J* = 9.1 Hz, 2 H, CH*H*NCH*H*), 3.73 (s, 3 H, OCH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 158.7 (Ar-*C*$_q$-OCH$_3$), 156.3 (C=O), 136.3 (Ar-*C*$_q$-CH$_2$), 135.6 (2 × Ar-CH), 134.3 (Ar-*C*$_q$-C$_q$), 131.4 (Ar-*C*$_q$-C$_{q(pyrazole)}$), 131.1 (S-C$_q$-Ar), 129.7 (br, N-Ar-CH), 128.9 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.8 (2 × Ar-CH), 121.7 (q, $J_{C\text{-}F}$ = 268.9 Hz, CF$_3$), 121.0 (Ar-C$_q$-*C*$_{q(pyrazole)}$), 113.6 (2 × Ar-CH), 67.0 (OCH$_2$Ph), 61.7 (*C*H$_2$N*C*H$_2$), 55.3 (OCH$_3$), 50.4 (C$_q$); The Ar$_{(pyrazole)}$-*C*$_q$-CF$_3$ signal could not be observed; ^{19}F NMR (377 MHz, CDCl$_3$) δ –59.2; HRMS (ESI) *m/z* Calcd. for C$_{28}$H$_{25}$N$_3$O$_3$SF$_3$ [M+H]$^+$: 540.1569; Found: 540.1569.

ASSOCIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H and ^{13}C NMR spectra. (PDF)

All characterization data for synthesized compounds can be found at https://doi.org/10.14469/hpc/5435.

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