Supporting Information

Triphenylbutanamines – Kinesin Spindle Protein inhibitors with *in vivo* anti-tumour activity

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Abbreviations – CD, circular dichroism; DMF, dimethylformamide; DMEM, Dulbecco's modified eagle medium; DMSO, dimethyl sulfoxide; EC_{50}, half maximal effective concentration; EtOAc, ethyl acetate; FDVA, N_{α}-(2,4-dinitro-5-fluorophenyl)-L-valinamide; FMOC, fluorenylmethyloxycarbonyl; GC-MS, gas chromatography mass spectra; h, hour; hERG, human ether-ago-go related gene; HPLC, high performance liquid chromatography; HRMS, high resolution mass spectrometry; IC_{50}, median inhibitory concentration; K_i^{app}, apparent K_i values; LC, liquid chromatography; LC-MS, liquid chromatography–mass spectrometry; n.i.; no inhibition; NMR, nuclear magnetic resonance; PBS, phosphate buffered saline; RP(SP)-HPLC, reverse-phase (straight-phase) HPLC; RTV, relative tumour volume; STDC, *S*-trityl-*D*-cysteine; STLC, *S*-trityl-*L*-cysteine; T/C, relative test tumour versus control value; T3P, propylphosphonic anhydride solution; TLC, thin layer chromatography; THF, tetrahydrofuran.

Contents

1. Materials and Methods

A) Biology

ADME profiling

To determine turbidimetric solubility, compounds were measured at 1 μM, 3 μM, 10 μM, 30 μM and 100 μM at a final DMSO concentration of 1% in 10 mM phosphate buffered saline at pH 7.4. Pyrene and Nicardipine were used as controls. The temperature was 37°C with an incubation time of 2 h and the turbidimetry was measured at a wavelength of 620 nm. The number of replicates was n=7.

Log D (distribution coefficient) is used as a measure of lipophilicity. The log $D_{7.4}$ was measured using the miniaturized shake flask method. The partition solvent was *n*-octanol with ratios of buffer:octanol of 50:1, 5:1 and 1:2 (v/v). Acetobutolol and ketoconazole were used as positive controls. LC-MS/MS is used to quantify the samples.

The acid dissociation constant (pKa), the partition coefficient (log P) and the distribution coefficient (log D) were determined using the potentiometric method on a GLpKA 9902163 (Sirius, East Sussex, UK) under standard conditions.

Human and mouse microsomal stability was measured at a compound concentration of 3 μM and a microsome concentration of 0.5 mg/ml at time points of 0.5,15,30 and 45 min. The final DMSO concentration was 0.25%. NADPH was included as a cofactor to initiate the reaction. Dextromethorphan and verapamil and diazepam and diphenydramine were included as controls for human and mouse microsomes, respectively. The disappearance of compounds was monitored using LC-MS/MS. The stability is expressed as the intrinsic clearance (Cl_{int}) ± its standard error and the half-life ($t_{1/2}$). Compounds with Cl_{int} values <8.6 (mouse: 8.8) or >47.0 (mouse (48.0) were classified as showing low and high clearance, respectively. Compounds with negative values are considered stable in microsomal stability assays.

Human hepatocyte stability was measured at a compound concentration of 3 μM using cryopreserved hepatocytes. Incubation time was 0, 5, 10, 20, 40 and 60 min. The final DMSO concentration was 0.25%. Compounds with known activity were included as controls. Data were analyzed using LC-MS/MS. The stability is expressed as the intrinsic clearance ± its standard error and the half-life.

The extent of binding to human plasma was determined by equilibrium dialysis at 50% plasma at compound concentrations of 5 μM. The experiments were performed as duplicates. Quantifications were performed in each compartment by LC-MS/MS equilibration at 37°C. Plasma protein binding is expressed as fraction unbound ($fu_{100\%}$) in 100% plasma and the recovery (%Recovery) is given.

Inhibition of the human ether-ago-go related gene (hERG) was investigated using the Ionworks HT system (Molecular Devices). CHO-hERG cells were used with amphotericin B as the perforating agent. The compound concentrations for the calculation of the IC_{50} values were 0.008, 0.04, 0.2, 1, 5, and 25 μM (4 replicates). The final DMSO concentration was 0.25%. Quinidine was used as a positive control.

To assess whether the compounds inhibit one of the main cytochrome P450 isoforms CYP1A, CYP2C9, CYP2C19, CYP2D6 or CYP3A4, which might lead to adverse drug reactions or toxicity, we performed cytochrome P450 inhibition assays. Assays were performed at a range of compound concentrations (0, 0.1, 0.25, 1, 2.5, 10, 25 μM) in the presence of isoform-specific substrates. Known isoform-specific inhibitors (α-naphthoflavone, sulphaphenazole, tranylcypromine, quinidine, and ketoconazole) were used as controls. The formation of metabolites was monitored using LC-MS/MS and IC_{50} values and their standard errors were calculated.

To determine bioavailability, the compounds are administered by intravenous and by oral routes to mice at 5 mg/kg. The vehicle used was 17.5-21.3 mM sodium citrate, pH 5.0, 15% DMSO, 0.5-1.0% Tween 80 and **35**, **36** or ispinesib. Up to eight blood samples were taken over a period of up to 8 h. The compound concentrations were quantified using LC-MS/MS. Pharmacokinetic parameters were extracted for oral (C_{max}, t_{max}, AUC_{last}) and intravenous (C_0, AUC_{last}, $t_{1/2}$, V_D, and CL) dosing.

B) Chemistry

Optical rotations

The optical rotations of resolved enantiomers were determined on a Perkin Elmer 341 polarimeter (PerkinElmer, San Jose, USA). The enantiomers were dissolved in methanol and their optical rotations were measured.

Circular dichroism

For the CD spectra of STLC **1**, **29-1** and **29-2**, they were dissolved in methanol and the measurements were carried out on an Applied Photophysics Chirascan CD spectropolarimeter (Applied Photophysics, Leatherhead, UK) at 20 °C using a 1 mm quartz cell with a volume of 350 µL. The following instrument settings were used: band width 1.0 nm, resolution 0.2 nm, accumulation 3, sensitivity 20 mdeg, response 1 sec, speed 50 nm/min.

Evaluation of acid stability at pH = 1 by LC-HRMS

Compounds **1,** and **6-10** (1 mg) were dissolved in 0.1 M HCl/CH_3OH (0.6 ml, pH = 1). Each solution was tested by LC-HRMS at t = 0, 2, 4, 8, 16, and 24 h. Compounds separated by LC were first identified by their accurate mass. Subsequently, peak areas obtained from the UV signals for the non-decomposed compound were plotted *versus* time to calculate the decomposition rate for each compound.

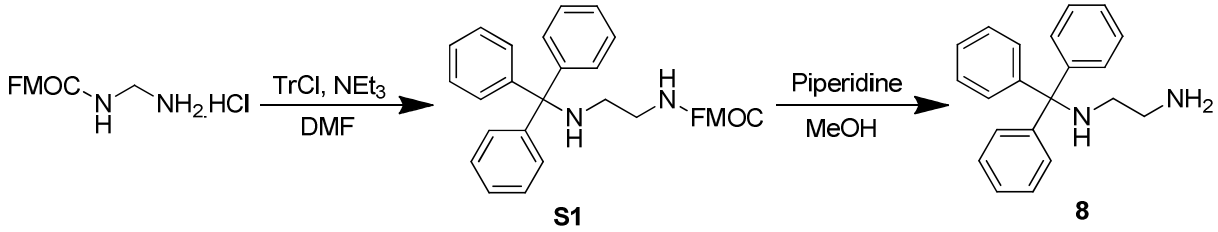
2. Experimental Procedures

A) Typical Procedures

This section contains a series of representative procedures and characterization data for the prepared examples. Synthesis of all remaining compounds and characterization of all other analogues by the general procedures described is found in Section 2B.

General procedure (i): Synthesis of *N*-trityl analogues

Diamino analogues **8** and **S12-15** were synthesized according to the route depicted in Scheme S1; a representative procedure is provided for the synthesis of **8**.



S1 **8**

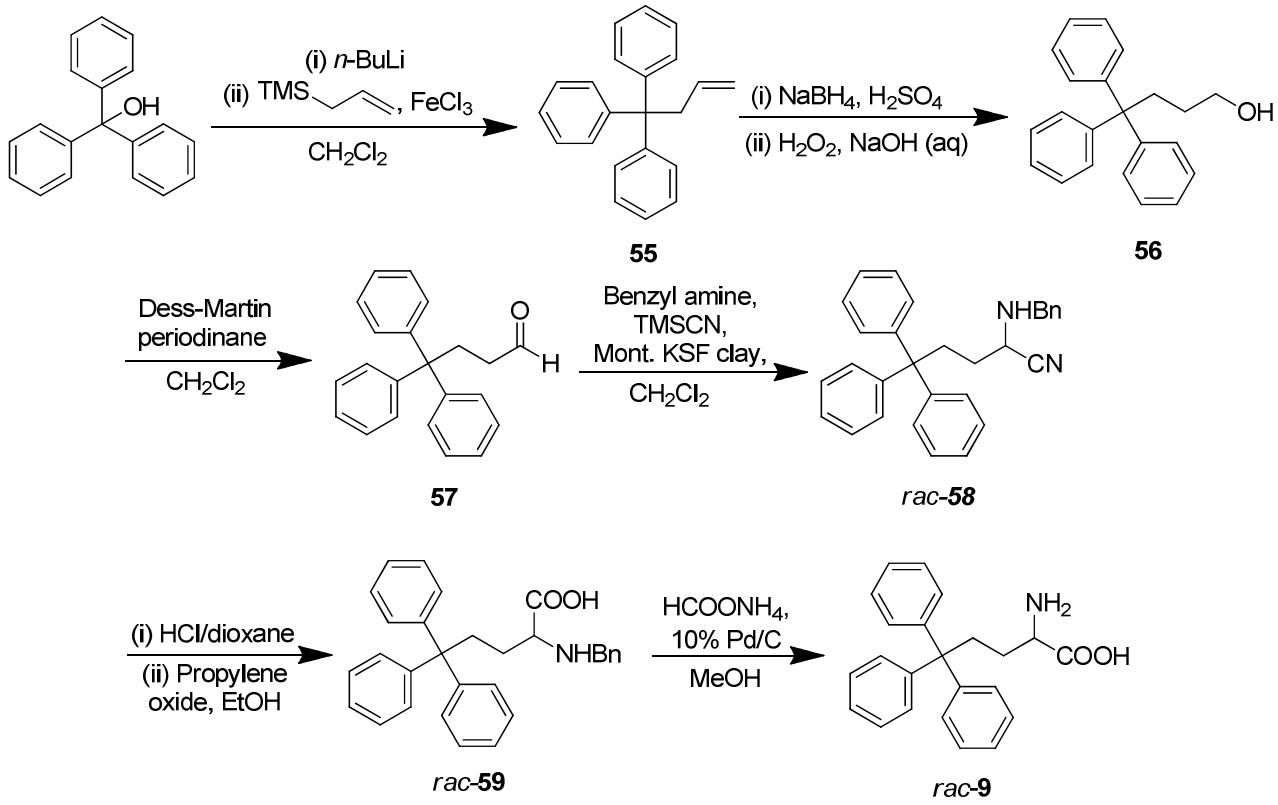
Scheme S1

***N*-Tritylethane-1,2-diamine (8).**

The title compound was prepared using an adaptation of the method reported by Will *et al.*[1] To a suspension of (9*H*-fluoren-9-yl)methyl-2-aminoethylcarbamate hydrochloride (319 mg, 1.0 mmol) in anhydrous DMF (5 mL) was added triethylamine (0.42 mL, 3.0 mmol). The mixture was cooled (*circa.* 4°C) and treated with a solution of trityl chloride (418 mg, 1.5 mmol) in CH_2Cl_2. The mixture was stirred at room temperature for 3 h, filtered and diluted with EtOH (2 mL) and concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 6-40% EtOAc in hexane with 0.5% NH_4OH] to give **S1** as a white solid (459 mg, 88%). (9*H*-Fluoren-9-yl)methyl-2-(tritylamino)ethylcarbamate **S1** (138 mg, 0.26 mmol) was dissolved in 20% piperidine-MeOH (10 mL), stirred at room temperature for 2 h, and then concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give **8** as a colorless solid (71 mg, 90%). Mpt. 94°C. ^{1}H NMR (400 MHz, CD_3OD) δ = 2.20-2.23 (t, 2H, CH_2), 2.71-2.74 (t, 2H, CH_2), 7.16-7.47 (m, 15H, Ph). ^{13}C NMR (100 MHz, CD_3OD) δ = 41.7, 45.8, 70.7, 125.9, 127.4, 128.6, 146.2. HRMS (ESI+) calcd. for $C_{21}H_{22}N_2$ $(M+H)^+$: 303.18558; found: 303.18539. Analysis calcd. for $C_{21}H_{22}N_2 \cdot 0.5H_2O$: C, 80.99; H, 7.44; N, 9.00. Found: C, 81.45; H, 7.30; N, 8.92.

General Procedure (ii): Synthesis of amino acid containing *C*-trityl analogues

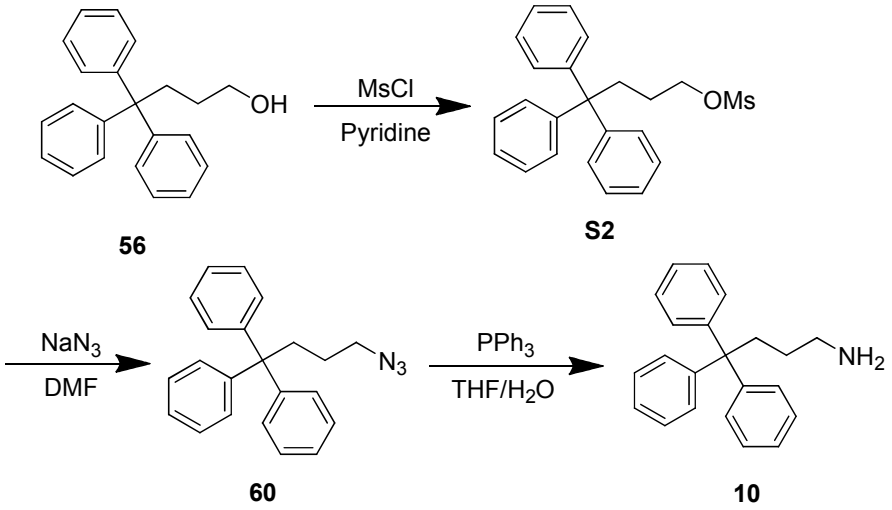
Racemic *C*-trityl analogues ***rac*-9**, ***rac*-29** and ***rac*-32** were synthesized by the route depicted in Scheme S2. Representative procedures for analogue **9** are described in the main text.



Scheme S2

General Procedure (iii): Synthesis of 4,4,4-Triphenylbutan-1-amine analogues

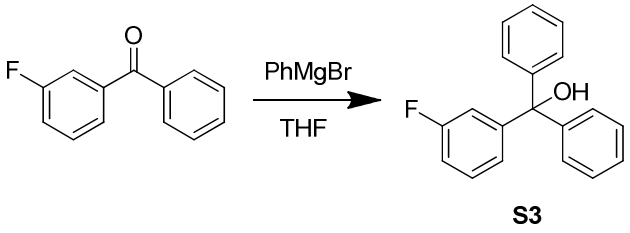
Triphenylbutan-1-amines **10**, **28, 30, 31** and **33** were synthesized by the route depicted in Scheme S3. Representative procedures for analogue **10** are described in the main text.



Scheme S3

General procedure (iv): Preparation of trityl alcohols by PhMgBr reduction of substituted benzophenones:

Representative procedure for the synthesis of intermediate trityl alcohols from commercially available substituted benzophenones (Scheme S4).



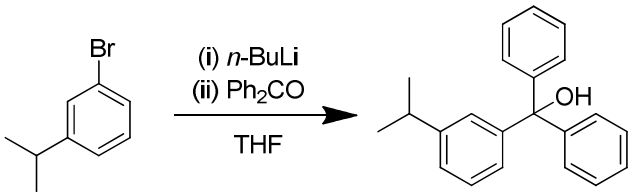
Scheme S4

(3-Fluorophenyl)(diphenyl)methanol (S3).

To a solution of (3- fluorophenyl)(phenyl)methanone (2.00 g, 10 mmol) in anhydrous THF (5 mL) was added PhMgBr (2M in THF, 12.5 ml, 25 mmol) and stirred at reflux for 20.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 25 mL). The organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash chromatography [SiO_2; 0-18% EtOAc in hexane] afforded the trityl alcohol

S3 as a white solid (1.79 g, 64%). Mpt. 112-113°C (lit. 117°C).[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.80 (s, 1H, OH), 6.96-7.00 (m, 1H), 7.05-7.10 (m, 1H), 7.26-7.36 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 81.86, 114.26 (d, *J* = 21.9 Hz), 115.24 (d, *J* = 22.7 Hz), 123.77, 127.68, 127.98, 128.23, 129.47 (d, *J* = 8.7 Hz), 146.49, 149.60 (d, *J* = 6.0 Hz), 162.71 (d, *J* = 245.7 Hz). HRMS (ESI+) calcd. for $C_{19}H_{14}F$ $(M+H-OH)^+$: 261.10741; found: 261.10742.

General procedure (v): Synthesis of trityl alcohols by reduction of benzophenone with lithiated aryl bromides.



S4

Scheme S5

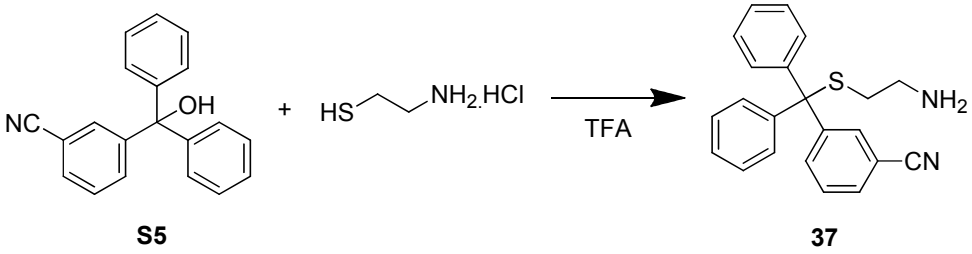
Diphenyl(3-(propan-2-yl)phenyl)methanol (S4).

The title compound was prepared using an adaptation of the procedures described by Zhang *et al*. and Deshpande *et al*.[3, 4] *n*-Butyllithium (2.5 M in hexane, 4.8 mL, 12.2 mmol) was added to a cooled (-78°C) solution of 1-bromo-3-(propan-2-yl)benzene (1.55 mL, 10 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred for 1 h at -78°C, treated with a solution of benzophenone (2.10 g, 11.5 mmol) in anhydrous THF (10 mL) and stirred for a further 3 h at the same temperature. The mixture was then warmed to room temperature, stirred for 24 h, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). Following washing the combined organic layers with H_2O (75 mL) and brine (75 mL), drying ($MgSO_4$) and concentrating *in vacuo*, the crude product was purified by flash chromatography [SiO_2; 0-12% EtOAc in petroleum ether (40/60)] to afford tertiary trityl alcohol **S4** as a colorless oil, which solidified on standing to a white solid (1.41 g, 47%). Mpt. 51-54°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.22 (d, *J* = 7.0 Hz, 6H, 2 x CH_3), 2.83-2.92 (m, 2H), 7.03-7.05 (m, 1H), 7.17-7.19 (m, 1H), 7.22-7.26 (m, 2H), 7.29-7.35 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.11, 34.29, 82.28, 125.29, 125.76, 126.36, 127.30, 127.90, 128.00, 128.08, 146.90, 147.17, 148.73. HRMS (ESI+) calcd. for $C_{22}H_{21}$ $(M+H-OH)^+$: 285.16378; found: 285.16408. Analysis calcd. for $C_{22}H_{22}O$: C, 87.38; H, 7.33 Found: C, 85.02; H, 7.24.

General procedure (vi): Thioetherification of trityl alcohols

Unless otherwise noted, thioethers were prepared from trityl alcohols by thioetherification in trifluoroacetic acid with cysteine or cysteamine hydrochloride by adaptation of the procedure reported by

Maltese *et al.*[5] A representative procedure is provided for synthesis 3-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile **37**.



S5 **37**

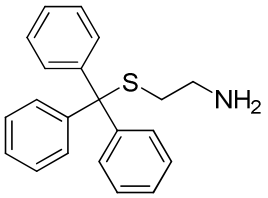
Scheme S6

3-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile (37).

A solution of the tertiary alcohol **S5** (1.0 mmol) with cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1.0 mL) was stirred for 3 h at room temperature. The volatiles were removed *in vacuo*, and the crude basified (*circa.* pH 10) with saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography on silica gel afforded the thioether **37** as a colorless oil (324 mg, 94%). ^{1}H NMR (400 MHz, MeOD) δ = 2.33 (t, *J* = 6.9 Hz, 2H, CH_2), 2.46 (t, *J* = 6.9 Hz, 2H, CH_2), 7.24-7.29 (m, 2H), 7.30-7.36 (m, 4H), 7.38-7.43 (m, 4H), 7.46-7.51 (m, 1H), 7.59-7.62 (m, 1H), 7.73-7.78 (m, 2H). ^{13}C NMR (100 MHz, MeOD) δ = 35.97, 41.46, 67.16, 82.00, 113.12, 119.57, 128.31, 129.30, 130.23, 130.60, 131.65, 133.86, 145.23, 148.32. HRMS (ESI+) Calcd. for $C_{22}H_{21}N_2S$ $(M+H)^+$: 345.1420; found: 345.1417. Analysis calcd. for $C_{22}H_{20}N_2S$: C, 76.71; H, 5.85; N, 8.13. Found: C, 74.01; H, 5.63; N, 7.45.

B) Characterisation and synthetic procedures for all other compounds.

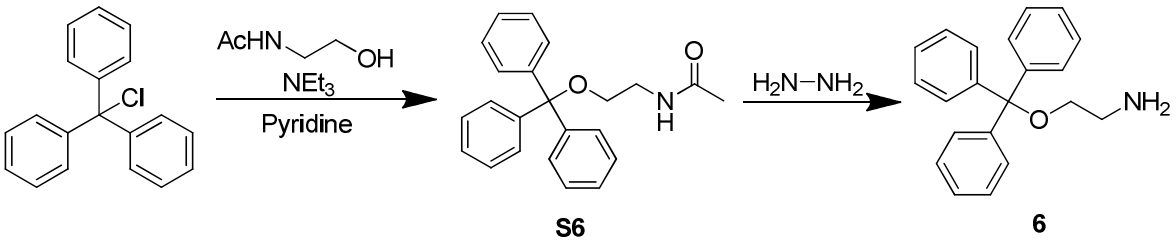
2-(Tritylsulfanyl)ethanamine (2).



2

The title compound was prepared following general procedure (vi) with triphenylmethanol (1.95 g, 7.5 mmol) and cysteamine hydrochloride (937 mg, 8.25 mmol) in trifluoroacetic acid (7.5 mL). Purification by flash chromatography [SiO_2; 0-16% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **2** as a white solid (1.94 g, 81%). Mpt. 87-90°C (lit 90-93°C from petroleum ether).[6] ^{1}H NMR (500 MHz, MeOD) δ = 2.32-2.36 (m, 2H, CH_2), 2.41-2.45 (m, 2H, CH_2), 7.19-7.24 (m, 3H), 7.25-7.31 (m, 6H), 7.39-7.41 (m, 6H). ^{13}C NMR (125 MHz, MeOD) δ = 36.11, 41.56, 67.77, 127.79, 128.89, 130.78, 146.34. HRMS (ESI+) calcd. for $C_{21}H_{22}NS$ $(M+H)^+$: 320.1467; found: 320.1466. Analysis calcd. for $C_{21}H_{21}NS$: C, 78.95; H, 6.63; N, 4.38. Found: C, 78.96; H, 6.63; N, 3.72.

2-(Trityloxy)ethanamine (6).



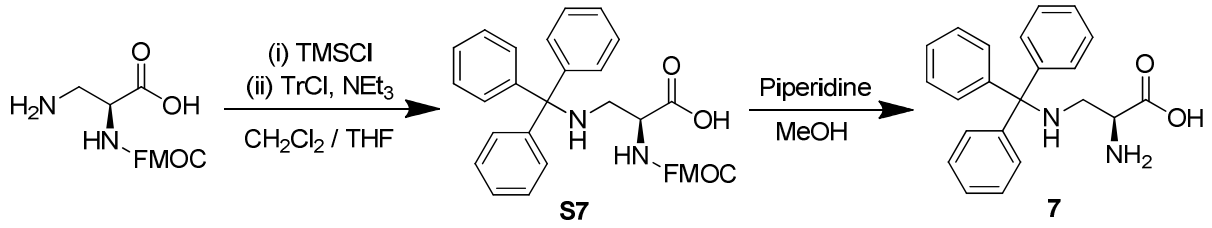
S6 **6**

Scheme S7

Triethylamine (0.5 mL, 3.6 mmol) was added to a solution of *N*-(2-hydroxyethyl)acetamide (500 mg, 0.45 mL, 4.8 mmol) and trityl chloride (2.0 g, 7.2 mmol) in anhydrous pyridine (10 mL). The reaction mixture was stirred at room temperature for 12 h, concentrated *in vacuo* and the crude product purified by flash chromatography [SiO_2; 0-5% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to afford acetamide **S6** as a white solid (1.39 g, 84%). Mpt. 166°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.82 (s, 3H, CH_3), 2.91-2.94 (t, 2H, CH_2), 3.23-3.28 (m, 2H, CH_2), 7.22-7.40 (m, 15H, Ph), 8.04 (t, 1H, NH). ^{13}C NMR (100 MHz,

DMSO-d_6) δ = 22.5, 38.6, 62.6, 85.8, 126.9, 127.8, 128.5, 143.8, 169.2. HRMS (ESI+) calcd. for $C_{23}H_{23}NO_2$ $(M+Na)^+$: 368.16210; found: 368.16223. Analysis calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.74; H, 6.85; N, 4.02. The title compound was then prepared using an adaptation of the method reported by Keith *et al.*[7] *N*-(2-(Trityloxy)ethyl)acetamide (**S6**, 600 mg, 1.74 mmol) was dissolved in 85 % hydrazine hydrate-dioxane (20 mL) and the mixture heated at reflux for 12 h. The reaction was concentrated *in vacuo* and the crude product purified by flash chromatography [SiO_2; 0-20% MeOH in (CH_2Cl_2 with 0.5% NH_4OH)] to give **6** as a white solid (380 mg, 72%). Mpt. 88°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.70-2.74 (t, 2H, CH_2), 2.91-2.94 (t, 2H, CH_2), 7.23-7.40 (m, 15H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 42.2, 66.6, 86.2, 127.5, 128.4, 128.8, 144.6. HRMS (ESI+) calcd. for $C_{21}H_{21}NO$ $(M+H)^+$: 304.16959; found: 304.16937. Analysis calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 82.33; H, 6.99; N, 4.86.

(2*S*)-2-Amino-3-(tritylamino)propanoic acid (7).

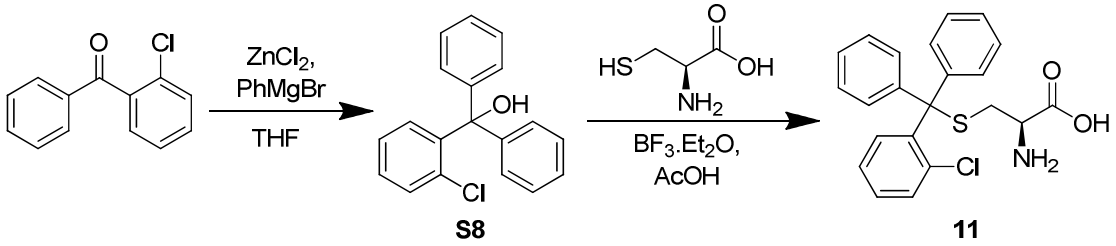


Scheme S8

The title compound was prepared using an adaptation of the method reported by Dubowchik *et al.*[8] Trimethylsilyl chloride (54.3 mg, 63.5 µL, 0.5 mmol) was added to a stirred suspension of Fmoc-Dap-OH (163 mg, 0.5 mmol) in CH_2Cl_2:THF (5:1, 18 mL), the mixture heated at reflux for 2 h and then cooled to room temperature. Triethylamine (0.14 mL, 1 mmol) and a solution of trityl chloride (140 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was then slowly added (CARE!) and the mixture stirred at room temperature for a further 1 h. The reaction was quenched with MeOH (10 mL), concentrated *in vacuo* and the crude product purified by flash chromatography [SiO_2; 0-40% MeOH in (CH_2Cl_2 with 0.5% NH_4OH)] to give **S7** as a white solid (213 mg, 75%). (*S*)-2-(((9*H*-Fluoren-9-yl)methoxy) carbonylamino)-3-(tritylamino)propanoic acid **S7** (213 mg, 0.37 mmol) was dissolved in 20% piperidine-MeOH (10 mL), stirred at room temperature for 2h, and then concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 0-40% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give **7** as a white solid (114 mg, 89%). Mpt. 150°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.20-2.35 (m, 2H, CH_2), 3.28 (m, 2H, NH and CH), 7.18-7.40 (m, 15H, Ph). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 44.9, 55.0, 70.7, 126.6, 128.2,

129.0, 146.3, 169.4. HRMS (ESI+) calcd. for $C_{22}H_{22}N_2O_2$ $(M+H)^+$: 347.17540; found: 347.17486. Analysis calcd. for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.19; H, 6.50; N, 8.04.

(2*R*)-2-Amino-3-(((2-chloroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (11).



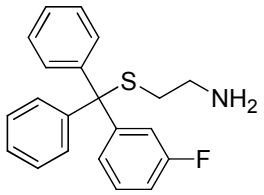
S8 **11**

Scheme S9

The tertiary trityl alcohol **S8** was prepared using an adaptation of the method reported by Hatano *et al.*[9] Zinc chloride (284 mg, 2.1 mmol) was added to a solution of PhMgBr (1M in THF, 45 mL, 45 mmol) and the mixture stirred at room temperature for 1 h. A solution of (2-chlorophenyl)(phenyl)methanone (4.33g, 20 mmol) in anhydrous THF (8 mL) was added, and the reaction heated at reflux for 120 h. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (4 x 30 mL). The organic extracts were washed with brine (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 0-10% EtOAc in hexane] to give (2-chlorophenyl)(diphenyl)methanol **S8** as a white solid (3.432g, 58%). Mpt. 83°C (lit. 89-91°C).[10] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.42 (s, 1H, OH), 6.71 (dd, *J* = 1.6, 7.9 Hz, 1H), 7.09-7.13 (m, 1H), 7.23-7.35 (m, 11H), 7.40 (dd, *J* = 1.2, 7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 82.73, 126.54, 127.52, 127.91, 128.14, 129.24, 131.50, 131.64, 133.38, 143.88, 145.69. HRMS (ESI+) calcd. for $C_{19}H_{14}Cl$ $(M+H-OH)^+$: 277.07785; found: 277.07770. Analysis calcd. for $C_{19}H_{15}ClO$: C, 77.42; H, 5.13. Found: C, 77.86; H, 5.21. The title compound was then prepared by an adaptation of the procedure reported by DeBonis *et al.*[11] To a solution of **S8** (325 mg, 1.1 mmol) and *L*-cysteine (121 mg, 1 mmol) in AcOH (1 mL) was added $BF_3.Et_2O$ solution (214 µL, 1.70 mmol) and stirred for 3 h at room temperature. A solution of aqueous NaOAc (10% *w/v*, 3 mL) was added, followed by H_2O (3 mL), and the solution extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude residue purified by flash chromatography [SiO_2; 10-20% MeOH in (CH_2Cl_2 with 1% NH_4OH)] to give **11** as a white solid (117 mg, 29%). Mpt. 159-161°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.24-2.29 (dd, *J* = 8.8, 12.4 Hz, 1H, CH_2), 2.24-2.29 (dd, *J* = 4.5, 12.4 Hz, CH_2), 2.37-2.41 (dd, *J* = 4.5, 8.7 Hz, 1H, CH_2), 2.91-2.94 (m, 1H, CH), 7.21-7.26 (m, 2H), 7.30-7.39 (m, 10H), 7.47-7.50 (m, 1H), 8.12-8.13 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 34.51, 53.18, 66.60, 126.73, 126.75, 127.30, 127.72, 127.80, 129.26, 129.40, 131.81, 131.99, 134.26, 140.00, 140.83, 141.32, 168.74. HRMS (ESI+)

calcd. for $C_{22}H_{21}ClNO_2S$ $(M+H)^+$: 398.09761; found: 398.09760. Analysis calcd. for $C_{22}H_{20}ClNO_2S$: C, 66.40; H, 5.07; N, 3.52. Found: C, 63.24; H, 5.28; N, 3.60.

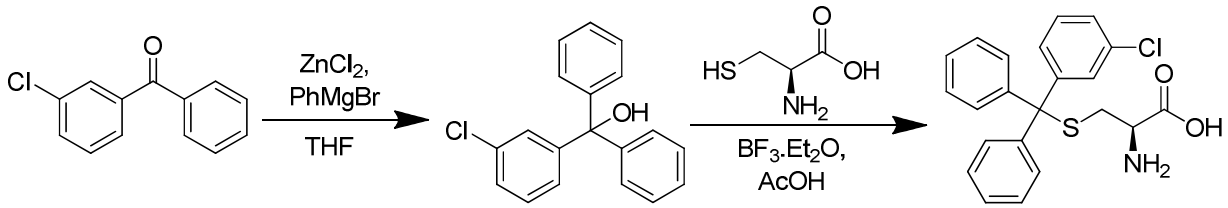
2-(((3-Fluorophenyl)(diphenyl)methyl)sulfanyl)ethanamine (12).



12

The title compound was prepared using general procedure (vi) with (3-fluorophenyl)(diphenyl)methanol **S3** (278 mg, 1 mmol) and cysteamine hydrochloride (114 mg, 1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction of the aqueous mixture (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **12** as a white solid (79 mg, 24%). Mpt. 62-63°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.14-2.18 (m, 2H, CH_2), 2.42-2.46 (m, 2H, CH_2), 7.06-7.17 (m, 3H), 7.24-7.29 (m, 2H), 7.31-7.41 (m, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.65, 40.78, 65.35, 113.57 (d, J = 20.6 Hz), 115.78 (d, J = 23.0 Hz), 125.37, 126.85, 128.09, 129.00, 129.91 (d, J = 8.3 Hz), 144.12, 147.66 (d, J = 6.4 Hz), 161.7 (d, J = 242.7 Hz). HRMS (ESI+) calcd. for $C_{21}H_{21}NFS$ $(M+H)^+$: 338.13733; found: 338.13739. Analysis calcd. for $C_{21}H_{20}FNS$: C, 74.74; H, 5.97; N 4.15. Found: C, 74.29; H, 5.92; N, 4.15.

(2*R*)-2-Amino-3-(((3-chloroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (13).



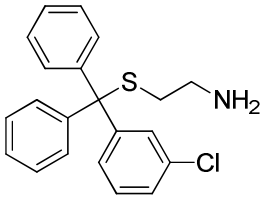
S9 **13**

Scheme S10

The title compound was prepared using an adaptation of the method described for **11**. Following the procedure described for **S8**, tertiary alcohol intermediate **S9** was using (3-

chlorophenyl)(phenyl)methanone (4.33 g, 20 mmol), zinc chloride (284 mg, 2.1 mmol), PhMgBr (1M in THF, 45 mL, 45 mmol), which afforded after 22 h reflux, aqueous workup and purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] (3-chlorophenyl)(diphenyl)methanol **S27** as a white solid (4.05 g, 69%). Mpt. 42°C (lit. 53-55°C).[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.80 (s, 1H, OH), 7.16-7.18 (m, 1H), 7.23-7.38 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 81.86, 126.37, 127.55, 127.72, 127.99, 128.16, 128.27, 129.62, 134.19, 146.41, 149.01. HRMS (ESI+) calcd. for $C_{19}H_{14}Cl$ $(M+H-OH)^+$: 277.07785; found: 277.07764. Analysis calcd. for $C_{19}H_{15}ClO$: C, 77.42; H, 5.13. Found: C, 77.08; H, 4.98. In a procedure analogous to **11**, (3-chlorophenyl)(diphenyl)methanol **S9** (325 mg, 1.1 mmol) and *L*-cysteine (121 mg, 1 mmol) in AcOH (1 mL) was treated with $BF_3.Et_2O$ (214 µl, 1.70 mmol). After stirring for 1 h a further portion of $BF_3.Et_2O$ (214 µl, 1.70 mmol) was added and the mixture stirred for a further 1.5 h. Aqueous workup and purification by flash chromatography [SiO_2; 8-20% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded **13** as an off-white solid (74 mg, 19%). Mpt. 160-163°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.43 (dd, *J* = 8.6, 12.4 Hz, 1H, CH_2), 2.56 (dd, *J* = 4.6, 12.4 Hz, 1H, CH_2), 3.01 (dd, *J* = 4.7, 8.6 Hz, 1H, CH), 7.26-7.40 (m, 14H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 34.41, 53.25, 65.62, 126.91, 127.04, 127.93, 128.27, 128.67, 129.03, 130.01, 132.78, 143.52, 143.55, 146.87, 168.37. HRMS (ESI+) calcd. for $C_{22}H_{21}ClNO_2S$ $(M+H)^+$: 398.09761; found: 398.09827. Analysis calcd. for $C_{22}H_{20}ClNO_2S$: C, 66.41; H, 5.07; N, 3.52. Found: C, 64.05; H, 4.80; N, 3.40.

2-(((3-Chlorophenyl)(diphenyl)methyl) sulfanyl)ethanamine (14).

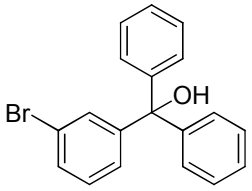


14

The title compound was prepared using general procedure (vi) with 3-chlorophenyl)(diphenyl)methanol **S9** (295 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction of the aqueous mixture (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **14** as a colorless oil (231 mg, 65%). ^{1}H NMR (MeOD, 500 MHz) 2.33-2.36 (m, 2H, CH_2), 2.45-2.48 (m, 2H, CH_2), 7.23-7.36 (m, 3H), 7.28-7.36 (m, 6H), 7.39-7.41 (m, 5H). ^{13}C NMR (MeOD, 125 MHz) δ 36.00, 41.50, 67.35, 127.91, 128.10, 129.11, 129.19, 130.44, 130.63, 130.67, 134.93, 145.64, 148.84. HRMS

(ESI+) calcd. for $C_{21}H_{21}ClNS$ $(M+H)^+$: 354.10777; found: 354.10754. Analysis calcd. for $C_{21}H_{20}ClNS$: C, 71.29; H, 5.70; N, 3.96. Found: C, 70.39; H, 5.86; N, 3.51.

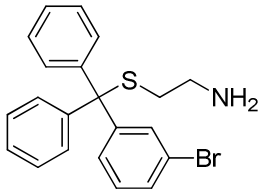
(3-Bromophenyl)(diphenyl)methanol (S10).



S10

The title compound was prepared using general procedure (iv) with (3-bromophenyl)(phenyl)methanone (2.61 g, 10 mmol) with PhMgBr (2M in THF, 12.5 ml, 25 mmol) in anhydrous THF (5 mL). Purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] (3-bromophenyl)(diphenyl)methanol **S10** as a colorless oil (1.55 g, 46%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.61-6.66 (m, 1H), 7.10-7.16 (m, 1H), 7.18-7.36 (m, 10H), 7.41-7.50 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 810.25, 21.22, 126.92, 127.00, 127.67, 127.70, 129.57, 129.74, 130.22, 147.00, 150.55. HRMS (ESI+) calcd. for $C_{19}H_{14}{}^{79}Br$ $(M+H-OH)^+$: 321.02734; found: 321.02750. Analysis calcd. for $C_{19}H_{15}BrO$: C, 67.27; H, 4.46. Found: C, 68.65; H, 4.32.

2-(((3-Bromophenyl)(diphenyl)methyl)sulfanyl)ethanamine (15).

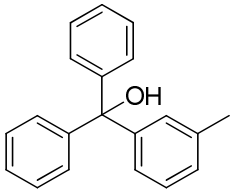


15

The title compound was prepared using general procedure (vi) with (3-bromophenyl)(diphenyl)methanol **S10** (339 mg, 1 mmol) and cysteamine hydrochloride (136 mg, 1.2 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction of the aqueous mixture (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **15** as a colorless oil which solidified on standing to a white solid (192 mg, 48%). Mpt. 59-61^{o}C.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.16 (t, J = 7.0 Hz, 2H, CH_2), 2.45 (t, J = 7.1 Hz, 2H, CH_2), 7.24-7.37 (m, 12H), 7.45-7.47 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.64, 40.78, 65.33, 121.29, 126.89, 128.14, 128.31, 128.98, 129.62, 130.17, 131.50, 143.98, 147.50. HRMS (ESI+) calcd. for $C_{21}H_{21}BrNS$ $(M+H)^+$: 398.05726; found: 398.05716. Analysis calcd. for $C_{22}H_{23}NS$ (%): C, 79.23; H, 6.95; N, 4.20. Found: C, 78.38; H, 6.65; N, 3.95.

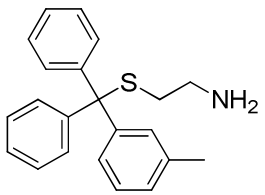
(3-Methylphenyl)(diphenyl)methanol (S11).



S11

The title compound was prepared using general procedure (iv) with (3-methylphenyl)(phenyl)methanone (1.84 mL, 10 mmol) with PhMgBr (2M in THF, 12.5 ml, 25 mmol) in anhydrous THF (5 mL). Purification by flash chromatography [SiO_2; 0-15% EtOAc in petroleum ether (40/60)] (3-methylphenyl)(diphenyl)methanol **S11** as a colorless oil which solidified on standing to a white solid (1.61 g, 59%). Mpt. 58°C (lit. 62-63°C).[12] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.33 (s, 3H, CH_3), 2.80 (s, 1H, OH), 7.03 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 7.4 Hz, 1H), 7.16 (s, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.28-7.35 (m, 10H).. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.74, 82.15, 125.32, 127.35, 127.89, 128.04, 128.08, 128.18, 128.61, 137.13, 146.98, 147.09. HRMS (ESI+) calcd. for $C_{20}H_{17}$ $(M+H-OH)^+$: 257.13248; found: 257.13235. Analysis calcd. for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.91; H, 6.51.

2-(((3-Methylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (16).

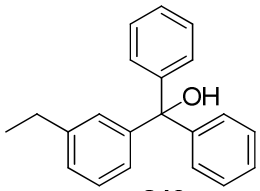


16

The title compound was prepared following general procedure (vi) with methylphenyl)(diphenyl)methanol **S11** (275 mg, 1 mmol) and cysteamine hydrochloride (136 mg, 1.2 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10mL).

Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **16** as a colorless oil (184 mg, 55%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.15 (t, J = 7.2 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.43 (t, J = 7.1 Hz, 2H, CH_2), 7.04-7.06 (m, 1H), 7.09-7.11 (m, 1H), 7.17-7.25 (m, 4H), 7.31-7.34 (m, 8H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 21.24, 35.62, 40.82, 65.74, 126.27, 126.56, 127.28, 127.80, 127.89, 129.13, 129.51, 136.94, 144.69, 144. 76. HRMS (ESI+) calcd. for $C_{22}H_{24}NS$ $(M+H)^+$: 334.16240; found: 334.16226. Analysis calcd. for $C_{22}H_{23}NS$: C, 79.23; H, 6.95; N, 4.20. Found: C, 78.31; H, 6.63; N, 5.68.

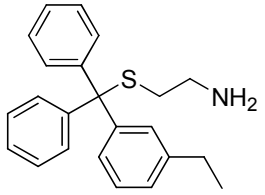
(3-Ethylphenyl)(diphenyl)methanol (S12).



S12

The title compound was prepared using an adaptation of general procedure (v).[4] *n*-Butyllithium (2.5M in hexane, 2.90 mL, 7.2 mmol) was added dropwise to a cooled (-78°C) solution of 1-bromo-3-ethylbenzene (1.11 g, 6 mmol) in anhydrous THF:toluene (1:4, 11.4 mL). The reaction mixture stirred for 1 h at -78°C, treated with a solution of benzophenone (1.33 g, 7.30 mmol) in anhydrous toluene (7.2 mL) and stirred for a further 4 h at the same temperature. The mixture was then warmed to room temperature, stirred for 16 h, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). Following washing the combined organic layers with brine (50 mL), drying ($MgSO_4$) and concentrating *in vacuo*, the crude product was purified by flash chromatography [SiO_2; 0-12% EtOAc in petroleum ether (60/80)] to afford tertiary alcohol **S12** as a colorless oil (859 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.20 (t, J = 7.6 Hz, 3H, CH_3), 2.62 (q, J = 7.6 Hz, 2H, CH_3), 2.80 (s, 1H, OH), 7.02-7.04 (m, 1H), 7.13-7.14 (m, 1H), 7.18-7.19 (m, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.27-7.34 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.70, 29.07, 125.60, 126.90, 127.33, 127.55, 127.94, 128.02, 128.08, 144.11, 146.99, 147.13. HRMS (ESI+) calcd. for $C_{22}H_{19}$ $(M+H)^+$: 271.14813; found: 271.14758. Analysis calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.41; H, 6.99.

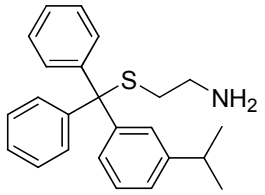
2-(((3-Ethylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (17).



17

The title compound was prepared following general procedure (vi) with (3-ethylphenyl)(diphenyl)methanol **S12** (298 mg, 1 mmol) and cysteamine hydrochloride (129 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. The reaction time was 2 h, basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **17** a colorless oil (157 mg, 44%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.11 (t, J = 7.5 Hz, 3H, CH_3), 2.16 (t, J = 7.3 Hz, 2H, CH_2), 2.42 (t, J = 7.1 Hz, 2H, CH_2), 2.54 (q, J = 7.5 Hz, 2H, CH_2), 7.07-7.10 (m, 2H), 7.21-7.25 (m, 4H), 7.30-7.34 (m, 8H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 15.52, 28.23, 35.66, 40.85, 65.83, 126.02, 126.57, 127.88, 128.48, 129.12, 143.23, 144.68, 144.75. HRMS (ESI+) calcd. for $C_{23}H_{26}NS$ $(M+H)^+$: 348.17805; found: 348.17786. Analysis calcd. for $C_{23}H_{25}NS$: C, 79.49; H, 7.25; N, 4.03. Found: C, 78.90; H, 7.10; N, 3.70.

2-(((3-Isopropylphenyl)diphenylmethyl)sulfanyl)ethanamine (18).

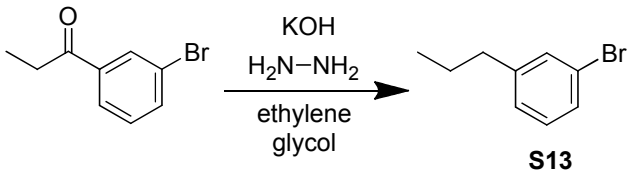


18

The title compound was prepared following general procedure (vi) with diphenyl(3-(propan-2-yl)phenyl)methanol (**S4**) (302 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. The reaction time was 2 h, basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **18** as a colorless oil (249 mg, 69%). ^{1}H NMR (500 MHz, DMSO-d_6) δ =

1.13 (d, J = 6.9 Hz, 6H, 2 x CH_3), 2.17 (t, J = 7.0 Hz, 2H, CH_2), 2.42 (t, J = 7.0 Hz, 2H, CH_2), 2.81 (h, J = 6.9 Hz, 1H, CH), 7.06-7.08 (m, 1H), 7.11-7.12 (m, 1H), 7.21-7.26 (m, 4H), 7.31-7.33 (m, 8H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 23.78, 33.36, 35.68, 40.87, 65.92, 124.44, 126.57, 126.74, 127.26, 127.82, 127.88, 129.09, 144.48, 144.82. HRMS (ESI+) calcd. for $C_{22}H_{28}NS$ $(M+H)^+$: 362.19370; found: 362.19351. Analysis calcd. for $C_{24}H_{27}NS$: C, 79.73; H, 7.53; N, 3.87. Found: C, 78.63; H, 7.42; N, 3.59.

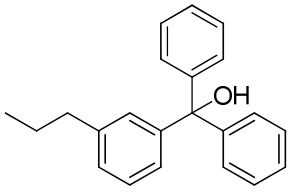
1-Bromo-3-propylbenzene (S13).



Scheme S11

The title compound was prepared using an adaptation of the method reported by Chackal-Catoen *et al.*[13] Hydrazine hydrate monohydrate (2.18 mL, 45 mmol) was added to a solution of 1-(3-bromophenyl)propan-1-one (3.20 g, 15 mmol) and powdered KOH (2.53 g, 45 mmol) in anhydrous ethylene glycol (18.6 mL) and refluxed for 4 h. After cooling to room temperature, the reaction was quenched was aqueous HCl (1M, 70 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organics were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by flash chromatography [SiO_2; hexane] to afford the alkane **S13** as a colorless oil (2.03 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.94 (t, J = 7.5 Hz, 3H, CH_3), 1.63 (p, J = 7.5 Hz, 2H, CH_2), 2.56 (t, 2H, J = 7.5 Hz, 2H, CH_2), 7.09-7.16 (m, 2H), 7.30-7.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.85, 24.47, 37.81, 122.46, 127.28, 128.88, 129.92, 131.66, 145.17. GC-MS (EI, 70eV) tr = 4.72 min (m/z = 197.9, M^+).

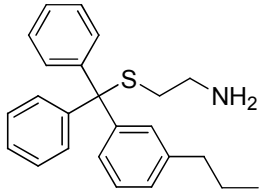
Diphenyl(3-propylphenyl)methanol (S14).



The title compound was prepared using general procedure (v) using 1-bromo-3-propylbenzene **S13** (1.78 g, 8.92 mmol) with *n*-BuLi (4.28 mL, 10.71 mmol) in anhydrous THF (8.92 mL) followed by benzophenone (1.79 g, 9.81 mmol) in anhydrous THF (9.81 mL) with the following modifications. The

reaction mixture was stirred for 2 h at -78°C then following warming to room temperature a further 21 h. Purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] afforded the trityl alcohol **S14** as a colorless oil, which solidified on standing to a white solid (1.12 g, 41%). Mpt 42-43°C ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.90 (t, *J* = 7.4 Hz, 3H, CH_3), 1.59 (p, *J* = 7.5 Hz, 2H, CH_2), 2.55 (t, *J* = 7.6 Hz, 2H, CH_2), 2.78 (s, 1H, OH), 7.02-7.04 (m, 1H), 7.10-7.11 (m, 1H), 7.13-7.14 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.27-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.92, 24.69, 38.25, 82.20, 125.56, 127.32, 127.54, 127.87, 128.02, 128.08, 128.18, 142.56, 146.90, 147.14. HRMS (ESI+) calcd. for $C_{22}H_{21}$ $(M\text{-}H\text{-}OH)^+$: 285.16378; found: 285.16354. Analysis calcd. for $C_{22}H_{22}O$: C, 87.38; H, 7.33. Found: C, 87.05; H, 7.60.

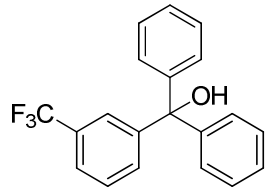
2-(((3-Propylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (19).



19

The title compound was prepared following general procedure (vi) with diphenyl(3-propylphenyl)methanol **S14** (302 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **19** as a pale clear yellow oil (227 mg, 63%). ^{1}H NMR (MeOD, 500 MHz) δ = 0.87 (t, *J* = 7.4 Hz, 3H, CH_3), 1.56 (p, *J* = 7.4 Hz, 2H, CH_2), 2.33-2.36 (m, 2H, CH_2), 2.41-2.44 (m, 2H, CH_2), 2.51 (t, *J* = 7.5 Hz, 2H, CH_2), 7.03-7.05 (m, 1H), 7.16-7.24 (m, 9H), 7.40-7.42 (m, 4H). ^{13}C NMR (MeOD, 125 MHz) δ 13.96, 25.69, 36.00, 39.04, 41.55, 67.83, 127.75, 127.94, 128.16, 128.78, 128.85, 130.77, 131.06, 143.06, 146.17, 146.42. HRMS (ESI+) calcd. for $C_{24}H_{28}NS$ $(M+H)^+$: 362.19370; found: 362.19293. Analysis calcd. for $C_{24}H_{27}NS$: C, 79.73; H, 7.53; N, 3.87. Found: C, 78.64; H, 7.31; N, 3.95.

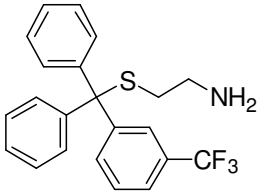
Diphenyl(3-(trifluoromethyl)phenyl)methanol (S15).



S15

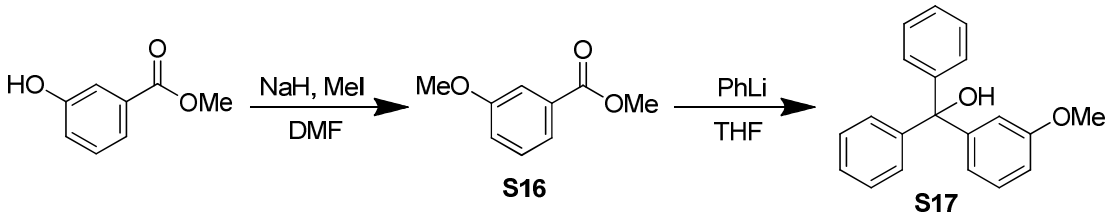
The title compound was prepared using general procedure (iv) with phenyl-(3-(trifluoromethyl)phenyl)methanone (2.50 g, 10 mmol) with PhMgBr (2M in THF, 12.5 ml, 25 mmol) in anhydrous THF (5 mL). Purification by flash chromatography [SiO_2; 0-15% EtOAc in petroleum ether (40/60)] afforded the tertiary alcohol **S15** as a pale yellow oil (1.38 g, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.83 (s, 1H, OH), 7.25-7.27 (m, 4H), 7.32-7.37 (m, 6H), 7.41-7.49 (m, 2H), 7.55-7.57 (m, 1H), 7.70-7.71 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 81.92, 124.24 (d, *J* = 3.5 Hz), 124.30 (d, *J* = 272.8 Hz), 124.57 (d, *J* = 3.6Hz), 127.84, 127.97, 128.36, 128.42, 130.51 (d, *J* = 31.9 Hz), 131.58, 146.35, 147.89. HRMS (ESI+) calcd. for $C_{20}H_{14}F_3$ $(M+H-OH)^+$: 257.13248; found: 257.13235. Analysis calcd. for $C_{20}H_{15}F_3O$: C, 73.16; H, 4.60. Found: C, 70.21; H, 4.40.

2-((Diphenyl(3-(trifluoromethyl)phenyl)methyl) sulfanyl)ethanamine (20).



The title compound was prepared following general procedure (vi) with diphenyl(3-(trifluoromethyl)phenyl)methanol **S15** (298 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. The reaction time was 2 h, basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **20** as a colorless oil (125 mg, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.16 (t, *J* = 7.2 Hz, 2H, CH_2), 2.44 (t, *J* = 7.0 Hz, 2H, CH_2), 7.26-7.29 (m, 2H), 7.32-7.38 (m, 8H), 7.57-7.66 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.61, 40.77, 65.46, 123.63 (d, *J* = 3.7 Hz, CH), 124.08 (d, *J* = 271.8 Hz), 125.06 (d, *J* = 3.6 Hz, CH), 127.00, 128.24, 128.68 (d, *J* = 31.2 Hz), 128.95, 129.26, 133.43, 143.91, 146.12. ^{19}F NMR (376.4 MHz, DMSO-d_6) δ = -61.18. HRMS (ESI+) calcd. for $C_{22}H_{21}NF_3S$ $(M+H)^+$: 388.13413; found: 388.13388. Analysis calcd. for $C_{22}H_{20}F_3NS$: C, 68.20; H, 5.20; N, 3.61. Found: C, 67.97; H, 5.41; N, 2.87.

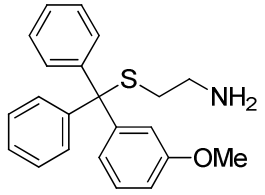
(3-Methoxyphenyl)(diphenyl)methanol (S17).



Scheme S12

The intermediate methyl ester **S16** was prepared using a modification of the procedure reported by Ulrik *et al.*[14] Methyl 3-hydroxybenzoate (3.80 g, 25 mmol), NaH (60% in mineral oil, 660 mg, 27.5 mmol) in anhydrous DMF (41 mL) and subsequent treatment with iodomethane (1.71 mL, 27.5 mmol) afforded after stirring for 22.5 h at room temperature, aqueous workup and purification by flash chromatography [SiO_2; 0-16% EtOAc in hexane] **S16** as a colorless oil (2.60 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.85 (s, 3H), 3.91 (s, 3H), 7.08-7.11 (m, 1H), 7.32-7.36 (m, 1H), 7.55-7.56 (m, 1H), 7.62-7.64 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 52.29, 55.56, 114.11, 119.65, 122.13, 129.52, 131.60, 159.71, 167.13. HRMS (ESI+) calcd. for $C_{19}H_{11}O_3$ $(M+H)^+$: 167.07027; found: 167.07028. Analysis calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.75; H, 6.06. The title compound was then prepared as follows. Phenyllithium (1.8 M in Et_2O, 22.2 mL, 40 mmol) was added to a solution of methyl 3-methoxybenzoate **S16** (1.52g, 10 mmol) in anhydrous THF (16.6 mL) at -78^{o}C, and stirred for 1 h, whilst maintaining the temperature below -70^{o}C. The reaction mixture warmed to room temperature and stirred for 20h, then quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted EtOAc (2 x 30 mL). The combined organic extracts were washed with the organics washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude material by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the tertiary alcohol **S17** as a pale yellow solid (3.52 g, 84%). Mpt. 80-81^{o}C (lit. 88-89 ^{o}C from Et_2O).[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.81 (s, 1H, OH), 3.75 (s, 3H, CH_3), 6.82-6.84 (m, 2H), 6.89-6.90 (m, 1H), 7.21-7.25 (m, 1H), 7.27-7.33 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.12, 82.13, 112.61, 114.13, 120.70, 127.43, 128.06, 129.01, 146.89, 148.66, 159.44. HRMS (ESI+) calcd. for $C_{19}H_{17}O$ $(M+H-OH)^+$: 273.12739; found: 273.12738. Analysis calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.75; H, 6.23.

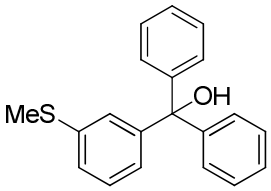
2-(((3-Methoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (21).



21

The title compound was prepared following general procedure (vi) with 3-methoxyphenyl)(diphenyl)methanol **S17** (290 mg, 1 mmol and cysteamine hydrochloride (114 mg, 1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. The reaction time was 2.5 h, basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **21** as a pale brown oil (282 mg, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.18 (t, J = 7.0 Hz, 2H, CH_2), 2.45 (t, J = 7.1 Hz, 2H, CH_2), 6.81-6.90 (m, 3H), 7.22-7.35 (m, 11H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.47, 40.74, 54.96, 65.70, 111.23, 115.66, 121.62, 126.66, 127.92, 129.02, 129.10, 144.53, 146.23, 158.73. HRMS (ESI+) calcd. for $C_{22}H_{24}NOS$ $(M+H)^+$: 350.15731; found: 350.15817. Analysis calcd. for $C_{22}H_{23}NOS$: C, 75.61; H, 6.63; N 4.01. Found: C, 74.69; H, 6.47; N, 3.57.

(3-(Methylsulfanyl)phenyl)(diphenyl)methanol (S18).

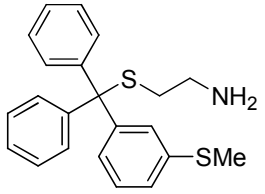


S18

The title compound was prepared using general procedure (v) with (3-bromophenyl)(methyl)sulfane (1.35 mL, 10 mmol) and *n*-butyllithium (2.5 M in hexane, 4.8 mL, 12.2 mmol) in anhydrous THF (10 mL), and subsequently benzophenone (2.10 g, 11.5 mmol) in anhydrous THF (10 mL), with the following modifications. The reaction mixture was stirred for 20 h following warming to room temperature. Purification by flash chromatography [SiO_2; 0-15% EtOAc in petroleum ether (40/60)] afforded the tertiary alcohol **S18** as a colorless oil (1.67 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H, CH_3),

2.83 (s, 1H, OH), 7.01-7.03 (m, 1H), 7.16-7.18 (m, 1H), 7.21-7.33 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.81, 82.08, 125.05, 125.34, 126.01, 127.51, 128.03, 128.12, 128.42, 138.37, 146.72, 147.65. HRMS (ESI+) calcd. for $C_{20}H_{17}S$ $(M+H-OH)^+$: 289.10455; found: 289.104581. Analysis calcd. for $C_{20}H_{19}O_2S$: C, 78.39; H, 5.92. Found: C, 77.42; H, 5.87.

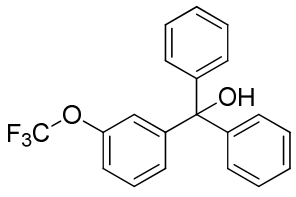
2-(((3-(Methylsulfanyl)phenyl)diphenylmethyl) sulfanyl)ethanamine (22).



22

The title compound was prepared following general procedure (vi) with (3-(methylsulfanyl)phenyl)(diphenyl)methanol **S18** (306 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. The reaction time was 2 h, basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **22** as a clear pale yellow oil (280 mg, 77%). ^{1}H NMR (500 MHz, MeOD) δ = 2.33-2.37 (m, 5H), 2.43-2.46 (m, 2H, CH_2), 7.11-7.13 (m, 1H), 7.15-7.18 (m, 1H), 7.20-7.24 (m, 3H), 7.27-7.32 (m, 5H), 7.39-7.42 (m, 4H). ^{13}C NMR (125 MHz, MeOD) δ = 15.67, 36.11, 41.57, 67.69, 125.80, 127.58, 127.92, 128.80, 128.96, 129.39, 130.74, 139.83, 146.04, 147.08. HRMS (ESI+) calcd. for $C_{22}H_{24}NS_2$ $(M+H)^+$: 366.13447; found: 366.13452. Analysis calcd. for $C_{22}H_{23}NS_2$: C, 72.78; H, 6.34; N, 3.83. Found: C, 72.28; H, 6.29; N, 3.44.

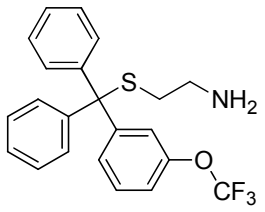
Diphenyl(3-(trifluoromethoxy)phenyl)methanol (S19).



S19

The title compound was prepared using general procedure (v) with 1-bromo-3-(trifluoromethoxy)benzene (1.49 mL, 10 mmol) and *n*-butyllithium (2.5 M in hexane, 4.8 mL, 12.2 mmol) in anhydrous THF (10 mL), and subsequently benzophenone (2.10 g, 11.5 mmol) in anhydrous THF (10 mL), with the following modifications. The reaction mixture was stirred for 22 h following warming to room temperature. Purification by flash chromatography [SiO_2; 0-12% EtOAc in petroleum ether (40/60)] afforded the trityl alchol **S19** as a colourless oil (798 mg, 23%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.85 (s, 1H, OH), 7.13-7.15 (m, 1H), 7.21-7.35 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 81.82, 119.61, 120.81, 121.64, 126.51, 127.77, 127.96, 128.29, 129.27, 146.37, 149.17, 149.37. ^{19}F NMR (376.4 MHz, DMSO-d_6) δ = -57.75. HRMS (ESI+) calcd. for $C_{20}H_{14}OF_3$ $(M+H-OH)^+$: 327.09913; found: 327.09950. Analysis calcd. for $C_{20}H_{15}F_3O_2$: C, 69.76; H, 4.39. Found: C, 68.90; H, 4.53.

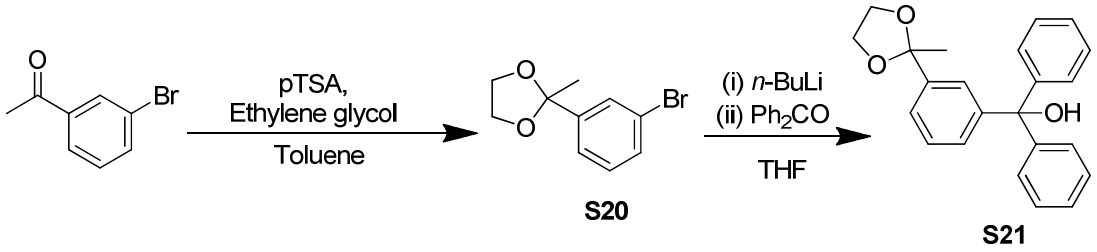
2-((Diphenyl(3-(trifluoromethoxy)phenyl)methyl) sulfanyl)ethanamine (23).



23

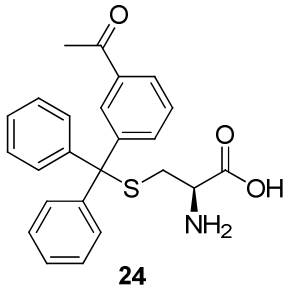
The title compound was prepared following general procedure (vi) with diphenyl(3-(trifluoromethoxy)phenyl)methanol **S19** (344 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **23** as a pale clear yellow oil (313 mg, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.17 (t, J = 7.0 Hz, 2H, CH_2), 2.43 (t, J = 7.0 Hz, 2H, CH_2), 7.24-7.29 (m, 4H), 7.31-7.39 (m, 9H), 7.48 (t, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.61, 40.77, 65.32, 119.12, 120.03 (d, J = 257.7 Hz), 121.45, 126.95, 128.17, 128.32, 128.92, 129.96, 143.96, 147.44, 147.92. ^{19}F NMR (376.4 MHz, DMSO-d_6) δ = -56.87. HRMS (ESI+) calcd. for $C_{22}H_{21}F_3NS$ $(M+H)^+$: 404.12905; found: 404.12881. Analysis calcd. for $C_{22}H_{20}F_3NOS$: C, 65.49; H, 5.00; N, 3.47. Found: C, 64.61; H, 4.91; N, 2.90.

(3-(2-Methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol (S21)



Anhydrous ethylene glycol (2.31 mL, 42.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol) were added to a solution of 1-(4-bromophenyl)ethanone (1.587 mL, 12 mmol) in anhydrous toluene (80 mL) and the reaction mixture refluxed, using a Dean-Stark trap, for 20 h. The reaction was cooled to room temperature, washed with brine (40 mL) and concentrated *in vacuo* to give the crude acetal **S20** as a colourless oil, which was taken to the next step without further purification (2.63 g, 90%). *n*-Butyllithium (2.5 M in hexane, 3.60 mL, 9.00 mmol) was added by slow dropwise addition over 2 min to a cooled (-78^{o}C) solution of 2-(3-Bromophenyl)-2-methyl-1,3-dioxolane **S20** (1.823 g mg, 7.50 mmol) in anhydrous THF (7.5 mL) stirred for 1 h at $\leq$-70^{o}C. A solution of benzophenone (1.572 g, 8.63 mmol) in anhydrous THF (8.63 mL) was then added by slow dropwise addition over 8 min and stirred with the temperature maintained $\leq$ -77^{o}C for 5 h, before allowing the reaction to warm slowly to room temperature and stirring for a further 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-30% EtOAc in hexane with 1% NH_4OH] afforded the tertiary alcohol **S21** as a white solid (1.82 g, 70%). Mpt. 104-105^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.62 (s, 3H, CH_3), 2.82 (s, 1H, OH), 3.69-3.73 (m, 2H, CH_2), 3.97-4.01 (m, 2H, CH_2), 7.15-7.18 (m, 1H), 7.25-7.34 (m, 11H), 7.39-7.43 (m, 1H), 7.49 (t, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.58, 64.53, 82.16, 108.95, 124.45, 124.81, 127.42, 127.66, 127.89, 128.04, 128.07, 143.08, 147.02. HRMS (ESI+) Calcd. for $C_{23}H_{23}O_3S$ $(M+H)^+$: 347.1642; found: 363.1639. Analysis calcd. for $C_{22}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.55; H, 6.15.

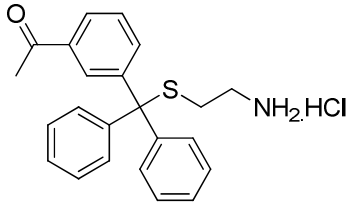
(*R*)-3-(((3-acetylphenyl)diphenylmethyl)sulfanyl)2-aminopropanoic acid (24).



24

A solution of (3-(2-methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol **S21** (346 mg, 1.0 mmol) and *L*-cysteine (133 mg, 1.1 mmol) in (1 mL) was stirred at room temperature for 4.5 h. The volatiles were removed *in vacuo*, and the residue suspended in aqueous HCl (0.5M, 2.5 mL) and stirred at room temperature for 2.5 h, during which time a colourless gum precipitated. The aqueous layer was poured off, and the gum washed with H_2O (10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 10 mL), the gum dissolved in CH_2Cl_2 (5 mL), and the combined organic extracts concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2] afforded the thioether **24** as a white solid (290 mg, 72%). Mpt. 109.5-112°C. ^{1}H NMR (400 MHz, MeOD) δ = 2.54 (s, 3H, CH_3), 2.68 (dd, *J* = 9.1, 13.3 Hz, 1H, CH_2), 2.80 (dd, *J* = 4.2, 13.2 Hz, 1H, CH_2), 3.09 (dd, *J* = 4.2, 9.0 Hz, 1H, CH), 7.24-7.29 (m, 2H), 7.31-7.37 (m, 4H), 7.43-7.50 (m, 5H), 7.70-7.73 (m, 1H), 7.89-7.92 (m, 1H), 8.08-8.09 (m, 1H). ^{13}C NMR (125 MHz, MeOD) δ = 26.76, 34.09, 54.96, 67.95, 128.32, 129.38, 129.69, 130.11, 130.65, 135.54, 138.19, 145.09, 145.19, 146.54, 172.06, 200.11. HRMS (ESI+) Calcd. for $C_{24}H_{24}NO_3S$ $(M+H)^+$: 406.1471; found: 406.1466. Analysis calcd. for $C_{24}H_{23}NO_3S \cdot ½H_2O$: C, 69.54; H, 5.84; N, 3.38. Found: C, 69.16; H, 5.55; N, 3.02.

1-(3-(((2-Aminoethyl)thio)diphenylmethyl)phenyl)ethanone hydrochloride (25).

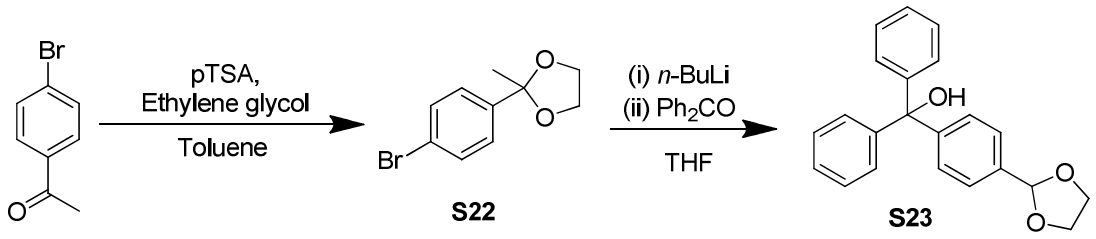


25

A solution of the tertiary alcohol (3-(2-methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol (**S21**) (346 mg, 1.0 mmol) with cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) was

stirred for 3 h at room temperature. The volatiles were removed *in vacuo*, and the crude basified (*circa.* pH 10) with saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was suspended in aqueous HCl (1M, 30 mL), stirred at room temperature for 62 h, basified (*circa.* pH 10) with saturated aqueous sodium carbonate solution and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 1% NH_4OH] yielded a white solid, which to generate the hydrochloride salt, was suspended in aqueous HCl (1M, 10 mL) and stirred at room temperature for 65 h. A white precipitate formed, which was filtered and washed successively with aqueous HCl (1M), petroleum ether (60/80) and Et_2O, and dried *in vacuo* to yield the hydrochloride salt **25** as a white solid (122 mg, 31%). Mpt. 96-98°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.40-2.44 (m, 2H, CH_2), 2.51-2.58 (m, 5H), 7.28-7.41 (m, 10H), 7.52-7.60 (m, 2H), 7.80 (br s, 3H, NH_3^+), 7.92-7.95 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 26.76, 28.39, 37.63, 66.26, 127.14, 127.55, 127.73, 128.37, 128.79, 128.97, 133.83, 136.56, 143.55, 144.69, 197.60. HRMS (ESI+) Calcd. for $C_{23}H_{24}NOS$ $(M+H)^+$: 362.1573; found: 362.1572. Analysis calcd. for $C_{23}H_{23}NOS \cdot 2HCl$: C, 66.31; H, 5.80; N, 3.22. Found: C, 66.02; H, 5.82; N, 3.24.

(4-(2-Methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol (S23)

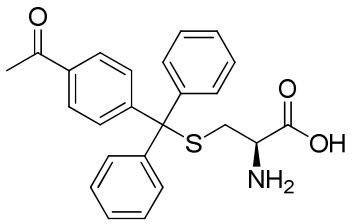


Scheme S13

Anhydrous ethylene glycol (1.32 mL, 24.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol) were added to a solution of 1-(4-bromophenyl)ethanone (2.389 g, 12 mmol) in anhydrous toluene (80 mL) and the reaction mixture refluxed, using a Dean-Stark trap, for 20 h. The reaction was cooled to room temperature, washed with brine (40 mL) and concentrated *in vacuo*. Purification by flash chromatography [SiO2; 0-12% EtOAc in hexane with 1% NH_4OH] yielded acetal **S22** as a white solid (1.88 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.64 (s, 3H, CH_3), 3.73-3.77 (m, 2H, CH_2), 4.01-4.05 (m, 2H, CH_2), 7.33-7.37 (m, 2H), 7.4 3-7.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl) δ = 27.74, 64.70, 108.67, 122.10, 127.39, 131.55, 142.67. The title compound was then prepared as follows. *n*-Butyllithium (2.5 M in hexane, 2.52 mL, 6.3 mmol) was added by slow dropwise addition over 2 min to a cooled (-84°C) solution of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane **S22** (1.459 g, 6.0

mmol) in anhydrous THF (6 mL) stirred for 1 h at ≤-70°C. A solution of benzophenone (1.20 g, 6.6 mmol) in anhydrous THF (5.30 mL) was then added by slow dropwise addition over 5 min and stirred with the temperature maintained ≤ -70°C for 2 h, before allowing the reaction to warm slowly to room temperature and stirring for 15 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; EtOAc/Hexane with 1% NH_4OH; 0-30%] afforded the tertiary alcohol **S23** as a white solid (1.01 g, 49%). Mpt. 129-130°C (lit. 128°C).[16] ^1H NMR (400 MHz, $CDCl_3$) δ = 1.65 (s, 3H, CH_3), 2.76 (s, 1H, OH), 3.75-3.84 (m, 2H, CH_2), 3.99-4.07 (m, 2H, CH_2), 7.22-7.33 (m, 12H), 7.39-7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.65, 64.64, 108.89, 125.00, 127.42, 127.93, 128.02, 128.08, 142.40, 146.54, 146.92. HRMS (ESI+) Calcd. for $C_{23}H_{23}O_3$ $(M+H)^+$: 347.1642; found: 347.1639. Analysis calcd. for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.63; H, 6.34.

(*R*)-3-(((4-acetylphenyl)diphenylmethyl)sulfanyl)2-aminopropanoic acid (26).

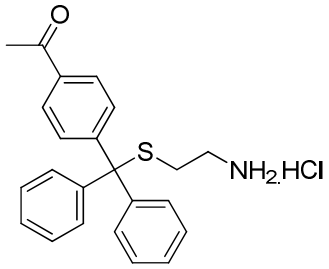


26

A solution of (4-(2-methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol **S23** (346 mg, 1.0 mmol) and *L*-cysteine (133 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) was stirred at room temperature for 4 h. The volatiles were removed *in vacuo*, and the residue suspended in aqueous HCl (0.5M, 2.5 mL) and stirred at room temperature for 30 min, during which time a white gum precipitated. The aqueous layer was separated, and extracted with CH_2Cl_2 (3 x 5 mL). The precipitated gum was washed with H_2O (5 mL), dissolved in CH_2Cl_2 (5 mL), and combined with the combined organic extracts concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded the thioether **26** as a white solid (221 mg, 55%). Mpt. 116-119°C. ^1H NMR (500 MHz, MeOD) δ = 2.58 (s, 3H, CH_3), 2.66-2.72 (m, 1H, CH_2), 2.80 (dd, *J* = 3.6, 13.3 Hz, 1H, CH_2) 3.13 (dd, *J* = 3.6, 13.3 Hz, 1H, CH), 7.24-7.29 (m, 2H), 7.30-7.36 (m, 4H), 7.42-7.47 (m, 4H), 7.58-7.62 (m, 2H), 7.92-7.96 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 26.73, 34.06, 54.87, 68.01, 128.34, 129.32, 129.36, 130.62, 130.66, 130.99, 136.86, 144.91, 145.03, 151.06, 171.97. HRMS (ESI+) Calcd. for $C_{24}H_{24}NO_3S$ $(M+H)^+$: 406.1471; found:

406.1468. Analysis calcd. for $C_{24}H_{23}NO_3S \cdot \frac{1}{3}CH_2Cl_2$: C, 67.34; H, 5.50; N, 3.23. Found: 67.84; H, 5.73; N, 3.20.

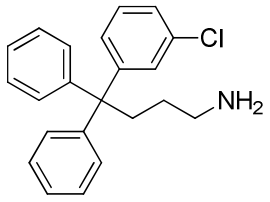
1-(4-(((2-Aminoethyl)thio)diphenylmethyl)phenyl)ethanone hydrochloride (27).



27

A solution of the tertiary alcohol (4-(2-methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol **S23** (346 mg, 1.0 mmol) with cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) was stirred for 3 h at room temperature. The volatiles were removed *in vacuo*, and the residue suspended in aqueous HCl (1M, 10 mL) and stirred at room temperature for 18 h, during which time a white precipitate formed. The mixture was filtered, and the precipitate washed successively with HCl (1M, 10 mL), petroleum ether (60/80) and Et_2O, and dried *in vacuo* to yield the hydrochloride salt **27** as a white solid (378 mg, 95%). Mpt. 186-188°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.40-2.43 (m, 2H, CH_2), 2.52-2.56 (m, 5H), 7.28-7.31 (m, 2H), 7.33-7.40 (m, 10H), 7.47-7.49 (m, 2H), 7.77 (br s, 3H, NH_3^+), 7.93-7.96 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.61, 28.36, 37.58, 66.29, 127.16, 128.17, 128.36, 128.96, 129.31, 135.21, 143.40, 149.04, 197.30. HRMS (ESI+) Calcd. for $C_{23}H_{24}NOS$ $(M+H)^+$: 362.1573; found: 362.1571. Analysis calcd. for $C_{23}H_{23}NOS \cdot 2HCl$: C, 63.59; H, 5.80; N, 3.22. Found: C, 65.08; H, 5.80; N, 3.22.

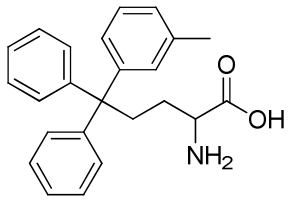
4-(3-Chlorophenyl)-4,4-diphenylbutan-1-amine (28).



28

The title compound was following the synthetic route and procedures described for **10** in general procedure (iii). A colorless solid (225 mg, overall yield 36%) was obtained. ^{1}H NMR (400 MHz, CD_3OD) δ = 1.24-1.28 (m, 2H, CH_2), 2.59-2.66 (m, 4H, CH_2 and CH_2), 7.15-7.27 (m, 14H, Ph). ^{13}C NMR (100 MHz, CD_3OD) δ = 28.2, 37.2, 41.3, 56.4, 125.8, 126.0, 127.4, 127.7, 128.9, 129.0, 133.5, 146.6, 150.1. HRMS (ESI+) calcd. for $C_{22}H_{22}NCl$ $(M+H)^+$: 336.15135; found: 336.15103. Analysis calcd. for $C_{22}H_{22}NCl·½H_2O$: C, 76.62; H, 6.72; N, 4.06. Found: C, 76.03; H, 6.48; N, 4.10.

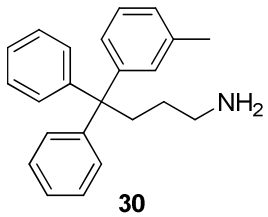
2-Amino-5-(3-methylphenyl)-5,5-diphenylpentanoic acid (*rac*-29).



rac-**29**

The title compound was following the synthetic route and procedures described for *rac*-**9** in general procedure (ii). A white solid (695 mg, overall yield 22%) was obtained. Mpt. 186°C. ^{1}H NMR(400 MHz, DMSO-d_6) δ = 1.22-1.40 (m, 2H, CH_2), 2.23 (s, 1H, CH_3), 2.54-2.71 (m, 2H, CH_2), 3.14-3.18 (t, 1H, CH), 7.08-7.27 (m, 14H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.9, 27.8, 36.1, 55.2, 56.4, 126.3, 128.2, 128.4, 129.5, 137.3, 147.6, 170.5. HRMS (ESI-) calcd. for $C_{24}H_{25}NO_2$ $(M-H)^-$: 358.18125; found: 358.18134. Analysis calcd. for $C_{24}H_{25}NO_2·H_2O$: C, 76.36; H, 7.21; N, 3.71. Found: C, 75.48; H, 6.76; N, 3.57.

4-(3-Methylphenyl)-4,4-diphenylbutan-1-amine (30).

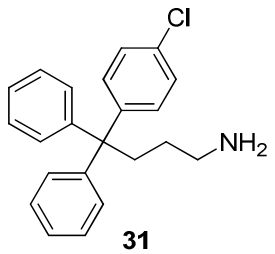


30

The title compound was following the synthetic route and procedures described for **10** in general procedure (iii). A colorless syrup (240 mg, overall yield 32%) was obtained. ^{1}H NMR (400 MHz, CD_3OD) δ = 1.22-1.26 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.57-2.63 (m, 4H, CH_2 and CH_2), 7.12-7.27 (m, 14H, Ph). ^{13}C NMR (100 MHz, CD_3OD) δ = 20.4, 28.9, 37.4, 41.7, 56.3, 125.5, 126.1, 126.2, 127.4,

127.5, 129.0, 129.7, 137.0, 147.5. HRMS (ESI+) calcd. for $C_{23}H_{25}N$ $(M+H)^+$: 316.20598; found: 316.20612. Analysis calcd for $C_{23}H_{25}N \cdot 0.5H_2O$: C, 85.14; H, 8.08; N, 4.32. Found: C, 84.93; H, 7.50; N, 5.19.

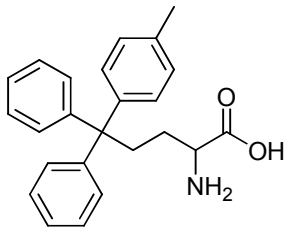
4-(4-Chlorophenyl)-4,4-diphenylbutan-1-amine (31).



31

The title compound was following the synthetic route and procedures described for **10** in general procedure (iii). A colorless solid (65 mg, overall yield 38%) was obtained. ^{1}H NMR (400 MHz, CD_3OD) δ = 1.28-1.32 (m, 2H, CH_2), 2.60-2.64 (m, 2H, CH_2), 2.72-2.76 (m, 2H, CH_2), 7.15-7.27 (m, 14H, Ph). ^{13}C NMR (100 MHz, CD_3OD) δ = 26.9, 37.0, 40.8, 56.0, 125.9, 127.6, 127.8, 128.9, 130.6, 131.6, 146.2, 146.7. HRMS (ESI+) calcd. for $C_{22}H_{22}NCl$ $(M+H)^+$: 336.15135; found: 336.15109. Analysis calcd. for $C_{22}H_{22}NCl \cdot 0.5H_2O$: C, 76.62; H, 6.72; N, 4.06. Found: C, 76.00; H, 6.53; N, 4.09.

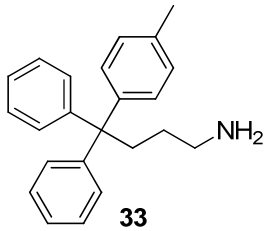
2-Amino-5,5-diphenyl-5-(4-methylphenyl)pentanoic acid (*rac*-32).



rac-**32**

The title compound was following the synthetic route and procedures described for *rac*-**9** in general procedure (ii). A white solid (182 mg, overall yield 25%) was obtained. Mpt. 180°C. ^{1}H NMR(400 MHz, DMSO-d_6) δ = 1.22-1.45 (m, 2H, CH_2), 2.25 (s, 1H, CH_3), 2.54-2.77 (m, 2H, CH_2), 3.15-3.18 (t, 1H, CH), 7.08-7.28 (m, 14H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.0, 27.8, 36.2, 55.2, 56.1, 126.3, 128.4, 129.0, 129.4, 135.3, 144.6, 147.8, 170.6. HRMS (ESI+) calcd. for $C_{24}H_{25}NO_2$ $(M+H)^+$: 360.19581; found: 360.19579. Analysis calcd. for $C_{24}H_{25}NO_2 \cdot H_2O$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.50; H, 7.08; N, 3.71.

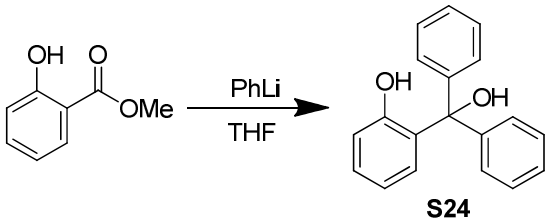
4-(4-Methylphenyl)-4,4-diphenylbutan-1-amine (33).



33

The title compound was following the synthetic route and procedures described for **10** in general procedure (iii). A colorless solid (70 mg, overall yield 33%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 0.99-1.03 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.50-2.54 (m, 4H, CH_2 and CH_2), 7.09-7.25 (m, 14H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.0, 30.2, 37.5, 42.6, 56.2, 126.2, 128.3, 129.0, 129.3, 129.4, 135.2, 145.0, 148.1. HRMS (ESI+) calcd. for $C_{23}H_{25}N$ $(M+H)^+$: 316.20598; found: 316.20663. Analysis calcd. for $C_{23}H_{25}N{\cdot}0.5H_2O$: C, 85.14; H, 8.08; N, 4.32. Found: C, 85.91; H, 7.94; N, 4.63.

2-(Hydroxy(diphenyl)methyl)phenol (S24).



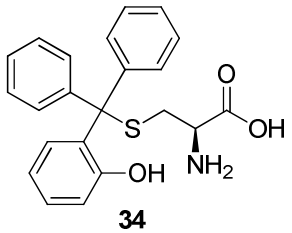
S24

Scheme S14

Phenyllithium (1.8M in Et_2O, 17.7 mL, 32 mmol) was added to a solution of methyl 2-hydroxybenzoate (699 μL, 8 mmol) in anhydrous THF (12 mL) at -78°C, and stirred for 1 h, whilst maintaining the temperature below -70°C. The reaction mixture warmed to room temperature, stirred for 2 h, then quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted EtOAc (2 x 30 mL). The combined organic extracts were washed with the organics washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude material by flash chromatography [SiO_2; 5-20% EtOAc in hexane] yielded the trityl alcohol **S42** as an off-white solid (1.26 g, 57%). Mpt. 133-134°C (lit. 135.5-138.5°C).[17] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.68 (br s, 1H, OH), 6.53 (dd, *J* = 1.6, 7.8 Hz, 1H), 6.73-6.76 (m, 1H), 6.90 (dd, *J* = 1.0, 8.1 Hz, 1H), 7.20-7.24 (m, 5H), 7.32-7.36 (m, 6H), 8.09 (br s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 84.61, 117.76, 119.22, 125.97, 127.91, 128.10, 128.35, 129.74, 130.15,

145.01, 156.02. HRMS (ESI-) calcd. for $C_{19}H_{15}O$ $(M-H)^-$: 275.10775; found: 275.10791. Analysis calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.65; H, 5.94.

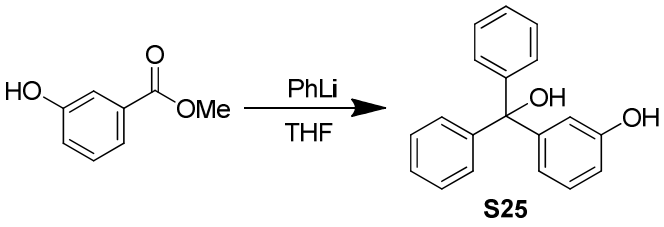
(2*R*)-2-Amino-3-(((2-hydroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (34).



34

The title compound was then prepared by an adaptation of the procedure reported by DeBonis *et al.*[11] A solution of (2-hydroxy(diphenyl)methyl)phenol **S24** (532 mg, 1.93 mmol) and *L*-cysteine (212 mg, 1.75 mmol) in AcOH (1.75 mL) was treated with $BF_3.Et_2O$ (376 μL, 2.99 mmol) at 0°C. After stirring for 2 h at room temperature the reaction was quenched with aqueous NaOAc (10% w/v, 5.3 mL), diluted with H_2O (5.3 mL) and the resulting white precipitate collected by filtration. The crude precipitate was dissolved in hot MeOH, filtered whilst hot and then concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 10-20% MeOH in CH_2Cl_2 with 1% NH_4OH] to afford the thioether **34** as a white solid (35 mg, 5%). Mpt. 156-159°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.20-2.25 (m, 1H), 2.40-2.44 (m, 1H), 2.81-2.84 (m, 1H), 6.71-6.73 (m, 1H), 6.85-6.88 (m, 1H), 7.12-7.36 (m, 11H), 7.73-7.75 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 35.32, 53.79, 65.12, 116.40, 118.49, 125.85, 126.99, 128.52, 128.99, 129.89, 142.92, 143.17, 155.09, 171.89. HRMS (ESI+) calcd. for $C_{22}H_{22}NO_3S$ $(M+H)^+$: 380.13149; found: 380.13141. Analysis calcd. for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 63.64; H, 5.53; N, 4.09.

3-(Hydroxy(diphenyl)methyl)phenol (S25).

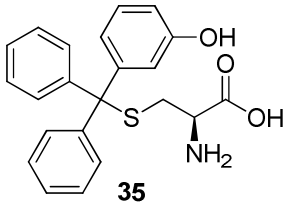


S25

Scheme S15

The title compound was prepared using an adaptation of the procedure for **S24** using methyl 3-hydroxybenzoate (1.52g, 10 mmol) and phenyllithium (1.8 M in Et_2O, 22.2 mL, 40 mmol) in anhydrous THF (16.6 mL) with the following modifications. The reaction mixture was allowed to stir for 4.5 h after warming to room temperature. Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the tertiary alcohol **S25** as an off-white powder (1.55g, 56%). Mpt. 139-142°C (lit. 148 °C from benzene).[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.85 (s, 1H, OH), 4.94 (br s, 1H, OH), 6.73-6.77 (m, 2H), 6.81 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.26-7.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 82.07, 114.42, 115.24, 120.72, 127.49, 128.05, 128.10, 129.33, 146.73, 148.66, 155.37. HRMS (ESI-) calcd. for $C_{19}H_{15}O$ $(M-H)^-$: 275.10775; found: 275.10793. Analysis calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.46; H, 5.89.

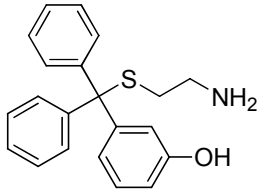
(2*R*)-2-Amino-3-(((3-hydroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (35).



35

The title compound was prepared by an adaptation of the method for **11** using (3-hydroxy(diphenyl)methyl)phenol **S25** (304 mg, 1.1 mmol) and *L*-cysteine (121 mg, 1 mmol) in AcOH (1 mL) followed by $BF_3.Et_2O$ solution (214 μL, 1.70 mmol), with a reaction time of 2 h. Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **35** as a white solid (161 mg, 62%). Mpt. 178-180°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.88 (s, 1H, OH), 2.40 (dd, *J* = 9.0, 12.4 Hz, 1H, CH_2), 2.58 (dd, *J* = 4.4, 12.4 Hz, 1H, CH_2), 2.99 (dd, *J* = 4.4, 9.0 Hz, 1H, CH), 6.64 (dd, *J* = 1.8, 8.0 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.78 (br s, 1H). 7.09 (t, *J* = 7.9 Hz, 1H), 7.22-7.26 (m, 2H), 7.30-7.34 (m, 8H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 34.02, 53.57, 65.94, 113.78, 116.39, 119.75, 126.64, 127.92, 128.80, 129.21, 144.30, 144.35, 145.83, 157.08, 169.26. HRMS (ESI+) calcd. for $C_{22}H_{22}NO_3NaS$ $(M+Na)^+$: 402.1134; found: 402.11453. Analysis calcd. for $C_{22}H_{21}NO_3S \cdot \frac{1}{3}CH_2Cl_2$: C, 65.78; H, 5.36; N, 3.43. Found: C, 65.83; H, 5.36; N, 3.43.

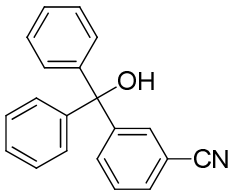
3-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)phenol (36).



36

The title compound was prepared following general procedure (vi) with 3-(hydroxy(diphenyl)-methyl)-phenol **S25** (276 mg, 1 mmol) and cysteamine hydrochloride (114 mg, 1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-16% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **36** as a as a white solid (259 mg, 77%). Mpt. 143°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.16 (t, J = 7.0 Hz, 2H, CH_2), 2.44 (t, J = 7.1 Hz, 2H, CH_2), 6.62 (ddd, J = 0.7, 2.4, 8.0 Hz, 1H), 6.71-6.73 (m, 1H), 6.78-6.79 (m, 1H), 7.10 (t, J = 8.0 Hz, 1H), 7.21-7.26 (m, 2H), 7.30-7.34 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 35.58, 40.81, 65.75, 113.64, 116.34, 119.88, 126.60, 127.90, 128.83, 129.18, 144.72, 146.20, 156.89. HRMS (ESI+) calcd. for $C_{21}H_{22}NOS$ $(M+H)^+$: 336.14166; found: 336.14172. Analysis calcd. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N 4.18. Found: C, 74.33; H, 6.33; N, 4.07.

3-(Hydroxy(diphenyl)methyl)benzonitrile (S5).

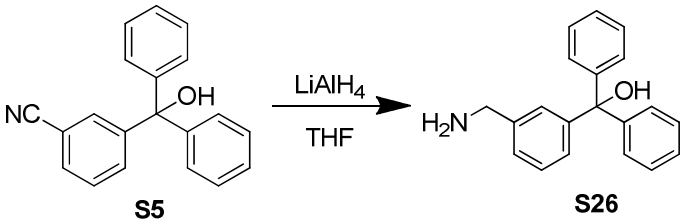


S5

The title compound was prepared by an adaptation of the reverse addition methodology by Luliński *et al.* and the procedure reported by Neumann *et al.*[19, 20] A solution of 3-bromobenzonitrile (1.82g, 10 mmol) in anhydrous THF (10 mL) was added by slow dropwise addition over 5 min to a solution of *n*-butyllithium (2.5 M in hexane, 4.2 mL, 10.5 mmol) at -94°C and stirred for 1 h, maintaining the temperature ≤ -80°C. After cooling again to -94°C, a solution of benzophenone (2.00g, 11 mmol) in anhydrous THF was then added by slow dropwise addition over 6 min and stirred with the temperature

maintained ≤ -50°C for 4 h, before allowing the reaction mixture to warm slowly to room temperature and stirring for a further 19 h. The reaction was quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed successively with H_2O (75 mL) and brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-25% EtOAc in hexane;] afforded the trityl alcohol **S5** as a white solid (2.30 g, 81%). Mpt. 90-92°C (lit. 96.5-97°C).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.85 (s, 1H, OH), 7.20-7.25 (m, 4H), 7.30-7.38 (m, 6H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.55-7.62 (m, 2H), 7.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 81.70, 112.18, 119.05, 127.90, 128.03, 128.47, 128.86, 131.02, 131.60, 132.48, 145.91, 148.41. HRMS (ESI+) Calcd. for $C_{20}H_{16}NO$ $(M+H)^+$: 286.1226; found: 286.1224. Analysis calcd. for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 83.71; H, 5.13; N, 4.80.

(3-(Aminomethyl)phenyl)(diphenyl)methanol (S44).

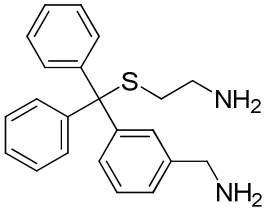


S5 **S26**

Scheme S16

A solution of lithium aluminium hydride (1M in THF, 7.87 mL, 7.87 mmol) was added by slow dropwise addition over 8 min to a solution of 3-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile **S5** (936 mg, 3.28 mmol) in anhydrous THF (10.90 mL) at 0°C. The reaction mixture was allowed to warm to room temperature stirred for 22 h. It was then cooled to 0°C and quenched by slow dropwise addition of H_2O (10 mL), followed by aqueous NaOH solution (15% w/v, 5 mL) and H_2O (15 mL). The suspension was filtered and the precipitate washed with CH_2Cl_2, and the filtrate then washed successively with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the tertiary alcohol **S26** as a white solid (643 mg, 68%). Mpt. 136-138°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.66 (s, 2H, CH_2), 6.38 (br s, 1H, OH), 6.97-6.99 (m, 1H), 7.19-7.34 (m, 13H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 45.72, 80.58, 125.35, 125.87, 126.35, 126.55, 127.17, 127.46, 127.78, 143.19, 147.55, 147.87. HRMS (ESI+) Calcd. for $C_{20}H_{20}NO$ $(M+H)^+$: 290.1539; found: 290.1537. Analysis calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.23; H, 6.43; N, 4.29.

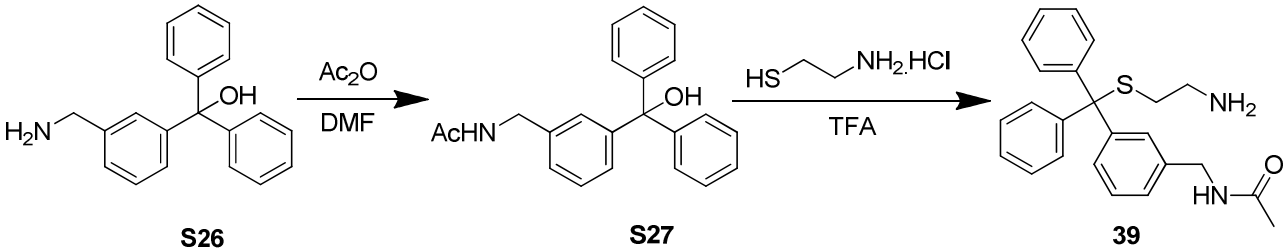
2-(((3-(Aminomethyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (38).



38

The title compound was prepared following general procedure (vi) with (3-(aminomethyl)phenyl)(diphenyl)methanol **26** (250 mg, 0.86 mmol) and cysteamine hydrochloride (108 mg, 0.95 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **38** as a clear yellow oil (250 mg, 72%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.15 (t, J = 7.1 Hz, 2H, CH_2), 2.42 (t, J = 7.0 Hz, 2H, CH_2), 3.67 (s, 2H, CH_2), 7.10-7.12 (m, 1H), 7.20-7.26 (m, 4H), 7.30-7.34 (m, 8H), 7.36-7.38 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.70, 40.85, 45.64, 65.87, 125.35, 126.54, 127.11, 127.62, 127.88, 129.16, 143.80, 144.52, 144.78. HRMS (ESI+) Calcd. for $C_{22}H_{25}N_2S$ $(M+H)^+$: 349.1733; found: 349.1731. Analysis calcd. for $C_{22}H_{24}N_2S$: C, 75.82; H, 6.94; N, 8.04. Found: C, 73.93; H, 6.97; N, 8.39.

***N*-(3-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzyl)acetamide (39).**



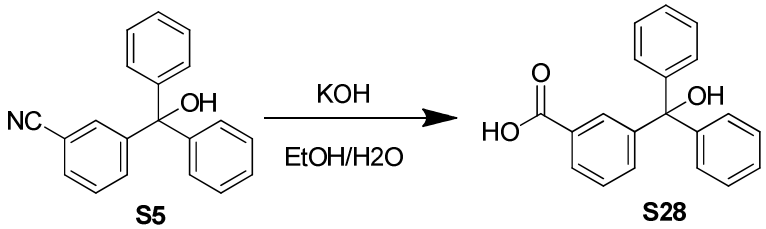
S26 **S27** **39**

Scheme S17

Acetic anhydride (97 µL, 1.02 mmol) was added to a solution of (3-(aminomethyl)phenyl)(diphenyl)methanol (270 mg, 0.93 mmol) **S26** in anhydrous DMF (1.17 mL) and stirred at room temperature for 4 h. The reaction mixture was diluted with aqueous HCl (0.25M, 5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (20 mL), H2O (2 x 20 mL) and brine (20 mL), dried (MgSO4), and concentrated *in vacuo* to yield *N*-(3-(Hydroxy(diphenyl)methyl)benzyl)acetamide **S27** as a white solid (290 mg, 88%), which was used in the next step without further purification. Mpt. 170-172°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.81 (s, 3H, CH_3), 4.19 (d, J = 6.0 Hz, 2H, CH_2), 6.42 (s, 1H, OH), 7.01-7.03

(m, 1H), 7.11-7.13 (m, 1H), 7.17-7.32 (m, 12H), 8.29 (t, J = 6.0 Hz, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 22.48, 42.14, 80.51, 125.50, 126.36, 126.43, 126.61, 127.35, 127.48, 127.77, 147.75, 168.89. HRMS (ESI+) Calcd. for $C_{22}H_{20}NO$ $(M+H-OH)^+$: 314.1539; found: 314.1538. Analysis calcd. for $C_{22}H_{21}NO_2$: C, 79.75; H, 6.39; N, 4.23. Found: C, 78.72; H, 6.23; N, 3.98. The title compound was then prepared following general procedure (vi) with *N*-(3-(Hydroxy(diphenyl)methyl)benzyl)acetamide **S27** (166 mg, 0.50 mmol) and cysteamine hydrochloride (63 mg, 0.55 mmol) in trifluoroacetic acid (0.5 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the amine **39** as a colourless oil (169 mg, 82%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.81 (s, 3H, CH_3), 2.16 (d, J = 7.0 Hz, 2H, CH_2), 2.42 (d, J = 7.0 Hz, 2H, CH_2), 4.19 (d, J = 6.0 Hz, m, NHC<u>H</u>$_2$), 7.10-7.15 (m, 2H), 7.22-7.35 (m, 12H), 8.32 (t, J = 6.0 Hz, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 22.45, 35.48, 40.75, 42.08, 65.77, 125.33, 126.61, 127.68, 127.74, 127.83, 127.91, 129.12, 139.37, 144.16, 169.05. HRMS (ESI+) Calcd. for $C_{24}H_{27}N_2OS$ $(M+H)^+$: 391.1839; found: 391.1836. Analysis calcd. for $C_{24}H_{26}N_2OS$: C, 73.81; H, 6.71; N, 7.17. Found: C, 70.87; H, 6.97; N, 6.84.

3-(Hydroxy(diphenyl)methyl)benzoic acid (S28).

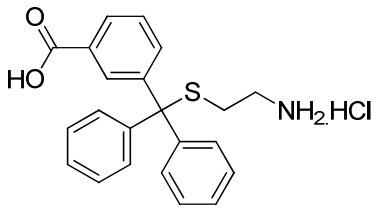


S5 **S28**

Scheme S18

A solution of 3-(hydroxy(diphenyl)methyl)benzonitrile **S5** (1.25 g, 4.37 mmol) and potassium hydroxide (2.728 g, 48.60 mmol) was refluxed in an EtOH/H_2O mixture (1:1, 49 mL) for 24 h. After cooling to room temperature, the EtOH was removed under reduced pressure, the solution washed with Et_2O (30 mL), acidified (*circa* pH 1) with aqueous HCl (1M) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield as a white solid **S28**, which was used without further purification (1.25 g, 94%). Mpt. 166-168°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.60 (s, 1H, OH), 7.19-7.22 (m, 4H), 7.24-7.28 (m, 2H), 7.29-7.34 (m, 4H), 7.41-7.44 (m, 2H), 7.81-7.85 (m, 1H), 7.86-7.88 (m, 1H), 12.82 (br s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 80.40, 126.82, 127.69, 127.58, 130.20, 132.19, 147.33, 148.29, 167.40. HRMS (ESI-) Calcd. for $C_{20}H_{15}O_3$ $(M-H)^-$: 303.1027; found: 303.1028. Analysis calcd. for $C_{20}H_{16}O_3 \cdot \frac{1}{3}CH_2Cl_2$: C, 73.42; H, 5.05. Found: C, 73.48; H, 5.06.

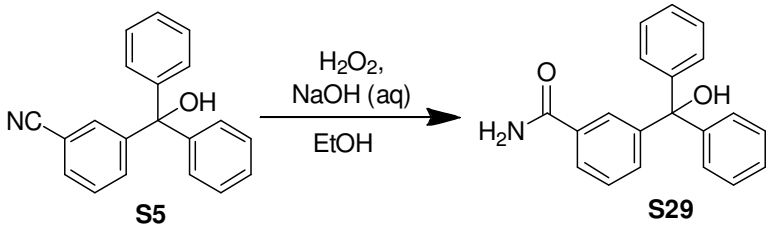
3-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzoic acid hydrochloride (40).



40

A solution of the tertiary alcohol 3-(hydroxy(diphenyl)methyl)benzoic acid **S28** (346 mg, 1.0 mmol) with cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) was stirred for 3.5 h at room temperature. The volatiles were removed *in vacuo*, and the residue suspended in aqueous HCl (1M, 10 mL) and stirred at room temperature for 18 h, during which time a white precipitate formed. The mixture was filtered, and the precipitate washed successively with HCl (1M, 10 mL), petroleum ether (60/80) and Et_2O, and dried *in vacuo* to yield the title thioether **40** as a white solid (145 mg, 36%). Mpt. 218-220°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.43 (m, 2H, CH_2), 2.50-2.55 (m, 2H, CH_2), 7.28-7.31 (m, 2H), 7.33-7.40 (m, 8H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.58 (ddd, *J* = 1.2, 2.0, 7.9 Hz, 1H), 7.85-7.87 (m, 1H), 7.88-8.05 (m, 4H), 13.06 (br s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.42, 37.65, 66.23, 127.15, 127.96, 128.39, 128.63, 128.96, 129.73, 130.67, 133.48, 143.59, 144.62, 167.01. HRMS (ESI-) Calcd. for $C_{22}H_{22}NO_2S$ $(M+H)^+$: 364.1366; found: 364.1363. Analysis calcd. for $C_{21}H_{21}NO_2S$·HCl: C, 66.07; H, 5.54; N, 3.37. Found: C, 64.12; H, 5.57; N, 3.37.

3-(Hydroxy(diphenyl)methyl)benzamide (S29).



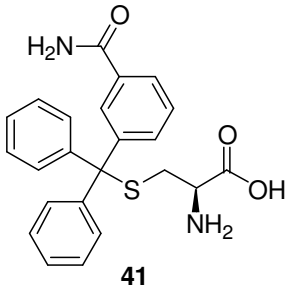
S5 **S29**

Scheme S19

This hydrolysis protocol is a modification of the literature procedure reported by Iso *et al.*[22] Hydrogen peroxide (30% in H_2O, 536 µl, 5.25 mmol) and aqueous NaOH (6M, 350 µL, 2.1 mmol) were added to a solution of 3-(hydroxy(diphenyl)methyl)benzonitrile **S5** (494 mg, 1.75 mmol) in EtOH (7.69 mL) and stirred at 60°C for 4 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (75 mL) and aqueous HCl (0.25M, 25mL). The organic layer was washed successively with H_2O

(75 mL) and brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the crude [SiO_2; 40-100% EtOAc in hexane] afforded the amide **S29** as a white solid (440 mg, 83%). Mpt. 168-169°C. ^{1}H NMR (400 MHz, MeOD) δ = 7.23-7.32 (m, 10H), 7.35-7.43 (m, 2H), 7.73-7.76 (m, 1H), 7.88-7.90 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ = 82.70, 127.06, 128.15, 128.46, 128.79, 129.26, 132.78, 134.57, 148.46, 149.61, 172.52. HRMS (ESI+) Calcd. for $C_{22}H_{23}N_2OS$ $(M+H)^+$: 363.1526; found: 363.1522. Analysis calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.99; H, 5.57; N, 4.49.

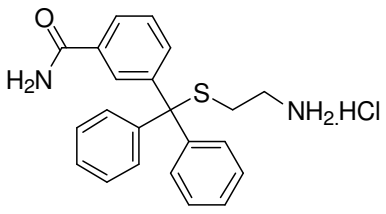
(*R*)-2-amino-3-(((3-carbamoylphenyl)diphenylmethyl)sulfanyl)propanoic acid (41).



41

The title compound was prepared following general procedure (vi) with 3-(hydroxy(diphenyl)methyl)benzamide **S29** (303 mg, 1.0 mmol) and *L*-cysteine (133 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-35% MeOH in CH_2Cl_2] afforded the title compound **41** as a white solid (139 mg, 34%). Mpt. 154-157°C. ^{1}H NMR (500 MHz, MeOD) δ = 2.69 (dd, *J* = 8.5, 13.2 Hz, 1H, CH_2), 2.77 (dd, *J* = 4.3, 13.2 Hz, 1H, CH_2), 3.09 (dd, *J* = 4.3, 8.5 Hz, 1H, CH), 7.22-7.27 (m, 2H), 7.30-7.35 (m, 4H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.43-7.56 (m, 4H), 7.54-7.59 (m, 1H), 7.74-7.76 (m, 1H), 8.11-8.13 (m, 1H). ^{13}C NMR (125 MHz, MeOD) δ = 34.16, 55.01, 67.95, 127.24, 128.22, 129.33, 129.75, 130.53, 130.71, 134.42, 135.09, 145.24, 145.49, 146.22, 172.24, 172.31. HRMS (ESI-) Calcd. for $C_{23}H_{21}NO_3S$ $(M-H)^-$: 405.1278; found: 405.1280. Analysis calcd. for $C_{23}H_{22}N_2O_3S \cdot \frac{1}{3}CH_2Cl_2$: C, 64.45; H, 5.25; N, 6.48. Found: C, 64.73; H, 5.20; N, 6.48.

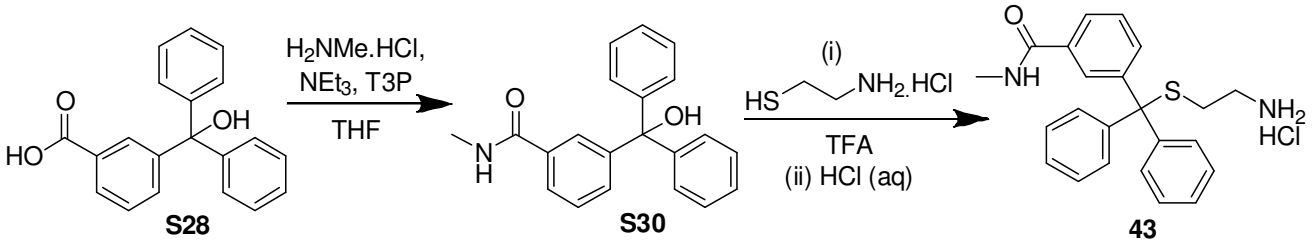
3-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzamide hydrochloride (42).



42

A solution of the tertiary alcohol 3-(hydroxy(diphenyl)methyl)benzamide **S29** (131 mg, 0.43 mmol) with cysteamine hydrochloride (54 mg, 0.48 mmol) in trifluoroacetic acid (0.86 mL) was stirred for 2.5 h at room temperature. The volatiles were removed *in vacuo*, and the crude basified (*circa.* pH 10) with aqueous NaOH (1M). The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] yielded a white solid, which was suspended in aqueous HCl (1M, 10 mL) and stirred at room temperature for 18 h, during which time a white precipitate formed. The mixture was filtered, and the precipitate washed successively with HCl, petroleum ether (60/80) and Et_2O, and dried *in vacuo* to afford the hydrochloride salt **42** as a white solid (48 mg, 28%). Mpt. 202-205°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.43-2.47 (m, 2H, CH_2), 7.26-7.31 (m, 2H), 7.33-7.49 (m, 11H), 7.78-7.81 (m, 1H), 7.91-7.98 (m, 4H), 7.99-8.03 (br s, 1H, $CONH_2$). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.38, 37.65, 66.36, 125.73, 127.03, 128.08, 128.29, 128.39, 129.02, 131.76, 134.17, 143.73, 144.40, 167.57. HRMS (ESI+) Calcd. for $C_{22}H_{23}N_2OS$ $(M+H)^+$: 363.1526; found: 363.1522. Analysis calcd. for $C_{22}H_{22}N_2OS \cdot 2HCl$: C, 60.69; H, 5.56; N, 6.43. Found: C, 61.21; H, 5.39; N, 6.38.

3-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)-*N*-methylbenzamide hydrochloride (43).

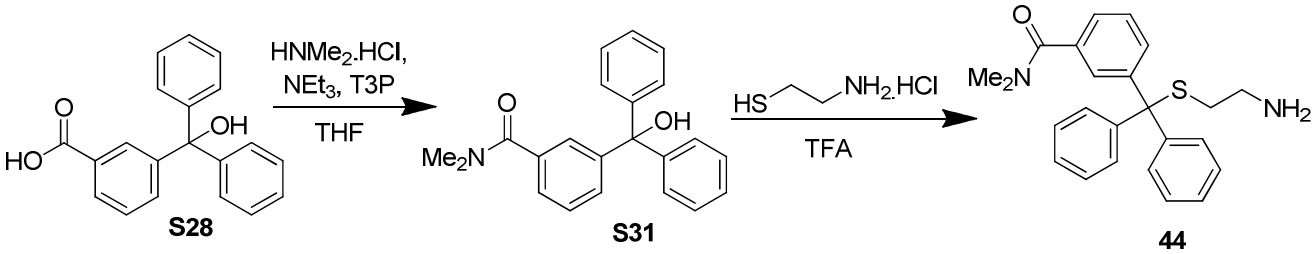


Scheme S20

Methanamine hydrochloride (203 mg, 3.0 mmol), followed by triethylamine (1.26 mL, 9.0 mmol) and T3P (50% in DMF, 876 µL, 1.5 mmol) were added to a cooled (0°C) solution of 3-(hydroxy(diphenyl)methyl)benzoic acid **S28** (304 mg, 1.0 mmol) in anhydrous THF (2 mL), and stirred at room temperature for 44 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and stirred for 45 min. The volatiles were removed *in vacuo* and the pH was adjusted (*circa.* pH 7) with aqueous HCl (1M) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed successively with H_2O (75 mL) and brine (75 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford 3-(hydroxy(diphenyl)methyl)-*N*-methylbenzamide **S30** as a white solid, which was taken to the next step without further purification (248 mg, 78%). Mpt. 137-138°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.90 (d, *J* = 4.9 Hz, 3H, CH_3), 3.15 (br s, OH), 6.18 (br s, NH), 7.22-7.36 (m, 12H), 7.67-7.70 (m, 1H), 7.78-7.80

(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.90, 82.03, 125.88, 126.25, 127.65, 128.03, 128.24, 131.17, 134.58, 146.59, 147.45, 168.32. HRMS (ESI+) Calcd. for $C_{21}H_{20}NO_2$ $(M+H)^+$: 318.1487; found: 318.1489. Analysis calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 78.44; H, 6.07; N, 5.12. The title compound was then prepared as follows. A solution of the tertiary alcohol 3-(hydroxy(diphenyl)methyl)-*N*-methylbenzamide **S30** (220 mg, 0.69 mmol) with cysteamine hydrochloride (87 mg, 0.76 mmol) in trifluoroacetic acid (692 μL) was stirred for 3 h at room temperature. The volatiles were removed *in vacuo* and the crude basified (*circa.* pH 10) with saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. After purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 1% NH_4OH], the crude product was suspended in aqueous HCl (1M, 10 mL) and stirred at room temperature for 18 h, during which time a white precipitate formed. The mixture was filtered, the precipitate washed successively with CH_2Cl_2 and H_2O, and dried *in vacuo* to yield the hydrochloride salt **43** as a white solid (69 mg, 24%). Mpt. 197-200°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.43-2.48 (m, 2H, CH_2), 2.74 (d, J = 4.5 Hz, 3H, CH_3), 7.26-7.47 (m, 12H), 7.74-7.77 (m, 2H), 7.88-7.99 (m, 4H), 8.51 (d, J = 4.5 Hz, 3H, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 26.23, 28.38, 37.64, 66.35, 125.31, 127.03, 128.02, 128.14, 128.29, 129.01, 131.59, 134.40, 143.74, 144.40, 166.24. HRMS (ESI+) Calcd. for $C_{23}H_{25}N_2OS$ $(M+H)^+$: 377.1682; found: 377.1679. Analysis calcd. for $C_{23}H_{24}N_2OS{\cdot}2HCl$: C, 61.47; H, 5.83; N, 6.23. Found: C, 58.67; H, 5.42; N, 5.90

3-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzamide (44).

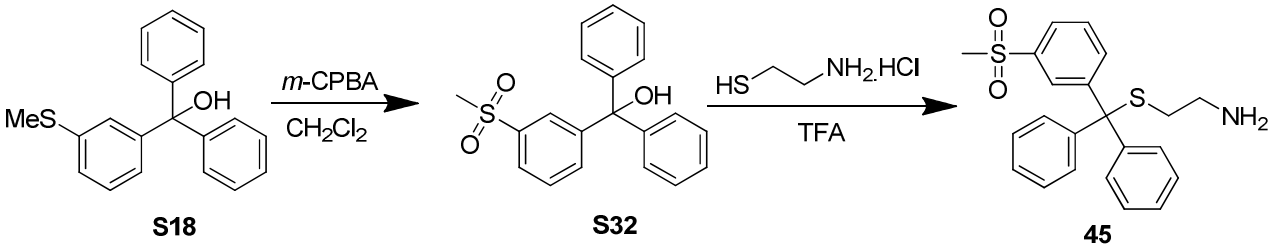


Scheme S21

N-methylmethanamine hydrochloride (245 mg, 3.0 mmol), followed by triethylamine (1.25 mL, 9.0 mmol) and T3P (50% in DMF, 876 μL, 1.5 mmol) were added to a cooled (0°C) solution of 3-(hydroxy(diphenyl)methyl)benzoic acid **S28** (304 mg, 1.0 mmol) in anhydrous THF (2 mL) and stirred at room temperature for 44 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and stirred for 1.5 h. The volatiles were removed *in vacuo*, and the mixture extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed successively with H_2O (75 mL) and brine (75 mL), dried ($MgSO_4$), then concentrated *in vacuo* to the amide **S31** as a white solid, which was taken to the next step

without further purification (259 mg, 78%). Mpt. 165-167°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.87 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 7.26-7.37 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 35.48, 39.65, 82.00, 126.34, 126.75, 127.58, 128.03, 128.18, 128.28, 129.23, 135.96, 146.65, 147.10, 171.60. HRMS (ESI+) Calcd. for $C_{22}H_{22}NO_2$ $(M+H)^+$: 332.1645; found: 332.1643. Analysis calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 78.87; H, 6.39; N, 4.57. The title compound was then prepared following general procedure (vi) with 3-(hydroxy(diphenyl)methyl)-*N,N*-dimethylbenzamide **S31** (199 mg, 0.6 mmol) and cysteamine hydrochloride (75 mg, 0.66 mmol) in trifluoroacetic acid (0.6 mL). Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **44** as a colourless oil (201 mg, 86%). ^{1}H NMR (500 MHz, MeOD) δ = 2.33-2.38 (m, 2H, CH_2), 2.43-2.48 (m, 2H, CH_2), 2.89-2.93 (m, 3H, CH_3), 3.03-3.07 (m, 3H, CH_3), 7.21-7.34 (m, 7H), 7.38-7.46 (m, 6H), 7.55-7.59 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ = 35.64, 35.92, 40.03, 41.51, 67.56, 126.51, 128.06, 129.11, 129.30, 129.37, 130.72, 132.17, 136.86, 145.80, 147.03, 173.51. HRMS (ESI+) Calcd. for $C_{24}H_{27}N_2OS$ $(M+H)^+$: 391.1839; found: 391.1836. Analysis calcd. for $C_{24}H_{26}N_2OS \cdot \frac{1}{3}CH_2Cl_2$: C, 69.78; H, 6.42; N, 6.69. Found: C, 70.87; H, 6.44; N, 6.69.

2-(((4-(Methylsulfonyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (45).



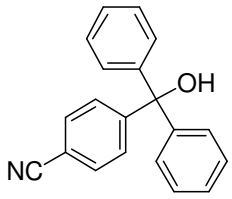
S18 **S32** **45**

Scheme S22

Intermediate sulfone **S32** was prepared by adaptation of the procedure reported by Yeon Hwang *et al.*[23] *m*-CPBA (68% pure, 620 mg, 3.59 mmol) was added to a cooled (0°C) solution of (3-(methylsulfanyl)phenyl)(diphenyl)methanol **S18** (500 mg, 1.63 mmol) in anhydrous CH_2Cl_2 (4.26 mL) and stirred at the same temperature for 3 h. The reaction was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (3 x 30 mL), brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 10-75% EtOAc in hexane] afforded the sulfone **S32** as a white solid (445 mg, 81%). Mpt. 143-146°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.02 (s, 3H, CH_3), 7.20-7.37 (m, 10H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.58 (ddd, *J* = 1.2, 1.8, 7.8 Hz, 1H), 7.87 (ddd, *J* = 1.2, 1.8, 7.7 Hz, 1H), 8.06-8.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 44.58, 81.93, 126.27, 126.49, 128.01, 128.06, 128.52, 129.04, 133.51, 140.64, 146.14, 148.96. HRMS (ESI+) Calcd. for $C_{20}H_{17}O_2S$ $(M+H-OH)^+$: 322.0944;

found: 322.0941. The title compound was then prepared following general procedure (vi) with (3-(methylsulfonyl)phenyl)(diphenyl)methanol **S32** (169 mg, 0.5 mmol) and cysteamine hydrochloride (63 mg, 0.55 mmol) in trifluoroacetic acid (0.6 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **45** as a colourless oil (163 mg, 82%). ^{1}H NMR (500 MHz, DMSO-d_6)) δ = 2.17 (t, J = 7.0 Hz, 3H, CH_3), 2.43 (t, J = 7.0 Hz, 3H, CH_3), 3.19 (s, 3H, CH_3), 7.26-7.30 (m, 2H), 7.33-7.40 (m, 8H), 7.62-7.64 (m, 2H), 7.84-7.88 (m, 1H), 7.92-7.93 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.33, 40.73, 43.56, 65.53, 125.55, 126.73, 126.99, 128.26, 128.95, 129.35, 134.40, 140.59, 143.86, 146.23. HRMS (ESI+) Calcd. for $C_{22}H_{24}NO_2S_2$ $(M+H)^+$: 398.1243; found: 398.1241. Analysis calcd. for $C_{22}H_{23}NO_2S_2 \cdot ½H_2O$: C, 64.99; H, 5.95; N, 3.45. Found: C, 64.42; H, 5.69; N, 3.32.

4-(Hydroxy(diphenyl)methyl)benzonitrile (S33).

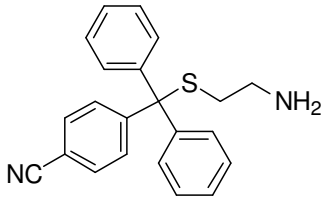


S33

The title compound was prepared by an adaptation of the reverse addition methodology by Luliński *et al.* and the procedure reported by Neumann *et al.*[19, 20] A solution of 4-bromobenzonitrile (3.64 g, 20 mmol) in anhydrous THF (20 mL) was added by slow dropwise addition over 5 min to a solution of *n*-butyllithium (2.5 M in hexane, 8.4 mL, 21 mmol) at -94°C and stirred for 30 min, maintaining the temperature ≤ -85°C. After cooling again to -94°C, a solution of benzophenone (4.01g, 22 mmol) in anhydrous THF (17 mL) was added by slow dropwise addition over 15 min and stirred for 5 h with the temperature maintained ≤ -80°C. The mixture was allowed to warm slowly to room temperature and stirred for a further 23 h. The reaction was quenched with saturated aqueous NH_4Cl solution (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed successively with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-30% EtOAc in hexane] afforded the tertiary alcohol **S33** as an off-white solid (3.86 g, 68%). Mpt. 85-87°C (lit. 92-93.5°C).[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.85 (s, 1H, OH), 7.22-7.25 (m, 4H), 7.30-7.36 (m, 6H), 7.46-7.49 (m, 2H), 7.59-7.61 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 81.92, 111.19, 118.92, 127.93, 128.00, 128.44, 128.72, 131.89, 145.90, 152.00. HRMS (ESI+) Calcd. for

$C_{20}H_{16}NO$ $(M+H)^+$: 286.1226; found: 286.1226. Analysis calcd. for $C_{20}H_{15}NO$: C, 84.19; H, 6.30; N, 4.91. Found: C, 83.91; H, 5.35; N, 4.81.

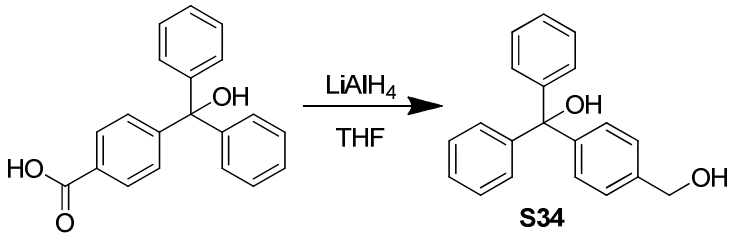
4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile (46).



46

The title compound was prepared following general procedure (vi) with 4-(hydroxy(diphenyl)methyl)benzonitrile **S33** (285 mg, 1 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **46** as a yellow oil (253 mg, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.15 (t, J = 7.1 Hz, 2H, CH_2), 2.44 (t, J = 7.1 Hz, 2H, CH_2), 7.24-7.30 (m, 2H), 7.31-7.39 (m, 8H), 7.49-7.53 (m, 2H), 7.80-7.84 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.38, 40.66, 54.88, 65.60, 109.46, 118.58, 127.01, 128.25, 130.08, 131.98, 143.65, 150.12. HRMS (ESI+) Calcd. for $C_{22}H_{21}N_2S$ $(M+H)^+$: 345.1420; found: 345.1418. Analysis calcd. for $C_{22}H_{20}N_2S \cdot \frac{1}{3}CH_2Cl_2$: C, 71.96; H, 5.59; N, 7.51. Found: C, 71.95; H, 5.54; N, 7.39.

(4-(Hydroxymethyl)phenyl)(diphenyl)methanol (S34).



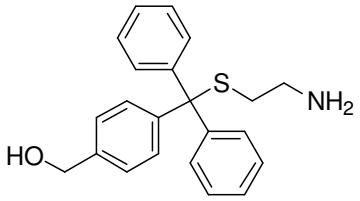
S34

Scheme S23

The title compound was prepared using a modification of the procedure reported by Zee-Cheng *et al.*[24] A solution of 4-(hydroxy(diphenyl)methyl)benzoic acid (304 mg, 1.0 mmol) in anhydrous THF (4 mL) was added by slow dropwise addition over 3 min to a cooled (0°C) solution of lithium aluminium hydride (1M in THF, 4.5 mL, 4.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20.5 h, then heated at 65°C for 1 h. The reaction was then cooled to 0°C, and quenched with EtOAc

(5 mL), H_2O (0.17 mL) aqueous NaOH (15% w/v, 0.17 mL) and H_2O (3 x 0.17 mL) and stirred for 45 min at room temperature. After filtering and washing the precipitate with EtOAc, the filtrate was washed successively with saturated aqueous $NaHCO_3$ solution (50 mL), H_2O (50 mL), and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-40% EtOAc in hexane] yielded **S34** as a clear oil (182 mg, 63%). Mpt. 112-115°C (lit. 115-117°C).[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.67 (s, 2H, CH_2), 7.25-7.33 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 65.23, 82.11, 126.80, 127.52, 128.11, 128.18, 128.36, 140.01, 146.59, 147.02. HRMS (ESI+) Calcd. for $C_{20}H_{17}O$ $(M+H-OH)^+$: 273.1274; found: 273.1272. Analysis calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.17; H, 6.23.

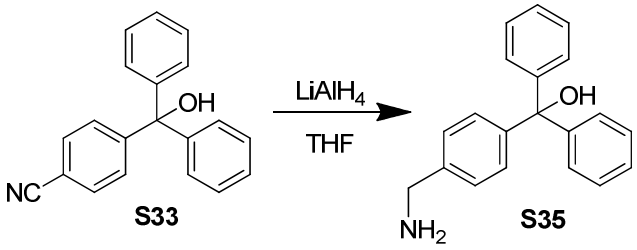
(4-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)phenyl)methanol (47).



47

The title compound was prepared following general procedure (vi) with 4(4-(hydroxymethyl)phenyl)(diphenyl)methanol **S34** (154 mg, 0.53 mmol) and cysteamine hydrochloride (66 mg, 0.58 mmol) in trifluoroacetic acid (0.53 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **47** as a yellow oil (54 mg, 29%). ^{1}H NMR (500 MHz, MeOD) δ = 2.35 (t, *J* = 6.7 Hz, 2H, CH_2), 2.43 (t, *J* = 6.7 Hz, 2H, CH_2), 4.58 (s, 2H, CH_2), 7.18-7.31 (m, 8H), 7.36-7.44 (m, 6H). ^{13}C NMR (125 MHz, MeOD) δ = 35.94, 41.50, 64.75, 67.61, 127.55, 127.80, 128.90, 130.74, 141.31, 145.33, 146.33. HRMS (ESI+) Calcd. for $C_{22}H_{24}NOS$ $(M+H)^+$: 350.1573; found: 350.1571. Analysis calcd. for $C_{22}H_{23}NOS$: C, 75.61; H, 6.63; N, 4.01. Found: C, 72.36; H, 6.19; N, 3.50.

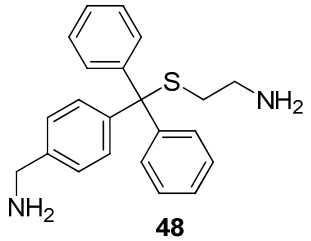
(4-(Aminomethyl)phenyl)(diphenyl)methanol (S33).



Scheme S24

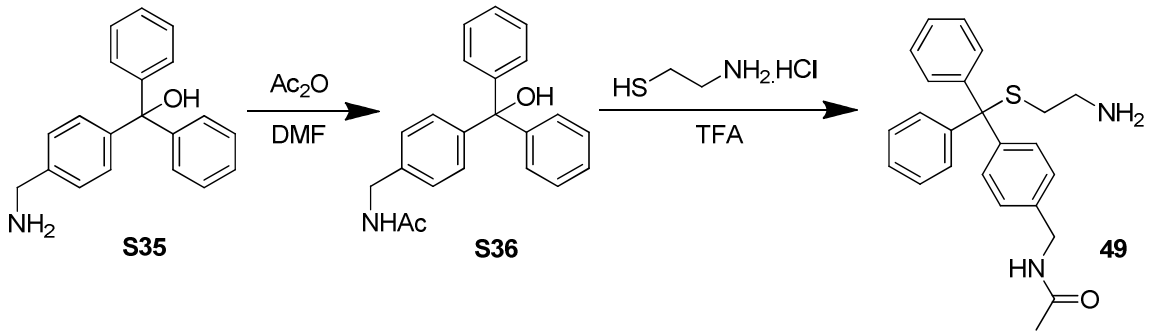
A solution of lithium aluminium hydride (1M in THF, 19.2 mL, 19.2 mmol) was added by slow dropwise addition over 10 min to a solution of 4-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile **S33** (2.28 g, 8.0 mmol) in anhydrous THF (25 mL) at 0°C. The reaction mixture was allowed to warm to room temperature stirred for 22 h. It was then cooled to 0°C and quenched by slow dropwise addition of H_2O (40 mL), followed by aqueous NaOH solution (15% w/v, 20 mL) and H_2O (20 mL). As this failed to break up the aluminium salt emulsion, saturated aqueous Na_2SO_4 solution (250 mL) was added and the mixture stirred for 30 min at room temperature. The mixture was filtered, the precipitate washed with CH_2Cl_2 and MeOH, and the filtrate concentrated to ~50 mL *in vacuo,* diluted with saturated aqueous Na_2SO_4 solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and and concentrated *in vacuo.* Purification by flash chromatography [SiO_2; 0-22% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the title compound **S35** as an off-white solid (1.34 g, 59%). Mpt. 138-140°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.68 (s, 2H, CH_2), 6.36 (br s, 1H, OH), 7.11-7.14 (m, 2H), 7.19-7.25 (m, 8H), 7.27-7.31 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 45.29, 80.43, 126.13, 126.55, 127.45, 127.52, 127.75, 142.49, 145.69, 147.92**.** HRMS (ESI+) Calcd. for $C_{20}H_{20}NO$ $(M+H)^+$: 290.1539; found: 290.1536. Analysis calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.54; H, 6.52; N, 4.66.

2-(((4-(Aminomethyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (48).



The title compound was prepared following general procedure (vi) using (4-(aminomethyl)phenyl)(diphenyl)methanol **S35** (145 mg, 0.5 mmol) and cysteamine hydrochloride (63 mg, 0.55 mmol) in trifluoroacetic acid (0.5 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **48** as an off-white solid (250 mg, 72%). Mpt. 70-72°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.15 (t, J = 7.1 Hz, 2H, CH_2), 2.43 (t, J = 7.1 Hz, 2H, CH_2), 3.69 (s, 2H, CH_2), 7.21-7.34 (m, 14H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 35.67, 40.86, 45.16, 65.58, 126.55, 127.90, 128.82, 129.09, 142.52, 142.60, 144.85. HRMS (ESI+) Calcd. for $C_{22}H_{25}N_2S$ $(M+H)^+$: 349.1733; found: 349.1731. Analysis calcd. for $C_{22}H_{24}N_2S{\cdot}½H_2O$: C, 73.91; H, 7.05; N, 7.84. Found: C, 73.91; H, 6.76; N, 7.57.

***N*-(4-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzyl)acetamide (49).**

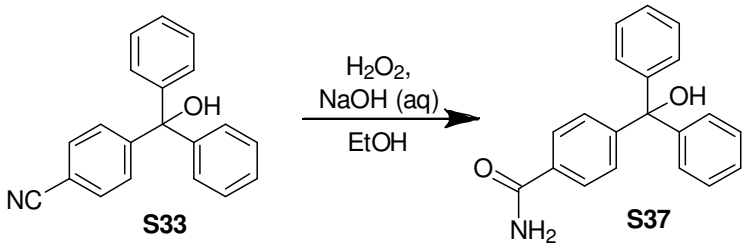


Scheme S25

Acetic anhydride (104 µL, 1.1 mmol) was added to a solution of (4-(aminomethyl)phenyl)(diphenyl)methanol (289 mg, 1 mmol) **S35** in anhydrous DMF (1.25 mL) and stirred at room temperature for 3 h. The reaction mixture was diluted with aqueous HCl (0.25M, 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (30 mL), H_2O (2 x 30 mL) and brine (30 mL), dried (MgSO4), and concentrated *in vacuo* to yield **S36** as a white solid (286 mg, 86%), which was taken to the next step without further purification. Mpt. 166-168.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.85 (s, 3H, CH_3), 4.22 (d, J = 6.0 Hz, 2H, CH_2), 6.39 (s, 1H, OH), 7.13-7.25 (m, 10H), 7.27-7.31 (m, 4H), 7.17-7.32 (m, 12H), 8.29 (t, J = 6.0 Hz, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 22.53, 41.78, 80.39, 126.48, 126.61, 127.49, 127.68, 127.74, 137.82, 146.34, 147.78, 169.05. HRMS (ESI+) Calcd. for $C_{22}H_{21}NO_2$ $(M+H)^+$: 332.1645; found: 332.1643. The title compound was then prepared following general procedure (vi) using *N*-(4-(Hydroxy(diphenyl)methyl)benzyl)acetamide **S36** (166 mg, 0.50 mmol) and cysteamine hydrochloride (63 mg, 0.55 mmol) in trifluoroacetic acid (0.5 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **49** as a pale yellow solid (143

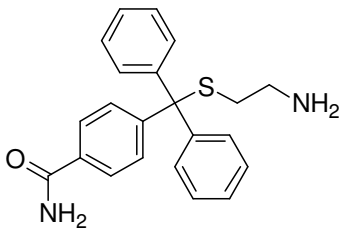
mg, 73%). Mpt. 74-77°C. ^{1}H NMR (400 MHz, MeOD) δ = 1.97 (s, 3H, CH_3), 2.31-2.35 (m, 2H, CH_2), 2.40-2.45 (m, 2H, CH_2), 4.33 (s, NHC<u>H</u>$_2$), 7.18-7.31 (m, 8H), 7.36-7.43 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ = 22.52, 35.92, 41.50, 43.77, 67.54, 127.82, 128.15, 128.91, 130.74, 130.91, 138.51, 145.37, 146.26, 173.13. HRMS (ESI+) Calcd. for $C_{24}H_{27}NO_2S$ $(M+H)^+$: 391.1839; found: 391.1835. Analysis calcd. for $C_{24}H_{26}N_2OS \cdot \frac{1}{3}CH_2Cl_2$: C, 69.78; H, 6.42; N, 6.69. Found: C, 70.47; H, 6.35; N, 6.64.

4-(Hydroxy(diphenyl)methyl)benzamide (S37).



This hydrolysis protocol is a modification of the literature procedure reported by Iso *et al.*[22] Hydrogen peroxide (30% in H_2O, 612 µl, 6.0 mmol) and aqueous NaOH (6M, 400 µL, 2.4 mmol) were added to a solution of 4-(hydroxy(diphenyl)methyl)benzonitrile **S33** (571 mg, 2.0 mmol) in EtOH (15mL) and stirred at 60°C for 3 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and aqueous HCl (0.25M, 25mL). The organic layer was washed successively with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the crude [SiO_2; 50-90% EtOAc in hexane] afforded the amide **S37** as a white solid (502 mg, 83%). Mpt. 176-179°C (lit. 188°C from MeOH).[25] ^{1}H NMR (500 MHz, MeOD) δ = 7.23-7.32 (m, 10H), 7.35-7.39 (m, 2H), 7.89-7.92 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 82.68, 128.03, 128.20, 128.79, 128.79, 129.23, 129.33, 133.48, 148.35, 152.91, 172.18. HRMS (ESI+) Calcd. for $C_{20}H_{18}NO_2$ $(M+H)^+$: 304.1332; found: 304.1330. Analysis calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.01; H, 5.60; N, 4.56.

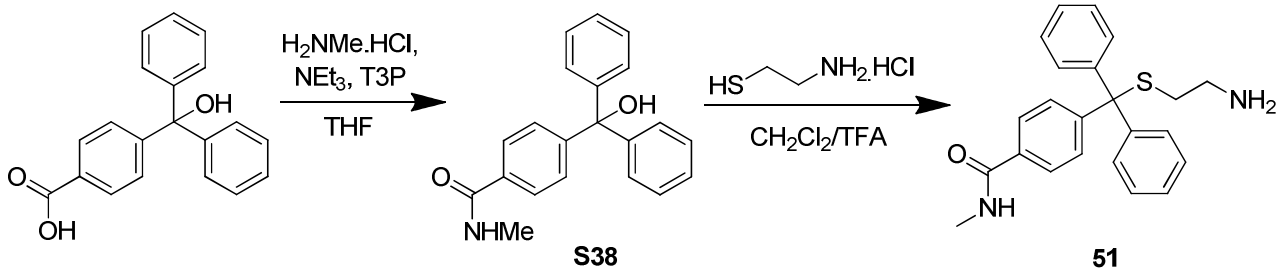
4-(((2- Aminoethyl)sulfanyl)(diphenyl)methyl)benzamide (50).



50

A solution of the tertiary alcohol 4-(hydroxy(diphenyl)methyl)benzamide **S37** (303.4 mg, 1.0 mmol) with cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) was stirred for 2 h at room temperature. The volatiles were removed *in vacuo* and the residue suspended in aqueous HCl (1M, 10 mL) and stirred at room temperature for 18.5 h, during which time a precipitate formed. The mixture was filtered, and the precipitate washed successively with HCl (1M, 10 mL), petroleum ether (60/80) and Et_2O, and dried *in vacuo* to yield the crude hydrochloride salt as an off-white solid. This was basified (*circa.* pH 10) with saturated sodium carbonate solution, extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the title compound **50** as a white solid (252 mg, 70%). Mpt. 62-65°C. ^{1}H NMR (500 MHz, MeOD) δ = 2.32-2.37 (m, 2H, CH_2), 2.42-2.47 (m, 2H, CH_2), 7.21-7.26 (m, 2H), 7.26-7.33 (m, 4H), 7.40-7.44 (m, 4H), 7.50-7.54 (m, 2H), 7.79-7.82 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 36.04, 41.51, 67.55, 128.04, 128.29, 129.08, 130.71, 130.84, 133.31, 145.76, 150.38, 171.86. HRMS (ESI+) Calcd. for $C_{22}H_{23}N_2OS$ $(M+H)^+$: 363.1526; found: 363.1523. Analysis calcd. for $C_{22}H_{22}N_2OS$: C, 72.89; H, 6.12; N, 7.73. Found: C, 71.88; H, 5.96; N, 7.33.

4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)-*N*-methylbenzamide (51).

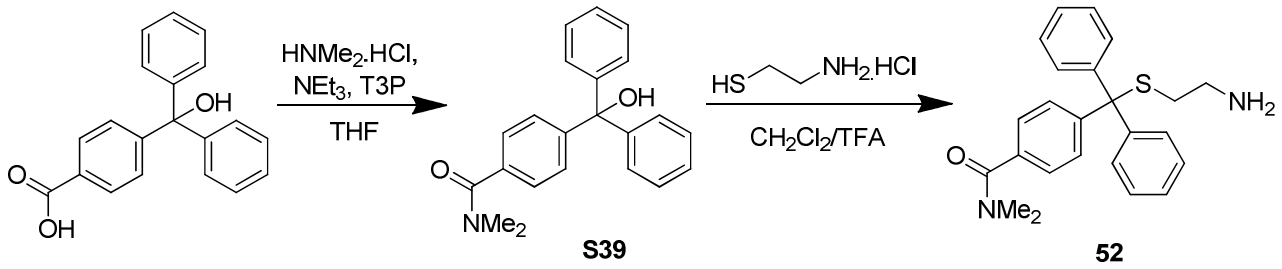


Scheme S26

Methanamine hydrochloride (203 mg, 3.0 mmol), followed by triethylamine (1.26 mL, 9.0 mmol) and T3P (50% in DMF, 876 μL, 1.5 mmol) were added to a cooled (0°C) solution of 4-(hydroxy(diphenyl)methyl)benzoic acid (304 mg, 1.0 mmol) in anhydrous THF (2 mL) and stirred at room temperature for 44 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and stirred for 45 min. The volatiles were removed *in vacuo* and the pH was adjusted (*circa.* pH 7) with aqueous HCl (1M) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed successively with H_2O (75 mL) and brine (75 mL) then concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 25-90% EtOAc in hexane] afforded 4-(hydroxy(diphenyl)methyl)-*N*-methylbenzamide **S38** as an off-white solid (181 mg, 57%). Mpt. 62-64°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.97 (d, *J* = 4.9 Hz, 3H, CH_3), 3.01 (s, 1H, OH), 6.17 (br s, 1H, NH), 7.22-7.33 (m, 10H), 7.36-7.38

(m, 2H), 7.65-7.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.96, 81.97, 126.59, 127.65, 128.01, 128.21, 128.23, 133.60, 146.53, 150.28, 168.15. HRMS (ESI+) Calcd. for $C_{21}H_{20}NO_2$ $(M+H)^+$: 318.1489; found: 318.1487. Analysis calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.27; H, 5.99; N, 4.33. The title compound was then prepared following general procedure (vi) using 4-(hydroxy(diphenyl)methyl)-*N*-methylbenzamide **S38** (150 mg, 0.47 mmol) with cysteamine hydrochloride (59 mg, 0.52 mmol) in trifluoroacetic acid (0.5 mL) and CH_2Cl_2 (2 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **51** as a white solid (122 mg, 69%). Mpt. 62-64°C. ^{1}H NMR (400 MHz, MeOD) δ = 2.32-2.36 (m, 2H, CH_2), 2.41-2.46 (m, 2H, CH_2), 2.91 (s, 3H, CH_3), 7.21-7.26 (m, 2H), 7.27-7.33 (m, 4H), 7.39-7.44 (m, 4H), 7.49-7.54 (m, 2H), 7.71-7.76 (m, 2H). ^{13}C NMR (100 MHz, MeOD) δ = 26.89, 35.99, 41.49, 67.54, 127.80, 128.03, 129.07, 130.71, 130.86, 133.92, 145.77, 150.01, 170.22. HRMS (ESI+) Calcd. for $C_{23}H_{25}N_2OS$ $(M+H)^+$: 377.1682; found: 377.1679. Analysis calcd. for $C_{23}H_{24}N_2OS$: C, 73.37; H, 6.42; N, 7.44. Found: C, 71.50; H, 6.19; N, 7.12.

4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)-*N*,*N*-dimethylbenzamide (52).

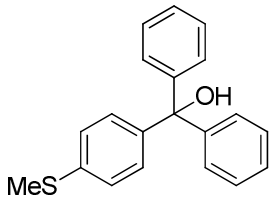


Scheme S27

N-methylmethanamine hydrochloride (245 mg, 3.0 mmol), followed by triethylamine (1.25 mL, 9.0 mmol) and T3P (50% in DMF, 876 µL, 1.5 mmol) were added to a cooled (0°C) solution of 4-(hydroxy(diphenyl)methyl)benzoic acid (304 mg, 1.0 mmol) in anhydrous THF (2.5 mL) and stirred at room temperature for 45 h. The volatiles were removed *in vacuo* and the residue suspended in saturated aqueous NaHCO3 (10 mL) and stirred for 1 h at room temperature. The pH was adjusted (*circa.* pH 7) with aqueous HCl (1M) and extracted with EtOAc (3 x 30 mL). The organic extracts were washed successively with H_2O (75 mL) and brine (75 mL) then concentrated *in vacuo* to afford 4-(hydroxy(diphenyl)methyl)-*N*,*N*-dimethylbenzamide **S39** as a white solid, which was used without further purification (246 mg, 74%). Mpt. 142-143°C. ^{1}H NMR (500 MHz, MeOD) δ = 3.00 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 7.23-7.32 (m, 10H), 7.34-7.38 (m, 4H). ^{13}C NMR (125 MHz, MeOD) δ = 35.64, 40.06, 82.64, 127.48, 128.17, 128.78, 129.23, 129.38, 135.81, 148.42, 150.91, 173.70. HRMS (ESI+) Calcd. for $C_{22}H_{22}NO_2$ $(M+H)^+$: 332.1645; found: 332.1642. Analysis calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N,

4.23. Found: C, 79.25; H, 6.27; N, 4.02. The title compound was then prepared following general procedure (vi) using 4-(hydroxy(diphenyl)methyl)-*N*,*N*-dimethylbenzamide **S39** (125 mg, 0.37 mmol) with cysteamine hydrochloride (51 mg, 0.42 mmol) in trifluoroacetic acid (0.5 mL) and CH_2Cl_2 (2 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **52** as a clear yellow crystalline solid (129 mg, 88%). Mpt. 60-62°C. ^{1}H NMR (400 MHz, MeOD) δ = 2.32-2.38 (m, 2H, CH_2), 2.42-2.48 (m, 2H, CH_2), 3.01 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 7.21-7.26 (m, 2H), 7.27-7.33 (m, 4H), 7.35-7.45 (m, 6H), 7.50-7.55 (m, 2H). ^{13}C NMR (100 MHz, MeOD) δ = 35.65, 36.01, 40.07, 41.52, 67.56, 127.73, 128.02, 129.06, 130.74, 130.87, 135.66, 145.82, 148.40, 173.41. HRMS (ESI+) Calcd. for $C_{24}H_{27}N_2OS$ $(M+H)^+$: 391.1839; found: 391.1835. Analysis calcd. for $C_{24}H_{26}N_2OS \cdot \frac{1}{3}CH_2Cl_2$: C, 69.78; H, 6.42; N, 6.69. Found: C, 69.78; H, 6.10; N, 6.56.

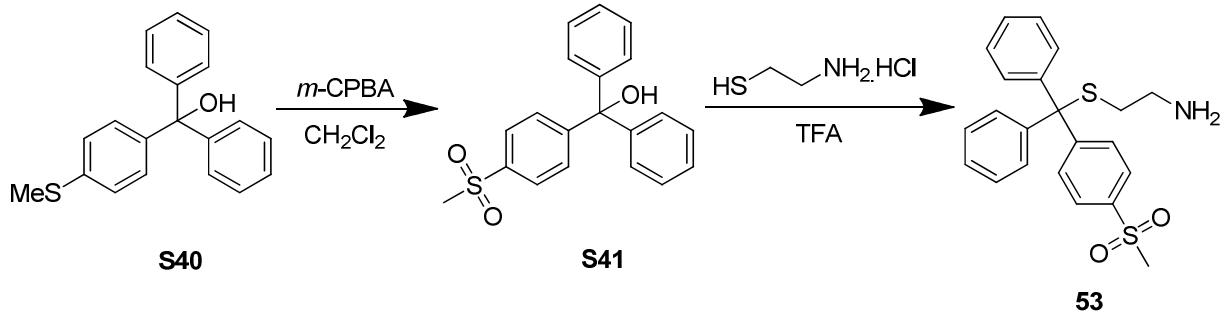
(4-(Methylsulfanyl)phenyl)(diphenyl)methanol (S40).



S40

n-Butyllithium (2.5M in hexane, 3.84 mL, 9.6 mmol) was added by slow dropwise addition over 2 min to a cooled (-77°C) solution of 1-bromo-4-(methylsulfanyl)benzene (1.625 g, 8.0 mmol) in anhydrous THF (8 mL) stirred for 1 h at the same temperature. A solution of benzophenone (1.676 g, 9.2 mmol) in anhydrous THF (9.2 mL) was then added by slow dropwise addition over 10 min and stirred, with the temperature maintained ≤ -70°C for 2 h, before allowing the reaction to warm slowly to room temperature and stirring for 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed successively with H_2O (75 mL) and brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-25% EtOAc in hexane;] afforded the tertiary alcohol **S40** as an opaque white oil (1.86 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.47 (s, 3H, CH_3), 2.75 (s, 1H, OH), 7.16-7.21 (m, 4H), 7.24-7.34 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.80, 81.92, 126.04, 127.47, 128.01, 128.12, 128.58, 137.65, 143.91, 146.89. HRMS (ESI+) Calcd. for $C_{20}H_{17}S$ $(M+H-OH)^+$: 289.1045; found: 289.1043. Analysis calcd. for $C_{20}H_{18}OS$: C, 78.39; H, 5.92. Found: C, 78.05; H, 5.69.

2-(((4-(Methylsulfonyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (53).



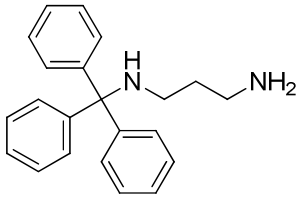
S40 **S41** **53**

Scheme S28

Intermediate sulfoxide **S50** was prepared by adaptation of the procedure reported by Yeon Hwang *et al*.[23] *m*-CPBA (68% pure, 1.12 g, 4.41 mmol) was added to a cooled (0°C) solution of (4-(methylsulfanyl)phenyl)(diphenyl)methanol **x** (759 mg, 2.50 mmol) in anhydrous CH_2Cl_2 (8 mL) and stirred at the same temperature for 7 h. The reaction was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were washed successively with aqueous NaOH (1M, 3 x 30 mL), H_2O (30 mL), brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 10-100% EtOAc in hexane] afforded (4-(methylsulfonyl)phenyl)(diphenyl)methanol **S41** as a white solid (395 mg, 58%). Mpt. 179-180°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.20 (s, 3H, CH_3), 6.72 (s, 1H, OH), 7.20-7.24 (m, 4H), 7.25-7.36 (m, 6H), 7.49-7.53 (m, 2H), 7.86-7.89 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 43.52, 80.41, 126.41, 127.02, 127.73, 127.79, 128.53, 139.14, 146.82, 153.37. , 65.53, 125.55, 126.73, 126.99, 128.26, 128.95, 129.35, 134.40, 140.59, 143.86, 146.23. HRMS (ESI+) Calcd. for $C_{20}H_{17}O_2S$ $(M+H-OH)^+$: 322.0944; found: 322.0941. Analysis calcd. for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36. Found: C, 70.35; H, 5.39. The title compound was then prepared following general procedure (vi) using (4-(methylsulfonyl)phenyl)(diphenyl)methanol **S41** (197 mg, 0.58 mmol) and cysteamine hydrochloride (73 mg, 0.64 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **53** as a colourless oil (143 mg, 62%). ^{1}H NMR (400 MHz, MeOD) δ = 2.32-2.37 (m, 2H, CH_2), 2.43-2.48 (m, 2H, CH_2), 3.12 (s, 3H, CH_3), 7.23-7.28 (m, 2H), 7.30-7.36 (m, 4H), 7.41-7.45 (m, 4H), 7.70-7.74 (m, 2H), 7.87-7.91 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 35.50, 40.71, 43.45, 65.54, 126.79, 126.97, 128.23, 129.02, 129.95, 138.97, 143.97, 150.38. HRMS (ESI+) Calcd. for $C_{22}H_{24}NO_2S_2$ $(M+H)^+$: 398.1243; found: 398.1239. Analysis calcd. for $C_{22}H_{23}NO_2S \cdot \frac{1}{3}CH_2Cl_2$: C, 62.99; H, 5.60; N, 3.29. Found: C, 63.14; H, 5.55; N, 2.90.

C) Synthesis and characterization of supplementary compounds

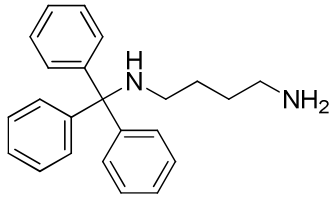
***N*^{1}-Tritylpropane-1,3-diamine (S42).**



S42

The title compound was prepared following general procedure (i) using 377 mg of N-FMOC-1,3-diaminopropane hydrobromide (1.0 mmol), 418 mg of trityl chloride (1.5 mmol) and 0.35 mL of triethyl amine. The crude product was purified by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give **S42** as a colorless solid (249 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.57 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 7.19-7.40 (m, 15H, Ph). ^{13}C NMR (100MHz, DMSO-d_6) δ = 32.7, 41.3, 70.4, 125.9, 127.7, 128.4, 146.2. HRMS (ESI+) calcd. for $C_{22}H_{24}N_2$ $(M+H)^+$: 317.20177; found: 317.20104. Analysis calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.96; H, 7.35; N, 8.45.

***N*^{1}-Tritylbutane-1,4-diamine (S43).**

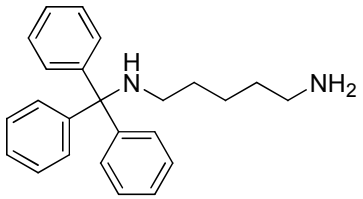


S43

The title compound was prepared following general procedure (i) using 391 mg of N-FMOC-1,4-diaminobutane hydrobromide (1.0 mmol), 418 mg of trityl chloride (1.5 mmol) and 0.35 mL of triethyl amine. The crude product was purified by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give **S43** as a colorless solid (240 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.45 (m, 4H, CH_2CH_2), 1.95 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 7.19-7.40 (m, 15H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 27.8, 29.7, 41.3, 43.8, 70.9, 126.6, 128.2, 128.9, 146.8. HRMS (ESI+) calcd. for

$C_{23}H_{26}N_2$ $(M+H)^+$: 331.21688; found: 331.21667. Analysis calcd. for $C_{23}H_{26}N_2 \cdot H_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 80.43; H, 7.52; N, 7.53.

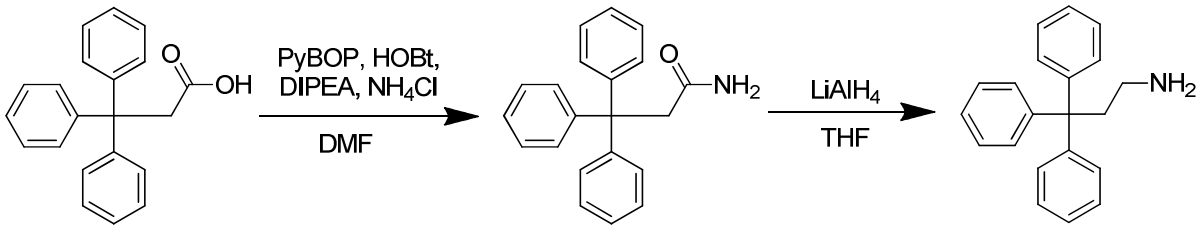
N^1-Tritylpentane-1,5-diamine (S44).



S44

The title compound was prepared following general procedure (i) using 405 mg of N-FMOC-1,5-diaminopentane hydrobromide (1.0 mmol), 418 mg of trityl chloride (1.5 mmol) and 0.35 mL of triethyl amine. The crude product was purified by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give **S44** as a colorless solid (256 mg, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.25 (m, 4H, CH_2CH_2), 1.45 (m, 2H, CH_2), 1.94 (m, 2H, CH_2), 2.49 (m, 2H, CH_2), 7.19-7.40 (m, 15H, Ph). ^{13}C NMR (100MHz, DMSO-d_6) δ = 24.9, 30.6, 33.8, 42.2, 44.0, 70.9, 126.5, 128.2, 128.9, 146.9. HRMS (ESI+) calcd. for $C_{24}H_{28}N_2$ $(M+H)^+$: 345.23253; found: 345.23226. Analysis calcd. for $C_{24}H_{28}N_2 \cdot H_2O$: C, 79.52; H, 8.34; N, 7.73. Found: C, 80.21; H, 7.64; N, 7.05.

3,3,3-Triphenylpropan-1-amine (S46).



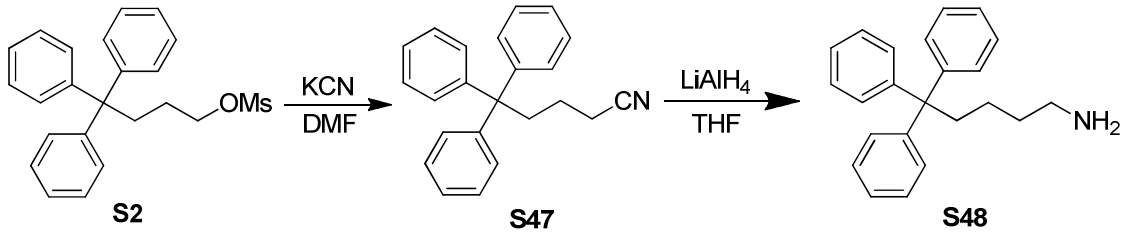
S45 **S46**

Scheme S29

The title compound was prepared using an adaptation of the method reported by Wang *et al.*[26] 3,3,3-Triphenylpropionic acid (1.0 g, 3.3 mmol) was treated with PyBOP (2.6 g, 5.0 mmol), HOBt (676 mg, 5.0 mmol), DIPEA (2.3 mL, 13.2 mmol) and NH_4Cl (353 mg, 6.6 mmol) in DMF (4 mL/mmol of acid,13.2 mL) at room temperature for 2 h to form the amide, followed by aqueous work-up. The residue was purified by flash chromatography [SiO_2; 20-50% EtOAc in hexane] to give 3,3,3-triphenylpropanamide **S45** as a white solid (759 mg, 76%). The amide **S45** (255 mg, 0.85 mmol) was

dissolved in dry THF (10 mL) at N_2 atmosphere in ice-bath cooling, $LiAlH_4$ solution (1.0 M in THF, 1.5 mL) was added to the solution. The reaction mixture was refluxed for 2 h. The flask was immersed in an ice bath, and water (2 mL), 10% aqueous KOH (6 mL), and again water (2 mL) were added cautiously with very vigorous stirring. Then filtered, the solution was concentrated *in vacuo*. The residue was purified by flash chromatography [SiO_2; 2-20% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to afford the amine **S46** as a colorless solid (177 mg, 73%). ^{1}H NMR (400MHz, CD_3OD): δ = 2.60-2.65 (m, 2H, CH_2), 2.92-2.96 (m, 2H, CH_2), 7.22-7.31 (m, 15H, Ph). ^{13}C NMR (100MHz, CD_3OD): δ = 37.2, 37.4, 55.1, 126.3, 128.0, 128.6, 145.9. HRMS (ESI+) calcd. for $C_{21}H_{21}N$ $(M+H)^+$: 288.17468; found: 288.17465. Analysis calcd. for $C_{21}H_{21}N \cdot H_2O$: C, 82.58; H, 7.59; N, 4.59. Found: C, 83.24; H, 7.07; N, 4.12.

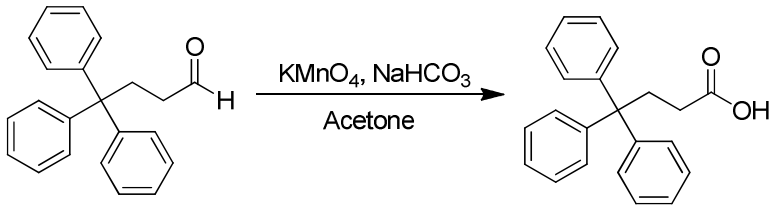
5,5,5-Triphenylpentan-1-amine (S48).



Scheme S30

Potassium cyanide (101 mg, 1.56 mmol) was added to a solution of 4,4,4-triphenylbutyl methanesulfonate **S2** (150 mg, 0.39 mmol) in anhydrous DMF (2 mL) and the mixture irradiated with microwave radiation at 175°C for 10 min. The mixture was cooled, the solid residue filtered off and the filtrate was concentrated *in vacuo.* The crude product was purified by flash chromatography [SiO_2; 0-12% EtOAc in hexane] to give nitrile **S47** as a white solid (116 mg, 94%). 5,5,5-Triphenylpentanenitrile **S47** (116 mg, 0.37 mmol) was slowly added to a 1.0M solution of lithium aluminium hydride in THF (3.7 mL) and the mixture stirred at room temperature for 12 h. The reaction was cooled to 0^{o}C and cautiously quenched with saturated Na_2SO_4 solution (8 mL), concentrated *in vacuo* and the crude product purified by flash chromatography [SiO_2; 0-10% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to afford the amine **S48** as a colorless solid (85 mg, 73%). ^{1}H NMR(400 MHz, DMSO-d_6) δ = 0.95 (m, 2H, CH_2), 1.38-1.44 (m, 2H, CH_2), 2.43-2.56 (m, 4H, CH_2 and CH_2), 3.17-3.40 (br s, 2H, NH_2), 7.21-7.28 (m, 15H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 23.4, 29.8, 33.7, 41.8, 56.8, 126.3, 128.4, 129.4, 147.8. HRMS (ESI+) calcd. for $C_{23}H_{25}N$ $(M+H)^+$: 316.20598; found: 316.20667. Analysis calcd. for $C_{23}H_{25}N \cdot 0.5H_2O$: C, 85.14; H, 8.08; N, 4.32. Found: C, 84.65; H, 7.73; N, 4.59.

4,4,4-Triphenylbutanoic acid (S49).

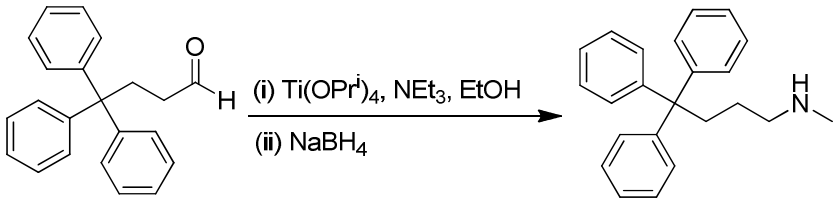


57 **S49**

Scheme S31

The title compound was prepared using an adaptation of the method reported by Ōki *et al.*[27] To a cooled (0°C, ice-water) solution of 4,4,4-triphenylbutanal **57** (113 mg, 0.38 mmol) in acetone (8 mL) was added $KMnO_4$ (65.5 mg, 0.41 mmol) and $NaHCO_3$ (65.5 mg, 0.78 mmol) and the mixture stirred at room temperature for 1 h. The reaction was treated with saturated $NaHSO_3$ solution (5 mL, stir for 1h) to destroy the excess oxidant. The mixture was extracted with CH_2Cl_2 (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 10-35% EtOAc in hexane] to give **S49** as a white solid (85 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.85-1.89 (t, 2H, CH_2), 2.81-2.85 (t, 2H, CH_2), 7.21-7.30 (m, 15H, Ph), 12.12 (br s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 30.7, 34.5, 55.6, 126.0, 127.9, 128.7, 146.5, 174.1. HRMS (ESI-) calcd. for $C_{22}H_{20}O_2$ (M-H)$^-$: 315.13905; found: 315.13919. Analysis calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.06; H, 6.35.

***N*-Methyl-4,4,4-triphenylbutan-1-amine (S50).**



57 **S50**

The title compound was prepared using an adaptation of the method by Neidigh *et al.*[28] A mixture of 4,4,4-triphenylbutanal **57** (100 mg, 0.33 mmol), titanium (IV) isopropoxide (0.20 mL, 0.66 mmol), methylamine hydrochloride (45 mg, 0.66 mmol) and triethylamine (0.10 mL, 0.66 mmol) in EtOH (10 mL) was stirred at room temperature for 8 h. Sodium borohydride (20 mg, 0.5 mmol) was added and the resulting mixture stirred for an additional 7 h. The reaction was quenched with NH_4OH (20 mL), filtered

and the precipitate washed with CH_2Cl_2. The combined organic washings were concentrated *in vacuo* and the crude product purified by flash chromatography [SiO_2; 0-10% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give the secondary amine **S50** as a colorless solid (89 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.07 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.45 (t, 2H, CH_2), 2.56 (t, 2H, CH_2), 7.15-7.29 (m, 15H, Ph). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 25.8, 36.4, 37.7, 52.1, 56.6, 126.2, 128.3, 129.3, 147.7. HRMS (ESI+) calcd. for $C_{23}H_{25}N$ $(M+H)^+$: 316.20598; found: 316.20615. Analysis calcd. for $C_{23}H_{25}N \cdot H_2O$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.02; H, 7.89; N, 4.03.

3. Supplementary Results

Table S1: 0-24 h acid stability tests for *S*-trityl, *N*-trityl, *O*-trityl and *C*-trityl analogues.

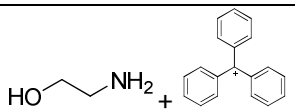
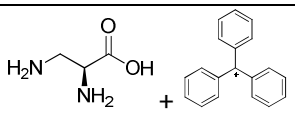
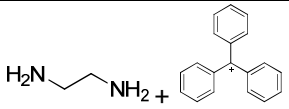
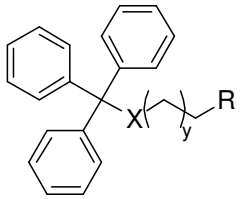
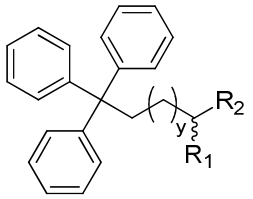
Compound	$t_{1/2}$ [h]	Decomposition fragments
1	stable	**-**
6	2.5	
7	2.9	
8	7.0	
9	stable	**-**
10	stable	**-**

Table S2: Variation of amino-alkyl chain length with *N*-trityl and *C*-trityl series



Cmpd	X	y	R	Ligand Efficiency	Inhibition basal ATPase activity K_i^{app} [nM]
8	**NH**	**1**	NH_2	0.33	2659 ± 296
S42	**NH**	**2**	NH_2	0.29	>7600
S43	**NH**	**3**	NH_2	-	n.i.
S44	**NH**	**4**	NH_2	-	n.i.
S47	**CH_2**	**0**	NH_2	0.33	4892 ± 1134
10	**CH_2**	**1**	NH_2	0.40	214.7 ± 30.1
S48	**CH_2**	**2**	NH_2	0.33	1674 ± 443

Table S3: Modification to the butan-1-amine tail



Cmpd	y	R_1	R_2	Basal ATPase activity IC_{50} [nM]
55 (FW25)	**0**	$CH=CH_2$		n.i.
56 (FW26)	**1**	H	OH	n.i.
57 (FW28)	**1**	H	CHO	n.i.
S49 (FW30)	**1**	H	COOH	>28000
rac-58 (FW29)	**1**	CN	NHBn	n.i.
***rac*-59** (FW 37)	**1**	CO_2H	NHBn	>49210
60 (FW27)	**1**	H	N_3	n.i.
S50 (FW39)	**1**	H	NHMe	386.0 ± 39.2

Table S4: Optical rotations of enantiomers.

Compound	**1 (STLC)**	**9-1**	**9-2**	**32-1**	**32-2**	**29-1**	**29-2**
$[\alpha]_D^{20}$ (in MeOH)	+64.94 (c 0.22)	+1.40 (c 0.21)	-4.85 (c 0.22)	+1.02 (c 0.20)	-4.25 (c 0.28)	+2.10 (c 0.22)	-5.96 (c 0.23)

Table S5: Values used for plotting Craig plot.

Aromatic Substituent	**π**	**σ**
3-F	0.13	0.337
3-Cl	0.76	0.373
3-Br	0.94	0.391
3-Me	0.51	-0.069
3-Et	0.97	-0.043
3-*i*-Pr	1.30	-0.151
3-*n*-Pr	1.43	-0.126
3-CF_3	1.07	0.415
3-OMe	-0.28	0.115
3-SMe	0.62	0.144
3-OCF_3	1.21	0.39*
3-$COCH_3$	-0.28	0.306
3-OH	-0.49	-0.02
4-Cl	0.7	0.227
4-Me	0.52	-0.17
4-OMe	-0.04	-0.268
4-$COCH_3$	-0.37	0.516
3,4-$(CH)_4$	1.24	0.17

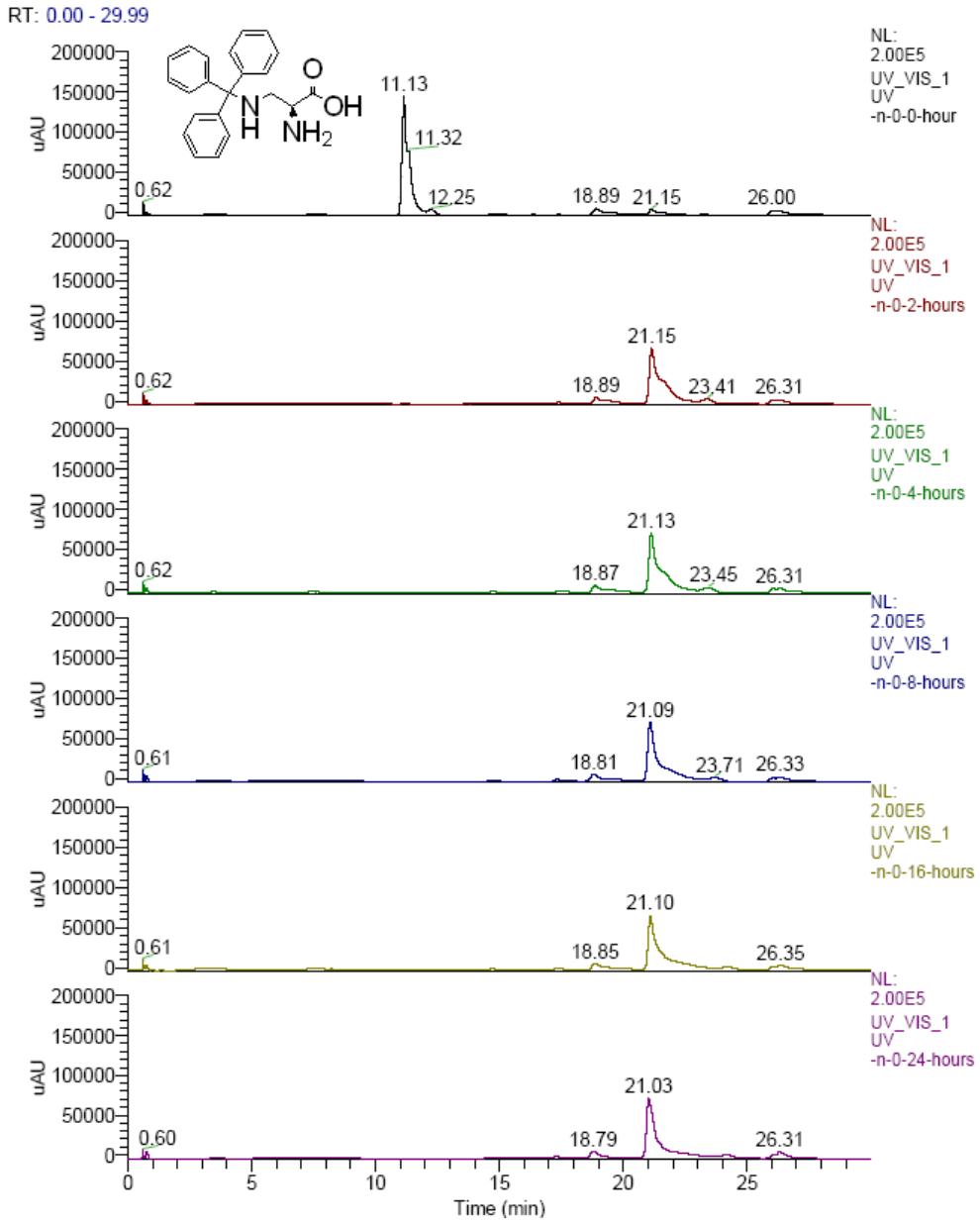
π values from *meta*-phenoxyacetic acid series as measured by Fujita *et al*. unless otherwise stated.[29]

σ values from Jaffe unless otherwise stated.[30]

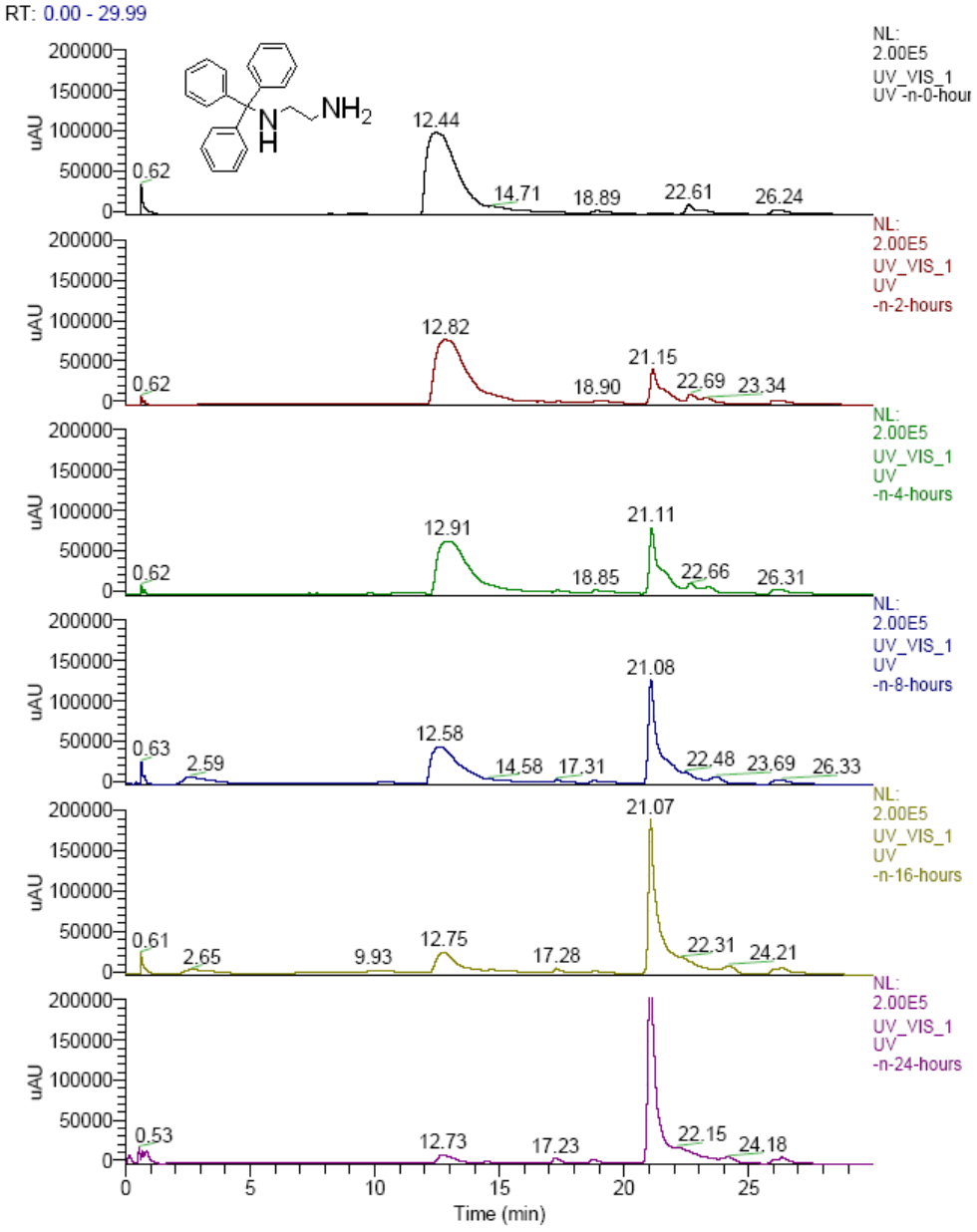
* From Craig.[31]

Figure S1: 24-hour acid stability test for nitrogen, oxygen and sulphur analogues.

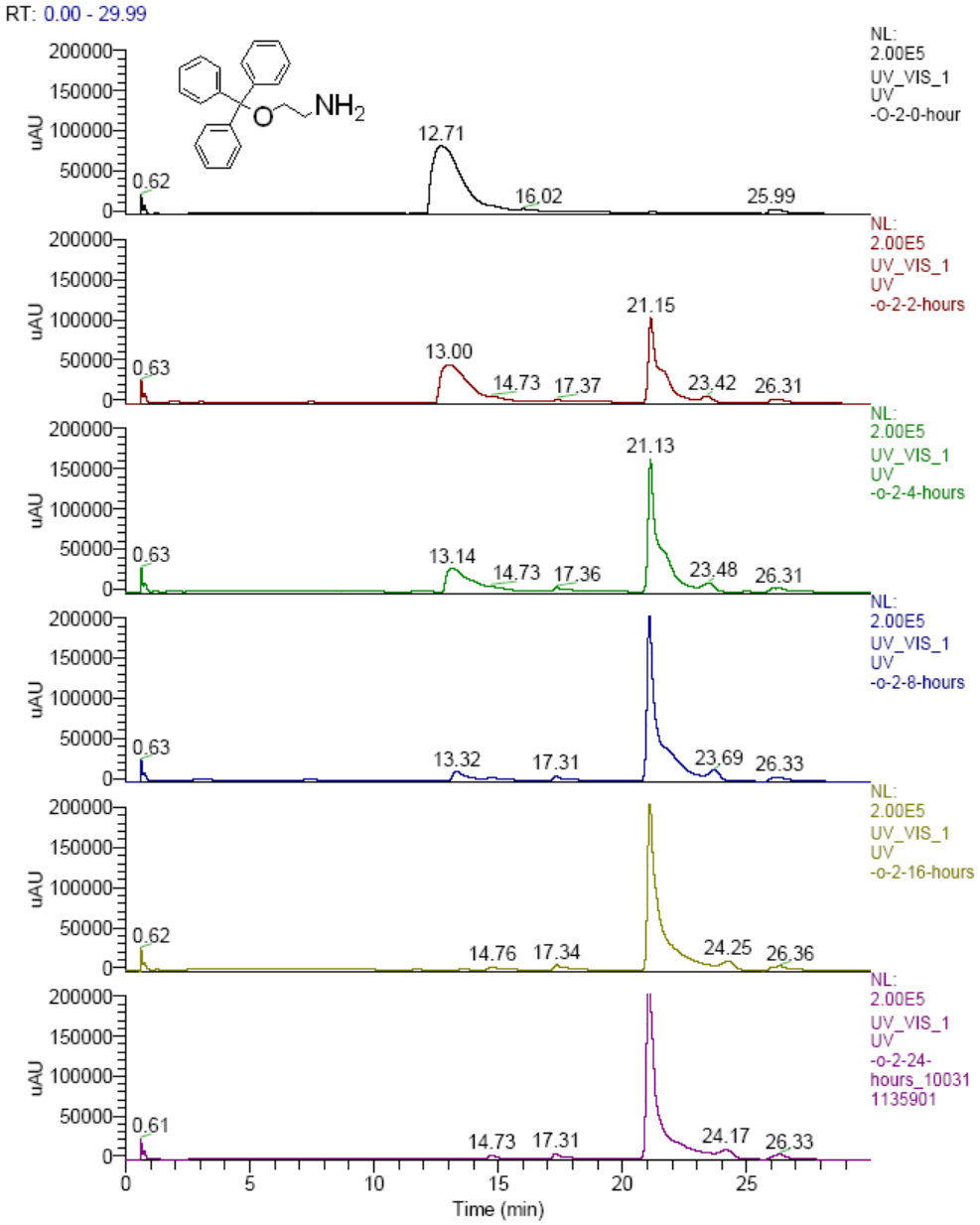
A)



B)


RT: 0.00 - 29.99
NL:
2.00E5
UV_VIS_1
UV -n-0-hour
0.62
12.44
14.71
18.89
22.61
26.24
NL:
2.00E5
UV_VIS_1
UV
-n-2-hours
0.62
12.82
18.90
21.15
22.69
23.34
NL:
2.00E5
UV_VIS_1
UV
-n-4-hours
0.62
12.91
18.85
21.11
22.66
26.31
NL:
2.00E5
UV_VIS_1
UV
-n-8-hours
0.63
2.59
12.58
14.58
17.31
21.08
22.48
23.69
26.33
NL:
2.00E5
UV_VIS_1
UV
-n-16-hours
0.61
2.65
9.93
12.75
17.28
21.07
22.31
24.21
NL:
2.00E5
UV_VIS_1
UV
-n-24-hours
0.53
12.73
17.23
22.15
24.18
uAU
Time (min)

C)


RT: 0.00 - 29.99
NL:
2.00E5
UV_VIS_1
UV
-O-2-0-hour
0.62
12.71
16.02
25.99
NL:
2.00E5
UV_VIS_1
UV
-o-2-2-hours
0.63
13.00
14.73
17.37
21.15
23.42
26.31
NL:
2.00E5
UV_VIS_1
UV
-o-2-4-hours
0.63
13.14
14.73
17.36
21.13
23.48
26.31
NL:
2.00E5
UV_VIS_1
UV
-o-2-8-hours
0.63
13.32
17.31
23.69
26.33
NL:
2.00E5
UV_VIS_1
UV
-o-2-16-hours
0.62
14.76
17.34
24.25
26.36
NL:
2.00E5
UV_VIS_1
UV
-o-2-24-hours_10031
1135901
0.61
14.73
17.31
24.17
26.33
uAU
200000
150000
100000
50000
0
0
5
10
15
20
25
Time (min)

D)

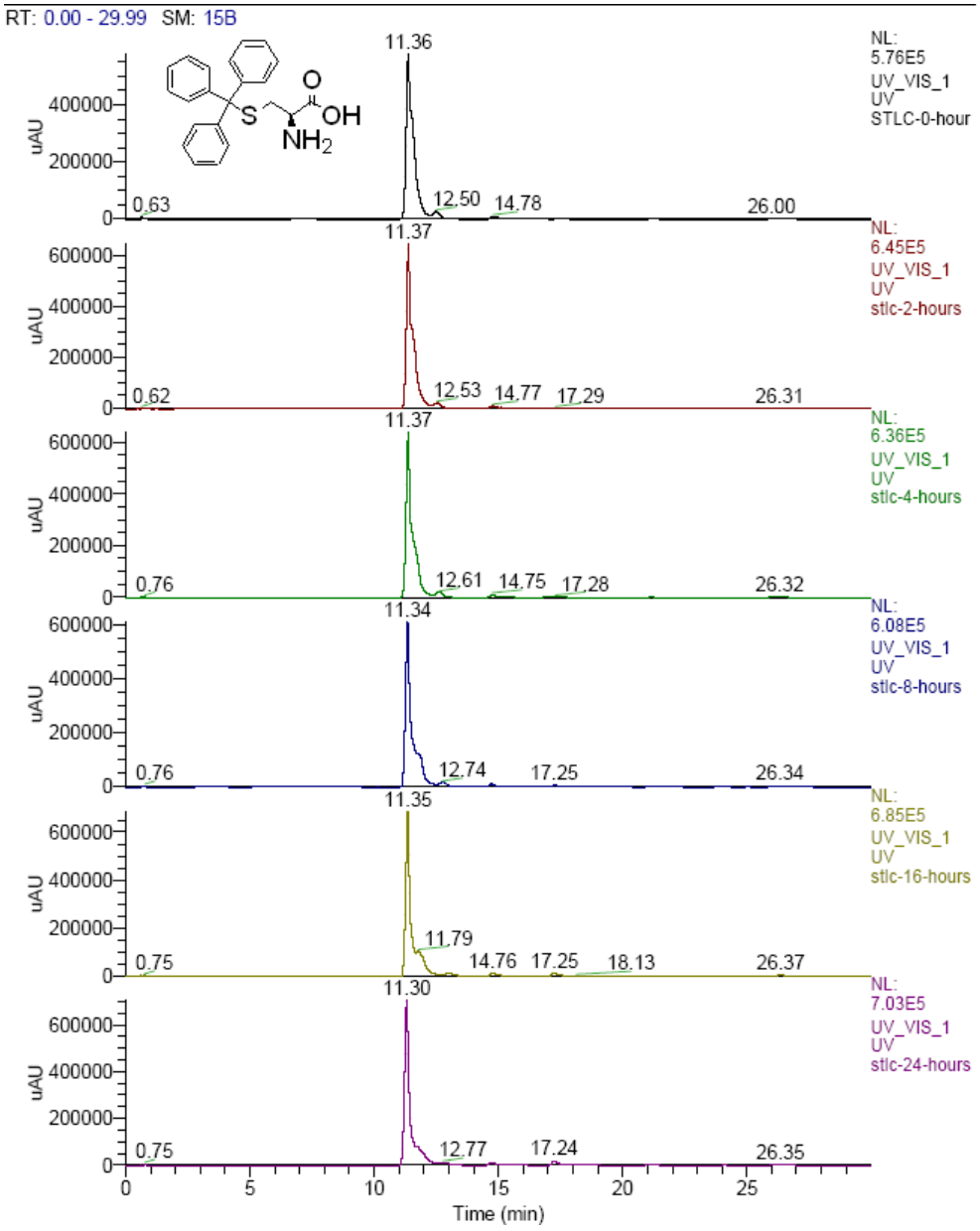
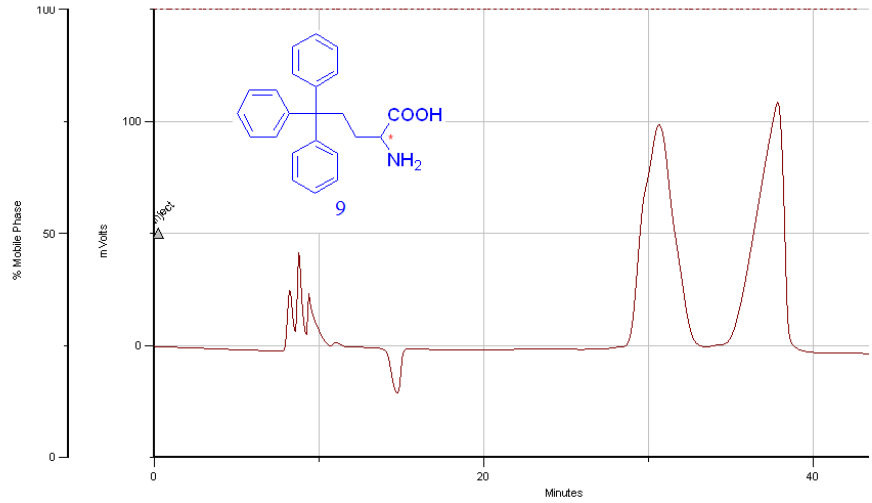
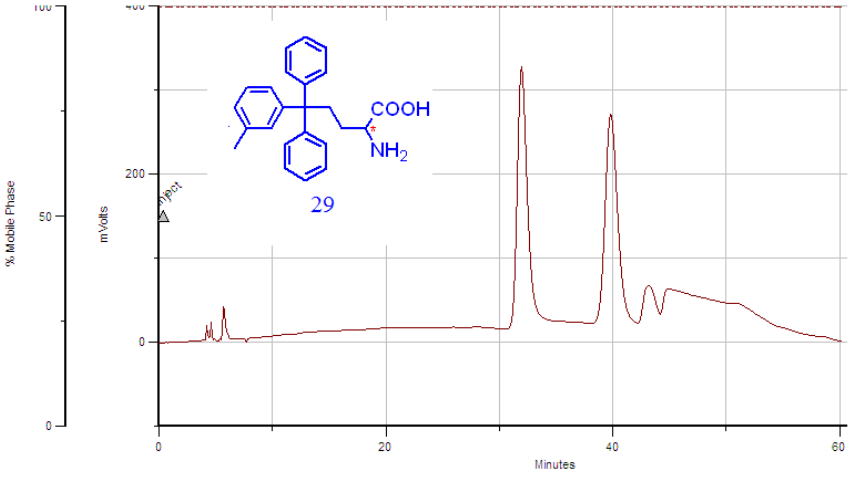

RT: 0.00 - 29.99 SM: 15B
11.36
NL:
5.76E5
UV_VIS_1
UV
STLC-0-hour
0.63
12.50
14.78
26.00
11.37
NL:
6.45E5
UV_VIS_1
UV
stlc-2-hours
0.62
12.53
14.77
17.29
26.31
11.37
NL:
6.36E5
UV_VIS_1
UV
stlc-4-hours
0.76
12.61
14.75
17.28
26.32
11.34
NL:
6.08E5
UV_VIS_1
UV
stlc-8-hours
0.76
12.74
17.25
26.34
11.35
NL:
6.85E5
UV_VIS_1
UV
stlc-16-hours
0.75
11.79
14.76
17.25
18.13
26.37
11.30
NL:
7.03E5
UV_VIS_1
UV
stlc-24-hours
0.75
12.77
17.24
26.35
uAU
Time (min)

Figure S2: Enantiomer separation using semipreparative chiral chromatography.

A)



B)



C)

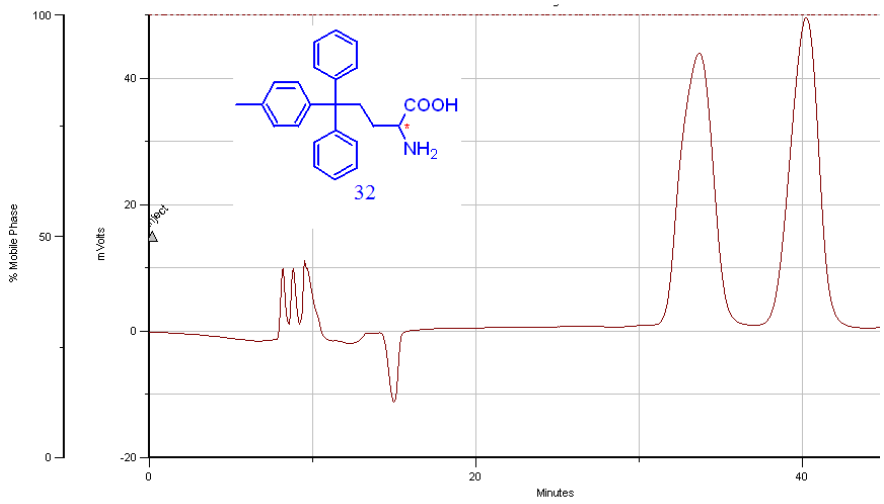
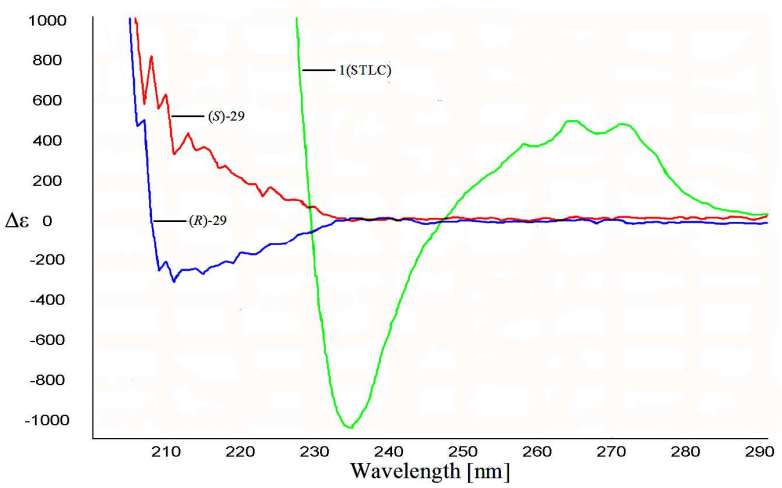

100
50
0
% Mobile Phase
40
20
0
-20
mVolts
Inject
COOH
NH2
32
0
20
40
Minutes

Figure S3: Circular dichroism spectra of **1** (STLC), **29-1** and **29-2**.



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