Supporting Information

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

Fang Wang¹, James A. D. Good¹, Oliver Rath¹, Hung Yi Kristal Kaan¹, Oliver B. Sutcliffe², Simon P. MacKay², Frank Kozielski¹

¹The Beatson Institute for Cancer Research Garscube Estate, Switchback Road, Glasgow G61 1BD, Scotland, UK.

²Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, Scotland, UK

Correspondence: f.kozielski@beatson.gla.ac.uk

Abbreviations – CD, circular dichroism; DMF, dimethylformamide; DMEM, Dulbecco’s modified eagle medium; DMSO, dimethyl sulfoxide; EC₅₀, half maximal effective concentration; EtOAc, ethyl acetate; FDVA, Nα-(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; IC₅₀, median inhibitory concentration; Kᵢᵦᵦ, apparent Kᵢ 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.
1. Materials and Methods S5
   A) Biology S5
       ADME profiling S5
   
   B) Chemistry S7
       Optical rotation S7
       Circular dichroism S7
       Evaluation of acid stability at pH = 1 by LC-HRMS S7

2. Experimental Procedures S8
   A) General Procedures S8
   (i): Synthesis of N-trityl analogues S8
       \( N\text{-Tritylethane-1,2-diamine (8) } \) S8
   (ii): Synthesis of amino acid C-trityl analogues S9
   (iii): Synthesis of 4,4,4-triphenylbutan-1-amine analogues S10
   (iv): Synthesis of trityl alcohols by \( \text{PhMgBr} \) reduction of substituted benzophenones S10
   (v): Synthesis of trityl alcohols by reduction of benzophenone with lithiated aryl bromides S11
   (vi): Thioetherification of trityl alcohols S11
       \( 3-(((2\text{-Aminoethyl})\text{sulfanyl})(\text{diphenyl})\text{methyl})\text{benzonitrile (43) } \) S11
B) Synthesis and characterization for all other compounds and intermediate

2-(Tritylsulfanyl)ethanamine (2) S13
2-(Trityloxy)ethanamine (6) S13
(2S)-2-Amino-3-(tritylamino)propanoic acid (7) S14
(2R)-2-Amino-3-(((2-chloroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (11) S15
2-(((3-Fluorophenyl)(diphenyl)methyl)sulfanyl)ethanamine (12) S16
(2R)-2-Amino-3-(((3-chloroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (13) S16
2-(((3-Chlorophenyl)(diphenyl)methyl) sulfanyl)ethanamine (14) S17
2-(((3-Bromophenyl)(diphenyl)methyl)sulfanyl)ethanamine (15) S18
2-(((3-Methylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (16) S19
2-(((3-Ethylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (17) S21
2-(((3-Isopropylphenyl)diphenylmethyl)sulfanyl)ethanamine (18) S21
2-(((3-Propylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (19) S23
2-(((Diphenyl(3-(trifluoromethyl)phenyl)methyl) sulfanyl)ethanamine (20) S24
2-(((3-Methoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (21) S26
2-(((3-(Methylsulfanyl)phenyl)diphenylmethyl) sulfanyl)ethanamine (22) S27
2-(((Diphenyl(3-(trifluoromethoxy)phenyl)methyl) sulfanyl)ethanamine (23) S28
(R)-3-(((3-acetylphenyl)diphenylmethyl)sulfanyl)2-aminopropanoic acid (24) S30
1-((3-(((2-Aminoethyl)thio)diphenylmethyl)phenyl)ethanone hydrochloride (25) S30
(R)-3-(((4-acetylphenyl)diphenylmethyl)sulfanyl)2-aminopropanoic acid (26) S32
1-((4-(((2-Aminoethyl)thio)diphenylmethyl)phenyl)ethanone hydrochloride (27) S33
4-(3-Chlorophenyl)-4,4-diphenylbutan-1-amine (28) S33
2-Amino-5-(3-methylphenyl)-5,5-diphenylpentanoic acid (rac-29) S34
4-(3-Methylphenyl)-4,4-diphenylbutan-1-amine (30) S34
4-(4-Chlorophenyl)-4,4-diphenylbutan-1-amine (31) S35
2-Amino-5,5-diphenyl-5-(4-methylphenyl)pentanoic acid (rac-32) S35
4-(4-Methylphenyl)-4,4-diphenylbutan-1-amine (33) S36
(2R)-2-Amino-3-(((2-hydroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (34) S37
(2R)-2-Amino-3-(((3-hydroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (35) S38
3-(((2-Aminoethyl)sulfonyl)(diphenyl)methyl)phenol (36) S39
2-(((3-Aminomethyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (38) S41
N-(3-(((2-aminoethyl)sulfonyl)(diphenyl)methyl)benzyl)acetamide (39) S41
3-(((2-Aminoethyl)sulfonyl)(diphenyl)methyl)benzoic acid hydrochloride (40) S43
(R)-2-amino-3-(((3-carbamoylphenyl)diphenylmethyl)sulfanyl)propanoic acid (41)  S44
3-(((2-Aminoethyl)sulfanyl)(diphenylmethyl)benzamide hydrochloride (42)  S44
3-(((2-Aminoethyl)sulfanyl)(diphenylmethyl)-N-methylbenzamide hydrochloride (43)  S45
3-(((2-Aminoethyl)sulfanyl)(diphenylmethyl)benzamide (44)  S46
2-(((4-(Methylsulfonyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (45)  S47
4-(((2-Aminoethyl)sulfanyl)(diphenylmethyl)benzonitrile (46)  S49
(4-((2-aminoethyl)sulfanyl)(diphenyl)methyl)phenyl)methanol (47)  S50
2-(((4-(Aminomethyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (48)  S51
N-(4-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzyl)acetamide (49)  S52
4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzamide (50)  S53
4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)-N-methylbenzamide (51)  S54
4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)-N,N-dimethylbenzamide (52)  S55
2-(((4-(Methylsulfonyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (53)  S57

C) Synthesis and characterization of supplementary compounds  S58

3. Supplementary Results  S63

Tables  S63
Table S1: 0-24 h acid stability tests for S-trityl, N-trityl, O-trityl and C-trityl analogues  S63
Table S2: Variation of amino-alkyl chain length with N-trityl and C-trityl series  S64
Table S3: Modification to the butan-1-amine tail  S65
Table S4: Optical rotations of enantiomers  S66
Table S5: Values used for plotting Craig plot  S67

Figures  S68
Figure S1: 24-hour acid stability test for oxygen and sulphur analogues  S68
Figure S2: Enantiomeric separation using semipreparative chiral chromatography  S72
Figure S3: Circular dichroism spectra of 1 (STLC), 29-1 and 29-2.  S74

4. Supplementary References  S75
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$_{\text{max}}$, t$_{\text{max}}$, AUC$_{\text{last}}$) and intravenous (C$_{0}$, AUC$_{\text{last}}$, 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$_3$OH (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.

\[
\text{FMOC-} \begin{array}{c} \text{N} \\ \text{NH}_2 \text{HCl} \end{array} \xrightarrow{\text{TrCl, NEt}_3, \text{DMF}} \text{S1} \xrightarrow{\text{Piperidine, MeOH}} \begin{array}{c} \text{N} \\ \text{NMOC} \end{array} \begin{array}{c} \text{N} \\ \text{NH}_2 \end{array}
\]

\text{Scheme S1}

\text{N-Tritylethane-1,2-diamine (8).}

The title compound was prepared using an adaptation of the method reported by Will \textit{et al.} To a suspension of (9H-fluoren-9-yl)methyl-2-aminoethylycarbamate hydrochloride (319 mg, 1.0 mmol) in anhydrous DMF (5 mL) was added triethylamine (0.42 mL, 3.0 mmol). The mixture was cooled (\textit{circa.} 4°C) and treated with a solution of trityl chloride (418 mg, 1.5 mmol) in CH\textsubscript{2}Cl\textsubscript{2}. The mixture was stirred at room temperature for 3 h, filtered and diluted with EtOH (2 mL) and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 6-40% EtOAc in hexane with 0.5% NH\textsubscript{4}OH] to give S1 as a white solid (459 mg, 88%). (9H-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 \textit{in vacuo}. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 0-20% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 0.5% NH\textsubscript{4}OH] to give 8 as a colorless solid (71 mg, 90%). Mpt. 94°C. \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD) \(\delta = 2.20-2.23\) (t, 2H, CH\textsubscript{2}), 2.71-2.74 (t, 2H, CH\textsubscript{2}), 7.16-7.47 (m, 15H, Ph). \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{3}OD) \(\delta = 41.7, 45.8, 70.7, 125.9, 127.4, 128.6, 146.2\). HRMS (ESI+) calcd. for C\textsubscript{21}H\textsubscript{22}N\textsubscript{2} (M+H): 303.18558; found: 303.18539. Analysis calcd. for C\textsubscript{21}H\textsubscript{22}N\textsubscript{2}·0.5H\textsubscript{2}O: 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.

| 56 | MsCl  | Pyridine |
|----|-------|----------|
|    |       |          |

\[
| OH | MsCl  | Pyridine |
|----|-------|----------|
|    |       |          |
| S2 |       |          |

\[
| NaN₃ | DMF |
|------|-----|
| 60   |     |
|      |     |

\[
| NaN₃ | DMF |
|------|-----|
| 60   |     |
|      |     |
| S2   |     |

\[
| PPh₃ | THF/H₂O |
|------|----------|
| 10   |          |

| PPh₃ | THF/H₂O |
|------|----------|
| 10   |          |

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).

\[
| F   | PhMgBr |
|-----|--------|
| 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 NH₄Cl solution (15 mL) and extracted with EtOAc (3 x 25 mL). The organic extracts were washed with brine (75 mL), dried (MgSO₄) and concentrated \textit{in vacuo}. Purification of the crude residue by flash chromatography [SiO₂: 0-18% EtOAc in hexane] afforded the trityl alcohol.
**General procedure (v): Synthesis of trityl alcohols by reduction of benzophenone with lithiated aryl bromides.**

![Scheme S5](image_url)

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\(_4\)Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). Following washing the combined organic layers with H\(_2\)O (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\(_3\)) \(\delta = 1.22\) (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). \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 24.11, 34.29, 82.28, 125.29, 125.76, 126.36, 127.30, 127.90, 128.00, 128.08, 146.90, 147.17, 148.73\). 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...
Malte et al.5 A representative procedure is provided for synthesis 3-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile 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 CH₂Cl₂ (3 x 10 mL) and the organic layer dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography on silica gel afforded the thioether 37 as a colorless oil (324 mg, 94%). ¹H NMR (400 MHz, MeOD) δ = 2.33 (t, J = 6.9 Hz, 2H, CH₂), 2.46 (t, J = 6.9 Hz, 2H, CH₂), 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). ¹³C 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 C₂₂H₂₁N₂S (M+H)⁺: 345.1420; found: 345.1417. Analysis calcd. for C₂₂H₂₀N₂S: 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).

![Structure Image](image)

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\(_2\)Cl\(_2\) with 1% NH\(_4\)OH] afforded the thioether 2 as a white solid (1.94 g, 81%). Mpt. 87-90\(^\circ\)C (lit 90-93\(^\circ\)C from petroleum ether).\(^6\) \(^1\)H NMR (500 MHz, MeOD) \(\delta = 2.32-2.36\) (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). \(^1\)C NMR (125 MHz, MeOD) \(\delta = 36.11, 41.56, 67.77, 127.79, 128.89, 130.78, 146.34\). 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).

![Scheme Image](image)

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\(_2\)Cl\(_2\) with 0.5% NH\(_4\)OH] to afford acetamide S6 as a white solid (1.39 g, 84%). Mpt. 166\(^\circ\)C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 1.82\) (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). \(^1\)C NMR (100 MHz,
DMSO-\textit{d}_6 \quad \delta = 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 \textit{et al.}^7  
\textit{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 \textit{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\^\circ C.  
\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \delta = 2.70-2.74 (t, 2H, CH_2), 2.91-2.94 (t, 2H, CH_2), 7.23-7.40 (m, 15H, Ph).  
\textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6) \delta = 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.  

\textbf{(2S)-2-Amino-3-(tritylamino)propanoic acid (7).}

The title compound was prepared using an adaptation of the method reported by Dubowchik \textit{et al.}^8  
Trimethylsilyl chloride (54.3 mg, 63.5 \mu L, 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 \textit{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-(((9H-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 2 h, and then concentrated \textit{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^\circ C.  
\textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \delta = 2.20-2.35 (m, 2H, CH), 3.28 (m, 2H, NH and CH), 7.18-7.40 (m, 15H, Ph).  
\textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}_6) \delta = 44.9, 55.0, 70.7, 126.6, 128.2,
The tertiary trityl alcohol S8 was prepared using an adaptation of the method reported by Hatano et al.\textsuperscript{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 (4.33 g, 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\textsubscript{4}Cl solution (30 mL) and extracted with EtOAc (4 x 30 mL). The organic extracts were washed with brine (2 x 100 mL), dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 0-10\% EtOAc in hexane] to give (2-chlorophenyl)(diphenyl)methanol S8 as a white solid (3.432 g, 58\%). Mpt. 83°C (lit. 89-91°C).\textsuperscript{10} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta = 4.42\) (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). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta = 82.73, 126.54, 127.52, 127.91, 128.14, 129.24, 131.50, 131.64, 133.38, 143.88, 145.69\). HRMS (ESI+) calcd. for C\textsubscript{19}H\textsubscript{14}Cl (M+H-OH\textsuperscript{+})\+: 277.07785; found: 277.07770. Analysis calcd. for C\textsubscript{19}H\textsubscript{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.\textsuperscript{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\textsubscript{3}.Et\textsubscript{2}O solution (214 \(\mu\)L, 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\textsubscript{2}O (3 mL), and the solution extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), concentrated \textit{in vacuo} and the crude residue purified by flash chromatography [SiO\textsubscript{2}; 10-20\% MeOH in (CH\textsubscript{2}Cl\textsubscript{2} with 1% NH\textsubscript{4}OH)] to give 11 as a white solid (117 mg, 29\%). Mpt. 159-161°C. \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \(\delta = 2.24-2.29\) (dd, \(J = 8.8, 12.4\) Hz, 1H, CH\textsubscript{2}), 2.24-2.29 (dd, \(J = 4.5, 12.4\) Hz, CH\textsubscript{2}), 2.37-2.41 (dd, \(J = 4.5, 8.7\) Hz, 1H, CH\textsubscript{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). \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}_6) \(\delta = 34.51, 53.18, 66.60, 126.73, 126.75, 127.30, 127.72, 127.80, 129.26, 129.40, 131.81, 131.99, 134.26, 140.00, 140.83, 141.32, 168.74\). HRMS (ESI+) calcd. for C\textsubscript{22}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2} (M+H\textsuperscript{+})\+: 347.17540; found: 347.17486. Analysis calcd. for C\textsubscript{22}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.19; H, 6.50; N, 8.04.
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).

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\textsubscript{2}; 0-18% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 1% NH\textsubscript{4}OH] afforded the amine 12 as a white solid (79 mg, 24%). Mpt. 62-63°C. \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \( \delta \) = 2.14-2.18 (m, 2H, CH\textsubscript{2}), 2.42-2.46 (m, 2H, CH\textsubscript{2}), 7.06-7.17 (m, 3H), 7.24-7.29 (m, 2H), 7.31-7.41 (m, 9H). \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}\textsubscript{6}) \( \delta \) = 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\textsubscript{21}H\textsubscript{21}NFS (M+H)^+: 338.13733; found: 338.13739. Analysis calcd. for C\textsubscript{21}H\textsubscript{20}FNS: C, 74.74; H, 5.97; N 4.15. Found: C, 74.29; H, 5.92; N, 4.15.

\((2R)-2\text{-Amino-3-(((3-chloroxyphenyl)(diphenyl)methyl)sulfanyl)propanoic acid (13).}

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 (1 M in THF, 45 mL, 45 mmol), which afforded after 22 h reflux, aqueous workup and purification by flash chromatography [SiO₂; 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). ¹H NMR (500 MHz, CDCl₃) δ = 2.80 (s, 1H, OH), 7.16-7.18 (m, 1H), 7.23-7.38 (m, 13H). ¹³C NMR (125 MHz, CDCl₃) 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 C₁₉H₁₄ClO: 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 BF₃·Et₂O (214 µl, 1.70 mmol). After stirring for 1 h a further portion of BF₃·Et₂O (214 µl, 1.70 mmol) was added and the mixture stirred for a further 1.5 h. Aqueous workup and purification by flash chromatography [SiO₂; 8-20% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded 13 as an off-white solid (74 mg, 19%). Mpt. 160-163°C. ¹H NMR (500 MHz, DMSO-d₆) δ = 2.43 (dd, J = 8.6, 12.4 Hz, 1H, CH₂), 2.56 (dd, J = 4.6, 12.4 Hz, 1H, CH₂), 3.01 (dd, J = 4.7, 8.6 Hz, 1H, CH), 7.26-7.40 (m, 14H). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₂H₂₁ClNO₂S (M+H)⁺: 398.09761; found: 398.09827. Analysis calcd. for C₂₂H₂₀ClNO₂S: 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).

![Structure of 14](image)

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 (1 M) and EtOAc was used for extraction of the aqueous mixture (3 x 10 mL). Purification by flash chromatography [SiO₂; 0-18% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the amine 14 as a colorless oil (231 mg, 65%). ¹H NMR (MeOD, 500 MHz) 2.33-2.36 (m, 2H, CH₂), 2.45-2.48 (m, 2H, CH₂), 7.23-7.36 (m, 3H), 7.28-7.36 (m, 6H), 7.39-7.41 (m, 5H). ¹³C 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\textsubscript{21}H\textsubscript{21}Cl\textsubscript{3}NS (M+H\textsuperscript{+})\textsuperscript{:} 354.10777; found: 354.10754. Analysis calcd. for C\textsubscript{21}H\textsubscript{20}Cl\textsubscript{3}NS: C, 71.29; H, 5.70; N, 3.96. Found: C, 70.39; H, 5.86; N, 3.51.

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

\begin{center}
\includegraphics[width=0.2\textwidth]{S10.png}
\end{center}

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\textsubscript{2}; 0-15\% EtOAc in hexane] (3-bromophenyl)(diphenyl)methanone S10 as a colorless oil (1.55 g, 46\%). \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta = 6.61-6.66 \text{ (m, 1H)}, 7.10-7.16 \text{ (m, 1H)}, 7.18-7.36 \text{ (m, 10H)}, 7.41-7.50 \text{ (m, 2H)}\). \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta = 810.25, 21.22, 126.92, 127.00, 127.67, 127.70, 129.57, 129.74, 130.22, 147.00, 150.55\). HRMS (ESI+) calcd. for C\textsubscript{19}H\textsubscript{14}\textsuperscript{79}Br (M+H-OH\textsuperscript{+}): 321.02734; found: 321.02750. Analysis calcd. for C\textsubscript{19}H\textsubscript{15}BrO: C, 67.27; H, 4.46. Found: C, 68.65; H, 4.32.

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

\begin{center}
\includegraphics[width=0.2\textwidth]{15.png}
\end{center}

The title compound was prepared using general procedure (vi) with (3-bromophenyl)(diphenyl)methanone 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 (\textit{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\textsubscript{2}; 0-18\% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 1\% NH\textsubscript{4}OH] afforded the amine 15 as a colorless oil which solidified on standing to a white solid (192 mg, 48\%). Mpt. 59-61\textdegree C.
1H 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). 13C 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).

\[
\text{S11}
\]

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). 1H 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). 13C 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$_{17}$O: 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).

\[
\text{16}
\]

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$_2$Cl$_2$ with 1% NH$_4$OH] afforded the amine 16 as a colorless oil (184 mg, 55%). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ = 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-$d_6$) $\delta$ = 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).

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$^\circ$C) solution of 1-bromo-3-ethyl benzene (1.11 g, 6 mmol) in anhydrous THF:toluene (1:4, 11.4 mL). The reaction mixture stirred for 1 h at -78$^\circ$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$_4$Cl 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$_3$) $\delta$ = 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$_3$) $\delta$ = 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).

![Chemical Structure 17](image)

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 [SiO2; 0-18% MeOH in CH2Cl2 with 1% NH4OH] afforded the amine 17 a colorless oil (157 mg, 44%). 1H NMR (500 MHz, DMSO-d6) δ = 1.11 (t, J = 7.5 Hz, 3H, CH3), 2.16 (t, J = 7.3 Hz, 2H, CH2), 2.42 (t, J = 7.1 Hz, 2H, CH2), 2.54 (q, J = 7.5 Hz, 2H, CH2), 7.07-7.10 (m, 2H), 7.21-7.25 (m, 4H), 7.30-7.34 (m, 8H). 13C NMR (125 MHz, DMSO-d6) 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 C23H26NS (M+H)+: 348.17805; found: 348.17786. Analysis calcd. for C23H25NS: 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).

![Chemical Structure 18](image)

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 [SiO2; 0-18% MeOH in CH2Cl2 with 1% NH4OH] afforded the amine 18 as a colorless oil (249 mg, 69%). 1H NMR (500 MHz, DMSO-d6) 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-\(d_6\)) \( \delta = 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. \( ^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta = 13.85, 24.47, 37.81, 122.46, 127.28, 128.88, 129.92, 131.66, 145.17. \) GC-MS (EI, 70eV) \( \text{tr} = 4.72 \) min (\( m/z = 197.9, M^+ \)).

**1-Bromo-3-propylbenzene (S13).**

![Scheme S11](image)

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 with aqueous HCl (1M, 70 mL) and extracted with CH\(_2\)Cl\(_2\) (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) \( \delta = 0.94 \) (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) \( \delta = 13.85, 24.47, 37.81, 122.46, 127.28, 128.88, 129.92, 131.66, 145.17. \) GC-MS (EI, 70eV) \( \text{tr} = 4.72 \) 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-H-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).

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$_2$Cl$_2$ with 1% NH$_4$OH] 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).

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). ^1^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_{3}O: 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). ^1^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}F_{3}S (M+H)^+: 388.13413; found: 388.13388. Analysis calcd. for C_{22}H_{20}F_{3}NS: C, 68.20; H, 5.20; N, 3.61. Found: C, 67.97; H, 5.41; N, 2.87.
The intermediate methyl ester S16 was prepared using a modification of the procedure reported by Ulrik et al.\textsuperscript{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\textsubscript{2}; 0-16% EtOAc in hexane] S16 as a colorless oil (2.60 g, 63%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ = 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). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) $\delta$ = 52.29, 55.56, 114.11, 119.65, 122.13, 129.52, 131.60, 159.71, 167.13. HRMS (ESI+) calcd. for C\textsubscript{19}H\textsubscript{11}O\textsubscript{3} (M+H)$^+$: 167.07027; found: 167.07028. Analysis calcd. for C\textsubscript{9}H\textsubscript{10}O\textsubscript{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\textsubscript{2}O, 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\textdegree C, and stirred for 1 h, whilst maintaining the temperature below -70\textdegree C. The reaction mixture warmed to room temperature and stirred for 20h, then quenched with saturated aqueous NH\textsubscript{4}Cl 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\textsubscript{4}) and concentrated \textit{in vacuo}. Purification of the crude material by flash chromatography [SiO\textsubscript{2}; 0-20% EtOAc in hexane] afforded the tertiary alcohol S17 as a pale yellow solid (3.52 g, 84%). Mpt. 80-81\textdegree C (lit. 88-89 \textdegree C from Et\textsubscript{2}O).\textsuperscript{15} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) $\delta$ = 2.81 (s, 1H, OH), 3.75 (s, 3H, CH\textsubscript{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). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) $\delta$ = 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\textsubscript{19}H\textsubscript{17}O (M+H-OH)$^+$: 273.12739; found: 273.12738. Analysis calcd. for C\textsubscript{20}H\textsubscript{18}O\textsubscript{2}: C, 82.73; H, 6.25. Found: C, 82.75; H, 6.23.
2-(((3-Methoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (21).

![Image of 21](image)

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$_2$Cl$_2$ with 1% NH$_4$OH] 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).

![Image of S18](image)

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$_3$) $\delta$ = 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$_2$S: C, 78.39; H, 5.92. Found: C, 77.42; H, 5.87.

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

![Chemical structure of 22](image)

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$_2$Cl$_2$ with 1% NH$_4$OH] afforded the thioether 22 as a clear pale yellow oil (280 mg, 77%). $^1$H NMR (500 MHz, MeOD) $\delta$ = 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) $\delta$ = 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).

![Chemical structure of S19](image)
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$_3$) $\delta$ = 2.85 (s, 1H, OH), 7.13-7.15 (m, 1H), 7.21-7.35 (m, 13H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 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-$d_6$) $\delta$ = -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$_3$O$_2$: C, 69.76; H, 4.39. Found: C, 68.90; H, 4.53.

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

\[ \text{23} \]

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$_2$Cl$_2$ with 1% NH$_4$OH] afforded the thioether 23 as a pale clear yellow oil (313 mg, 78%). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ = 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-$d_6$) $\delta$ = 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-$d_6$) $\delta$ = -56.87. HRMS (ESI+) calcd. for C$_{22}$H$_{21}$F$_3$NS (M+H)$^+$: 404.12905; found: 404.12881. Analysis calcd. for C$_{22}$H$_{20}$F$_3$NOS: 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°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 ≤-70°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 ≤ -77°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 NH₄Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed successively with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; 0-30% EtOAc in hexane with 1% NH₄OH] afforded the tertiary alcohol S21 as a white solid (1.82 g, 70%). Mpt. 104-105°C. ¹H NMR (400 MHz, CDCl₃) δ = 1.62 (s, 3H, CH₃), 2.82 (s, 1H, OH), 3.69-3.73 (m, 2H, CH₂), 3.97-4.01 (m, 2H, CH₂), 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). ¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₂₃O₃S (M+H)⁺: 347.1642; found: 363.1639. Analysis calcd. for C₂₃H₂₂O₃: C, 79.74; H, 6.40. Found: C, 79.55; H, 6.15.
(R)-3-(((3-acetylphenyl)diphenylmethyl)sulfanyl)2-aminopropanoic acid (24).

A solution of (3-(2-methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol \textbf{S21} (346 mg, 1.0 mmol) and \textit{L}-cysteine (133 mg, 1.1 mmol) in (1 mL) was stirred at room temperature for 4.5 h. The volatiles were removed \textit{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$_2$O (10 mL). The combined aqueous layers were extracted with CH$_2$Cl$_2$ (3 x 10 mL), the gum dissolved in CH$_2$Cl$_2$ (5 mL), and the combined organic extracts concentrated \textit{in vacuo}. Purification by flash chromatography [SiO$_2$; 0-20% MeOH in CH$_2$Cl$_2$] afforded the thioether \textbf{24} as a white solid (290 mg, 72%). 

M.pt. 109.5-112°C. $^1$H NMR (400 MHz, MeOD) $\delta$ = 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) $\delta$ = 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$_3$S (M+H)$^+$: 406.1471; found: 406.1466. Analysis calcd. for C$_{24}$H$_{24}$NO$_3$S·½H$_2$O: 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).

A solution of the tertiary alcohol (3-(2-methyl-1,3-dioxolan-2-yl)phenyl)(diphenyl)methanol \textbf{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$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$ with 1% NH$_4$OH] 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$_2$O, 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$_6$) $\delta$ = 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$_6$) $\delta$ = 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·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)

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 [SiO$_2$; 0-12% EtOAc in hexane with 1% NH$_4$OH] yielded acetal S22 as a white solid (1.88 g, 65% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 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$_3$) $\delta$ = 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 NH₄Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed successively with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; EtOAc/Hexane with 1% NH₄OH; 0-30%] afforded the tertiary alcohol S23 as a white solid (1.01 g, 49%). Mpt. 129-130°C (lit. 128°C).¹⁶¹H NMR (400 MHz, CDCl₃) δ = 1.65 (s, 3H, CH₃), 2.76 (s, 1H, OH), 3.75-3.84 (m, 2H, CH₂), 3.99-4.07 (m, 2H, CH₂), 7.22-7.33 (m, 12H), 7.39-7.43 (m, 2H).¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₂₃O₃ (M+H): 347.1642; found: 347.1639. Analysis calcd. for C₂₃H₂₂O₃: C, 79.74; H, 6.40. Found: C, 79.63; H, 6.34.

(R)-3-(((4-acetylphenyl)diphenylmethyl)sulfanyl)2-aminopropanoic acid (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 CH₂Cl₂ (3 x 5 mL). The precipitated gum was washed with H₂O (5 mL), dissolved in CH₂Cl₂ (5 mL), and combined with the combined organic extracts concentrated in vacuo. Purification by flash chromatography [SiO₂; 0-25% MeOH in CH₂Cl₂] 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, CH₃), 2.66-2.72 (m, 1H, CH₂), 2.80 (dd, J = 3.6, 13.3 Hz, 1H, CH₂) 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).¹³C 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 C₂₄H₂₄NO₃S (M+H): 406.1471; found:
1-(4-(((2-Aminoethyl)thio)diphenylmethyl)phenyl)ethanone hydrochloride (27).

\[
\begin{align*}
&\text{O} \\
&\text{S} \\
&\text{H}_2\text{HCl} \\
&\text{NH}_2\text{Cl}
\end{align*}
\]

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 \textit{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\textsubscript{2}O, and dried \textit{in vacuo} to yield the hydrochloride salt 27 as a white solid (378 mg, 95%). Mpt. 186-188°C. \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \delta = 2.40-2.43 (m, 2H, CH\textsubscript{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\textsubscript{3}\textsuperscript{+}), 7.93-7.96 (m, 2H). \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}_6) \delta = 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\textsubscript{23}H\textsubscript{23}NOS (M+H\textsuperscript{+}): 362.1573; found: 362.1571. Analysis calcd. for C\textsubscript{23}H\textsubscript{23}NOS⋅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).
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$_3$OD) $\delta =$ 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$_3$OD) $\delta =$ 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·$\frac{1}{2}$H$_2$O: 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).

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-$d_6$) $\delta =$ 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-$d_6$) $\delta =$ 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$_2$O: 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).

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$_3$OD) $\delta =$ 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$_3$OD) $\delta =$ 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·0.5H$_2$O: 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).

![Structure of 4-(4-Chlorophenyl)-4,4-diphenylbutan-1-amine](structure.png)

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$_3$OD) $\delta$ = 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$_3$OD) $\delta$ = 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·0.5H$_2$O: 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).

![Structure of 2-Amino-5,5-diphenyl-5-(4-methylphenyl)pentanoic acid](structure2.png)

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-$d_6$) $\delta$ = 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-$d_6$) $\delta$ = 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$_2$·H$_2$O: 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).

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-$d_6$) $\delta = 0.99-1.03$ (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-$d_6$) $\delta = 21.0, 30.2, 37.5, 42.6, 56.2, 126.2, 128.3, 129.0, 129.3, 129.4, 135.2, 145.0, 148.1$. HRMS (ESI+) calcd. for C$_{23}$H$_{25}$N (M+H)$^+$: 316.20598; found: 316.20663. Analysis calcd. for C$_{23}$H$_{25}$N·0.5H$_2$O: 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).

Phenyllithium (1.8M in Et$_2$O, 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$_4$Cl 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). $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 3.68$ (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$_3$) $\delta = 84.61, 117.76, 119.22, 125.97, 127.91, 128.10, 128.35, 129.74, 130.15,
HRMS (ESI-) calcd. for C_{19}H_{15}O (M-H): 275.10775; found: 275.10791. Analysis calcd. for C_{19}H_{16}O: C, 82.58; H, 5.84. Found: C, 82.65; H, 5.94.

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

The title compound was then prepared by an adaptation of the procedure reported by DeBonis et al.\textsuperscript{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\textsubscript{3}.Et\textsubscript{2}O (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\textsubscript{2}O (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 \textit{in vacuo}. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 10-20% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 1% NH\textsubscript{4}OH] to afford the thioether 34 as a white solid (35 mg, 5%). Mpt. 156-159°C. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \(\delta = 2.20-2.25\) (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). \textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6}) \(\delta = 35.32, 53.79, 65.12, 116.40, 118.49, 125.85, 126.99, 128.52, 128.99, 129.89, 142.92, 143.17, 155.09, 171.89\). HRMS (ESI+) calcd. for C\textsubscript{22}H\textsubscript{22}NO\textsubscript{3}S (M+H): 380.13149; found: 380.13141. Analysis calcd. for C\textsubscript{22}H\textsubscript{21}NO\textsubscript{3}S: 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).

![Scheme S15](image)
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 Et₂O, 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 [SiO₂; 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 ¹H NMR (500 MHz, CDCl₃) 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). ¹³C NMR (125 MHz, CDCl₃) 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 C₁₉H₁₅O (M-H): 275.10775; found: 275.10793. Analysis calcd. for C₁₉H₁₆O₂: C, 82.58; H, 5.84. Found: C, 82.46; H, 5.89.

(2R)-2-Amino-3-(((3-hydroxyphenyl)(diphenyl)methyl) sulfanyl)propanoic acid (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 BF₃·Et₂O solution (214 µL, 1.70 mmol), with a reaction time of 2 h. Purification by flash chromatography [SiO₂; 0-20% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the thioether 35 as a white solid (161 mg, 62%). Mpt. 178-180°C. ¹H NMR (500 MHz, DMSO-d₆) δ = 1.88 (s, 1H, OH), 2.40 (dd, J = 9.0, 12.4 Hz, 1H, CH₂), 2.58 (dd, J = 4.4, 12.4 Hz, 1H, CH₂), 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). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₂H₂₂NO₃NaS (M+Na)⁺: 402.1134; found: 402.11453. Analysis calcd. for C₂₂H₂₁NO₃S·½CH₂Cl₂: 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).

![Chemical Structure](image)

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\(_2\)Cl\(_2\) with 1% NH\(_4\)OH] afforded the thioether 36 as a white solid (259 mg, 77%). Mpt. 143°C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 2.16\) (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-\(d_6\)) \(\delta = 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).

![Chemical Structure](image)

The title compound was prepared by an adaptation of the reverse addition methodology by Luliński \textit{et al.} and the procedure reported by Neumann \textit{et al.} 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 \(\leq -80°C\). 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 NH₄Cl solution (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed successively with H₂O (75 mL) and brine (75 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; 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 ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₁₅NO (M+H)+: 286.1226; found: 286.1224. Analysis calcd. for C₂₀H₁₅NO: 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).

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 H₂O (10 mL), followed by aqueous NaOH solution (15% w/v, 5 mL) and H₂O (15 mL). The suspension was filtered and the precipitate washed with CH₂Cl₂, and the filtrate then washed successively with H₂O (50 mL) and brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; 0-18% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the tertiary alcohol S26 as a white solid (643 mg, 68%). Mpt. 136-138°C. ¹H NMR (500 MHz, DMSO-d₆) δ = 3.66 (s, 2H, CH₂), 6.38 (br s, 1H, OH), 6.97-6.99 (m, 1H), 7.19-7.34 (m, 13H). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₀H₂₀NO (M+H)+: 290.1539; found: 290.1537. Analysis calcd. for C₂₀H₁₉NO: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.23; H, 6.43; N, 4.29.

Scheme S16
2-(((3-(Aminomethyl)phenyl)(diphenyl)methyl)sulfanyl)ethanamine (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 [SiO₂; 0-25% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the thioether 38 as a clear yellow oil (250 mg, 72%). ¹H NMR (500 MHz, DMSO-d₆) δ = 2.15 (t, J = 7.1 Hz, 2H, CH₂), 2.42 (t, J = 7.0 Hz, 2H, CH₂), 3.67 (s, 2H, CH₂), 7.10-7.12 (m, 1H), 7.20-7.26 (m, 4H), 7.30-7.34 (m, 8H), 7.36-7.38 (m, 1H). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₂H₂₅N₂S (M+H)+: 349.1733; found: 349.1731. Analysis calcd. for C₂₂H₂₄N₂S: C, 75.82; H, 6.94; N, 8.04. Found: C, 73.93; H, 6.97; N, 8.39.

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

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 CH₂Cl₂ (3 x 10 mL). The organic extracts were washed successively with saturated aqueous NaHCO₃ solution (20 mL), H₂O (2 x 20 mL) and brine (20 mL), dried (MgSO₄), and concentrated in vacuo to yield N-((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. ¹H NMR (500 MHz, DMSO-d₆) δ = 1.81 (s, 3H, CH₃), 4.19 (d, J = 6.0 Hz, 2H, CH₂), 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-\(d_6\)) \( \delta = 22.48, 42.14, 80.51, 125.50, 126.36, 126.43, 126.61, 127.35, 127.48, 127.77, 147.75, 168.89. \) HRMS (ESI+) Calcd. for \( \text{C}_{22}\text{H}_{20}\text{NO} (\text{M+H-OH})^+ \): 314.1539; found: 314.1538. Analysis calcd. for \( \text{C}_{22}\text{H}_{21}\text{NO}_2 \): 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 \( \text{CH}_2\text{Cl}_2 \) with 1% \( \text{NH}_4\text{OH} \)] afforded the amine \( 39 \) as a colourless oil (169 mg, 82%). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta = 1.81 \) (s, 3H, \( \text{CH}_3 \)), 2.16 (d, \( J = 7.0 \) Hz, 2H, \( \text{CH}_2 \)), 2.42 (d, \( J = 7.0 \) Hz, 2H, \( \text{CH}_2 \)), 4.19 (d, \( J = 6.0 \) Hz, m, \( \text{NHCH}_2 \)), 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-\(d_6\)) \( \delta = 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 \( \text{C}_{24}\text{H}_{27}\text{N}_2\text{OS} (\text{M+H})^+ \): 391.1839; found: 391.1836. Analysis calcd. for \( \text{C}_{24}\text{H}_{26}\text{N}_2\text{OS} \): 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).

\( S5 \) \( \xrightarrow{\text{KOH}} \) \( S28 \)

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\(_2\)O 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\(_2\)O (30 mL), acidified (\textit{circa} pH 1) with aqueous HCl (1M) and extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The organic extracts were dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to yield as a white solid \( S28 \), which was used without further purification (1.25 g, 94%). Mpt. 166-168\(^\circ\)C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta = 6.60 \) (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-\(d_6\)) \( \delta = 80.40, 126.82, 127.69, 127.58, 130.20, 132.19, 147.33, 148.29, 167.40. \) HRMS (ESI-) Calcd. for \( \text{C}_{20}\text{H}_{15}\text{O}_3 \) (M-H): 303.1027; found: 303.1028. Analysis calcd. for \( \text{C}_{20}\text{H}_{16}\text{O}_3\text{·}\text{CH}_2\text{Cl}_2 \): C, 73.42; H, 5.05. Found: C, 73.48; H, 5.06.
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 Et₂O, and dried *in vacuo* to yield the title thioether **40** as a white solid (145 mg, 36%). Mpt. 218-220°C.

**1H NMR** (500 MHz, DMSO-*d*₆) δ = 2.43 (m, 2H, CH₂), 2.50-2.55 (m, 2H, CH₂), 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).

**13C 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 C₂₂H₂₂NO₂S (M+H)+: 364.1366; found: 364.1363. Analysis calcd. for C₂₁H₂₁NO₂S·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).**

This hydrolysis protocol is a modification of the literature procedure reported by Iso *et al.*²² Hydrogen peroxide (30% in H₂O, 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 CH₂Cl₂ (75 mL) and aqueous HCl (0.25M, 25mL). The organic layer was washed successively with H₂O
(75 mL) and brine (75 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the crude [SiO₂; 40-100% EtOAc in hexane] afforded the amide S₂⁹ as a white solid (440 mg, 83%). Mpt. 168-169°C. 

¹H 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). ¹³C 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 C₂₂H₂₃N₂O₅S (M+H)⁺: 363.1526; found: 363.1522. Analysis calcd. for C₂₀H₁₇NO₂: 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).

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 [SiO₂; 0-35% MeOH in CH₂Cl₂] afforded the title compound 4¹ as a white solid (139 mg, 34%). Mpt. 154-157°C. ¹H NMR (500 MHz, MeOD) δ = 2.69 (dd, J = 8.5, 13.2 Hz, 1H, CH₂), 2.77 (dd, J = 4.3, 13.2 Hz, 1H, CH₂), 3.09 (dd, J = 4.3, 8.5 Hz, 1H, CH), 7.22-7.27 (m, 2H), 7.30-7.45 (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). ¹³C 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 C₂₃H₂₃N₂O₃S (M-H)⁻: 405.1278; found: 405.1280. Analysis calcd. for C₂₃H₂₂N₂O₃S·⅓CH₂Cl₂: 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).
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 CH₂Cl₂ (3 x 10 mL) and the organic layer dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; 0-18% MeOH in CH₂Cl₂ with 1% NH₄OH] 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 Et₂O, and dried in vacuo to afford the hydrochloride salt 42 as a white solid (48 mg, 28%). Mpt. 202-205°C. ¹H NMR (500 MHz, DMSO-d₆) δ = 2.43-2.47 (m, 2H, CH₂), 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, CONH₂). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₂H₂₃N₂O₅ (M+H)+: 363.1526; found: 363.1522. Analysis calcd. for C₂₂H₂₂N₂O₅·2HCl: 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).

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 NaHCO₃ (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 CH₂Cl₂ (3 x 30 mL). The organic extracts were washed successively with H₂O (75 mL) and brine (75 mL), dried (MgSO₄), 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. ¹H NMR (400 MHz, CDCl₃) δ = 2.90 (d, J = 4.9 Hz, 3H, CH₃), 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$_3$) $\delta$ = 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$_{19}$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$_2$Cl$_2$ (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$_2$Cl$_2$ with 1% NH$_4$OH], 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$_2$Cl$_2$ and H$_2$O, and dried in vacuo to yield the hydrochloride salt 43 as a white solid (69 mg, 24%). Mpt. 197-200$^\circ$C. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ = 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-$d_6$) $\delta$ = 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$_2$OS (M+H)$^+$: 377.1682; found: 377.1679. Analysis calcd. for C$_{23}$H$_{24}$N$_2$OS·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).

$N$-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$^\circ$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$_2$Cl$_2$ (3 x 30 mL). The organic extracts were washed successively with H$_2$O (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. 1H NMR (500 MHz, CDCl3) δ = 2.87 (s, 3H, CH3), 3.05 (s, 3H, CH3), 7.26-7.37 (m, 14H). 13C NMR (125 MHz, CDCl3) 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 C22H22NO2 (M+H)+: 332.1645; found: 332.1643. Analysis calcd. for C22H21NO2: C, 79.73; H, 6.39; N, 4.57. 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 [SiO2; 0-20% MeOH in CH2Cl2 with 1% NH4OH] afforded the thioether 44 as a colourless oil (201 mg, 86%). 1H NMR (500 MHz, MeOD) δ = 2.33-2.38 (m, 2H, CH2), 2.43-2.48 (m, 2H, CH2), 2.89-2.93 (m, 3H, CH3), 3.03-3.07 (m, 3H, CH3), 7.21-7.34 (m, 7H), 7.38-7.46 (m, 6H), 7.55-7.59 (m, 1H). 13C NMR (100 MHz, MeOD) δ = 35.64, 35.92, 40.03, 41.51, 67.56, 126.51, 128.66, 129.11, 129.30, 129.37, 130.72, 132.17, 136.86, 145.80, 147.03, 173.51. HRMS (ESI+) Calcd. for C24H27N2OS (M+H)+: 391.1839; found: 391.1836. Analysis calcd. for C24H26N2OS·⅔CH2Cl2: 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).

Scheme S22

Intermediate sulfone S32 was prepared by adaptation of the procedure reported by Yeon Hwang et al.\textsuperscript{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 CH2Cl2 (4.26 mL) and stirred at the same temperature for 3 h. The reaction was poured into H2O (10 mL) and extracted with CH2Cl2 (3 x 10 mL). The organic extracts were washed successively with saturated aqueous NaHCO3 solution (3 x 30 mL), brine (30 mL), dried (MgSO4), and concentrated in vacuo. Purification by flash chromatography [SiO2; 10-75% EtOAc in hexane] afforded the sulfone S32 as a white solid (445 mg, 81%). Mpt. 143-146°C. 1H NMR (500 MHz, CDCl3) δ = 3.02 (s, 3H, CH3), 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). 13C NMR (125 MHz, CDCl3) 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 C20H17O2S (M+H-OH)+: 322.0944;
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$_2$Cl$_2$ with 1% NH$_4$OH] afforded the thioether 45 as a colourless oil (163 mg, 82%). $^{1}$H NMR (500 MHz, DMSO-d$_6$) $\delta = 2.17$ (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$_6$) $\delta = 35.33$, 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$_2$S$_2$ (M+H)$^+$: 398.1243; found: 398.1241. Analysis calcd. for C$_{22}$H$_{23}$NO$_2$S$_2$·½H$_2$O: 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).

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 $\leq$ -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 $\leq$ -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$_4$Cl solution (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed successively with H$_2$O (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$_3$) $\delta = 2.85$ (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$_3$) $\delta = 81.92$, 111.19, 118.92, 127.93, 128.00, 128.44, 128.72, 131.89, 145.90, 152.00. HRMS (ESI+) Calcd. for...
4-(((2-Aminoethyl)sulfanyl)(diphenyl)methyl)benzonitrile (46).

[Chemical structure image]

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 [SiO₂; 0-20% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the thioether 46 as a yellow oil (253 mg, 68%). ¹H NMR (500 MHz, DMSO-d₆) δ = 2.15 (t, J = 7.1 Hz, 2H, CH₂), 2.44 (t, J = 7.1 Hz, 2H, CH₂), 7.24-7.30 (m, 2H), 7.31-7.39 (m, 8H), 7.49-7.53 (m, 2H), 7.80-7.84 (m, 2H). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₂H₂₁N₂S (M+H)⁺: 345.1420; found: 345.1418. Analysis calcd. for C₂₂H₂₀N₂S·⅓CH₂Cl₂: 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).

[Chemical structure image]

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), H₂O (0.17 mL) aqueous NaOH (15% w/v, 0.17 mL) and H₂O (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 NaHCO₃ solution (50 mL), H₂O (50 mL), and brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; 0-40% EtOAc in hexane] yielded S₃₄ as a clear oil (182 mg, 63%). Mpt. 112-115°C (lit. 115-117°C).\(^{24}\) ¹H NMR (400 MHz, CDCl₃) \(\delta = 4.67 (s, 2H, CH₂), 7.25-7.33 (m, 14H)\). ¹³C NMR (100 MHz, CDCl₃) \(\delta = 65.23, 82.11, 126.80, 127.52, 128.11, 128.18, 128.36, 140.01, 146.59, 147.02\). HRMS (ESI+) Calcd. for C₂₀H₁₇O (M+H-OH)+: 273.1274; found: 273.1272. Analysis calcd. for C₂₀H₁₈O₂: C, 82.73; H, 6.25. Found: C, 82.17; H, 6.23.

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

\[
\text{HO-} \quad \begin{array}{c} \text{S} \\ \text{NH₂} \end{array} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NH}_2
\]

(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 [SiO₂; 0-25% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the thioether 47 as a yellow oil (54 mg, 29%). ¹H NMR (500 MHz, MeOD) \(\delta = 2.35 (t, J = 6.7 Hz, 2H, CH₂), 2.43 (t, J = 6.7 Hz, 2H, CH₂), 4.58 (s, 2H, CH₂), 7.18-7.31 (m, 8H), 7.36-7.44 (m, 6H).\) ¹³C NMR (125 MHz, MeOD) \(\delta = 35.94, 41.50, 64.75, 67.61, 127.55, 127.80, 128.90, 130.74, 141.31, 145.33, 146.33\). HRMS (ESI+) Calcd. for C₂₂H₂₄NOS (M+H)+: 350.1573; found: 350.1571. Analysis calcd. for C₂₂H₂₃NOS: 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).

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 H₂O (40 mL), followed by aqueous NaOH solution (15% w/v, 20 mL) and H₂O (20 mL). As this failed to break up the aluminium salt emulsion, saturated aqueous Na₂SO₄ solution (250 mL) was added and the mixture stirred for 30 min at room temperature. The mixture was filtered, the precipitate washed with CH₂Cl₂ and MeOH, and the filtrate concentrated to ~50 mL in vacuo, diluted with saturated aqueous Na₂SO₄ solution (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The organic extracts were washed with brine (100 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography [SiO₂; 0-22% MeOH in CH₂Cl₂ with 1% NH₄OH] afforded the title compound S35 as an off-white solid (1.34 g, 59%). Mpt. 138-140°C. ¹H NMR (500 MHz, DMSO-d₆) δ = 3.68 (s, 2H, CH₂), 6.36 (br s, 1H, OH), 7.11-7.14 (m, 2H), 7.19-7.25 (m, 8H), 7.27-7.31 (m, 4H). ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₀H₂₀NO (M+H)⁺: 290.1539; found: 290.1536. Analysis calcd. for C₂₀H₁₉NO: 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\textsubscript{2}; 0-25% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 1% NH\textsubscript{4}OH] afforded the thioether 48 as an off-white solid (250 mg, 72%). Mpt. 70-72°C. \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta = 2.15\) (t, \(J = 7.1\) Hz, 2H, CH\textsubscript{2}), 2.43 (t, \(J = 7.1\) Hz, 2H, CH\textsubscript{2}), 3.69 (s, 2H, CH\textsubscript{2}), 7.21-7.34 (m, 14H). \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta = 35.67, 40.86, 45.16, 65.58, 126.55, 127.90, 128.82, 129.09, 142.52, 142.60, 144.85\). HRMS (ESI+) Calcd. for C\textsubscript{22}H\textsubscript{25}N\textsubscript{2}S (M+H): 349.1733; found: 349.1731. Analysis calcd. for C\textsubscript{22}H\textsubscript{24}N\textsubscript{2}S\cdot\textfrac{1}{2}H\textsubscript{2}O: C, 73.91; H, 7.05; N, 7.84. Found: C, 73.91; H, 6.76; N, 7.57.

\textit{N}-(4-(((2-aminoethyl)sulfanyl)(diphenyl)methyl)benzyl)acetamide (49).

\begin{center}
\includegraphics[scale=0.5]{SchemeS25.png}
\end{center}

Acetic anhydride (104 \(\mu\)L, 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\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The organic extracts were washed successively with saturated aqueous NaHCO\textsubscript{3} solution (30 mL), H\textsubscript{2}O (2 x 30 mL) and brine (30 mL), dried (MgSO\textsubscript{4}), 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. \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta = 1.85\) (s, 3H, CH\textsubscript{3}), 4.22 (d, \(J = 6.0\) Hz, 2H, CH\textsubscript{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). \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta = 22.53, 41.78, 80.39, 126.48, 126.61, 127.49, 127.68, 127.74, 137.82, 146.34, 147.78, 169.05\). HRMS (ESI+) Calcd. for C\textsubscript{22}H\textsubscript{21}NO\textsubscript{2} (M+H): 332.1645; found: 332.1643. The title compound was then prepared following general procedure (vi) using \textit{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\textsubscript{2}; 0-18% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 1% NH\textsubscript{4}OH] afforded the thioether 49 as a pale yellow solid (143...
mg, 73%). Mpt. 74-77°C. \(^1\)H NMR (400 MHz, MeOD) \(\delta = 1.97\) (s, 3H, CH₃), 2.31-2.35 (m, 2H, CH₂), 2.40-2.45 (m, 2H, CH₂), 4.33 (s, NHCH₂), 7.18-7.31 (m, 8H), 7.36-7.43 (m, 6H). \(^{13}\)C NMR (100 MHz, MeOD) \(\delta = 22.52, 35.92, 41.50, 43.77, 67.54, 127.82, 128.15, 128.91, 130.74, 130.91, 138.51, 145.37, 146.26, 173.13\). HRMS (ESI+) Calcd. for C\(_{24}\)H\(_{27}\)NO\(_2\)S (M+H): 391.1839; found: 391.1835. Analysis calcd. for C\(_{24}\)H\(_{26}\)N\(_2\)O\(_2\)S·\(\frac{1}{3}\)CH\(_2\)Cl\(_2\): 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\(_2\)O, 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\(_2\)Cl\(_2\) (50 mL) and aqueous HCl (0.25M, 25mL). The organic layer was washed successively with H\(_2\)O (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) \(\delta = 7.23-7.32\) (m, 10H), 7.35-7.39 (m, 2H), 7.89-7.92 (m, 2H). \(^{13}\)C NMR (125 MHz, MeOD) \(\delta = 82.68, 128.03, 128.20, 128.79, 128.79, 129.23, 129.33, 133.48, 148.35, 152.91, 172.18\). 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).
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 Et2O, 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 CH2Cl2 (3 x 10 mL) and the organic layer dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography [SiO2; 0-15% MeOH in CH2Cl2 with 1% NH4OH] afforded the title compound 50 as a white solid (252 mg, 70%). Mpt. 62-65°C. 1H NMR (500 MHz, MeOD) δ = 2.32-2.37 (m, 2H, CH2), 2.42-2.47 (m, 2H, CH2), 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). 13C 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 C22H23N2OS (M+H)+: 363.1526; found: 363.1523. Analysis calcd. for C22H22N2OS: 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).

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 NaHCO3 (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 CH2Cl2 (3 x 30 mL). The organic extracts were washed successively with H2O (75 mL) and brine (75 mL) then concentrated in vacuo. Purification by flash chromatography [SiO2; 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. 1H NMR (400 MHz, CDCl3) δ = 2.97 (d, J = 4.9 Hz, 3H, CH3), 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$_2$Cl$_2$ (2 mL). Purification by flash chromatography [SiO$_2$; 0-15% MeOH in CH$_2$Cl$_2$ with 1% NH$_4$OH] 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$_2$OS (M+H)$^+$: 377.1682; found: 377.1679. Analysis calcd. for C$_{23}$H$_{24}$N$_2$OS: 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).

$^{1}$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, 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, 7.44. Found: C, 71.50; H, 6.19; N, 7.12.

$N$-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 NaHCO$_3$ (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$_2$O (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, 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, 7.44. Found: C, 71.50; H, 6.19; N, 7.12.
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$_2$Cl$_2$ (2 mL). Purification by flash chromatography [SiO$_2$; 0-15% MeOH in CH$_2$Cl$_2$ with 1% NH$_4$OH] afforded the thioether S2 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$_{23}$H$_{26}$N$_2$O$_2$·$\frac{1}{3}$CH$_2$Cl$_2$: 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).

$n$-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$_4$Cl solution (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed successively with H$_2$O (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).

Intermediate sulfoxide S50 was prepared by adaptation of the procedure reported by Yeon Hwang et al.\textsuperscript{23} m-CPBA (68% pure, 1.12 g, 4.41 mmol) was added to a cooled (0\degree C) solution of (4-(methylsulfonyl)phenyl)(diphenyl)methanol x (759 mg, 2.50 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (8 mL) and stirred at the same temperature for 7 h. The reaction was poured into H\textsubscript{2}O (10 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The organic extracts were washed successively with aqueous NaOH (1M, 3 x 30 mL), H\textsubscript{2}O (30 mL), brine (30 mL), dried (MgSO\textsubscript{4}), and concentrated \textit{in vacuo}. Purification by flash chromatography [SiO\textsubscript{2}; 10-100\% EtOAc in hexane] afforded (4-(methylsulfonyl)phenyl)(diphenyl)methanol S41 as a white solid (395 mg, 58%). Mpt. 179-180\degree C. \textit{H} NMR (500 MHz, DMSO-d\textsubscript{6}) \(\delta = 3.20\) (s, 3H, CH\textsubscript{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). \textit{C} NMR (125 MHz, DMSO-d\textsubscript{6}) \(\delta = 43.52, 80.41, 126.41, 127.02, 127.73, 127.79, 128.53, 139.14, 146.82, 153.37. \), 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\textsubscript{20}H\textsubscript{17}O\textsubscript{2}S (M+H-OH): 322.0944; found: 322.0941. Analysis calcd. for C\textsubscript{20}H\textsubscript{18}O\textsubscript{3}S: 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\textsubscript{2}; 0-20\% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 1\% NH\textsubscript{4}OH] afforded the thioether 53 as a colourless oil (143 mg, 62%). \textit{H} NMR (400 MHz, MeOD) \(\delta = 2.32-2.37\) (m, 2H, CH\textsubscript{2}), 2.43-2.48 (m, 2H, CH\textsubscript{2}), 3.12 (s, 3H, CH\textsubscript{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). \textit{C} NMR (125 MHz, DMSO-d\textsubscript{6}) \(\delta = 35.50, 40.71, 43.45, 65.54, 126.79, 126.97, 128.23, 129.02, 129.95, 138.97, 143.97, 150.38. \) HRMS (ESI+) Calcd. for C\textsubscript{22}H\textsubscript{24}NO\textsubscript{2}S\textsubscript{2} (M+H): 398.1243; found: 398.1239. Analysis calcd. for C\textsubscript{22}H\textsubscript{23}NO\textsubscript{2}S\textsubscript{1/3}CH\textsubscript{2}Cl\textsubscript{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

\textit{N^t-Triptylpropane-1,3-diamine (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 triethylamine. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 0-20% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 0.5% NH\textsubscript{4}OH] to give \textbf{S42} as a colorless solid (249 mg, 79\%). \textit{\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6})} \(\delta = 1.57\) (m, 2H, CH\textsubscript{2}), 2.00 (m, 2H, CH\textsubscript{2}), 2.62 (m, 2H, CH\textsubscript{2}), 7.19-7.40 (m, 15H, Ph). \textit{\textsuperscript{13}C NMR (100MHz, DMSO-d\textsubscript{6})} \(\delta = 32.7, 41.3, 70.4, 125.9, 127.7, 128.4, 146.2\). HRMS (ESI+) calcd. for C\textsubscript{22}H\textsubscript{24}N\textsubscript{2} (M+H): 317.20177; found: 317.20104. Analysis calcd. for C\textsubscript{22}H\textsubscript{24}N\textsubscript{2}: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.96; H, 7.35; N, 8.45.

\textit{N^t-Triptylbutane-1,4-diamine (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 triethylamine. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 0-20% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 0.5% NH\textsubscript{4}OH] to give \textbf{S43} as a colorless solid (240 mg, 73\%). \textit{\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6})} \(\delta = 1.45\) (m, 4H, CH\textsubscript{2}CH\textsubscript{2}), 1.95 (m, 2H, CH\textsubscript{2}), 2.55 (m, 2H, CH\textsubscript{2}), 7.19-7.40 (m, 15H, Ph). \textit{\textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6})} \(\delta = 27.8, 29.7, 41.3, 43.8, 70.9, 126.6, 128.2, 128.9, 146.8\). HRMS (ESI+) calcd. for
C<sub>23</sub>H<sub>26</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 331.21688; found: 331.21667. Analysis calcd. for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>·H<sub>2</sub>O: C, 79.27; H, 8.10; N, 8.04. Found: C, 80.43; H, 7.52; N, 7.53.

<sup>N</sup><sup>1</sup>-Tritylpentane-1,5-diamine (S44).

![S44](image)

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 triethylamine. The crude product was purified by flash chromatography [SiO<sub>2</sub>; 0-15% MeOH in CH<sub>2</sub>Cl<sub>2</sub> with 0.5% NH<sub>4</sub>OH] to give S44 as a colorless solid (256 mg, 74%).<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ = 1.25 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 1.45 (m, 2H, CH<sub>2</sub>), 1.94 (m, 2H, CH<sub>2</sub>), 2.49 (m, 2H, CH<sub>2</sub>), 7.19-7.40 (m, 15H, Ph).<sup>1</sup>C NMR (100MHz, DMSO-d<sub>6</sub>) 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<sub>24</sub>H<sub>28</sub>N<sub>2</sub>(M+H)<sup>+</sup>: 345.23253; found: 345.23226. Analysis calcd. for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>·H<sub>2</sub>O: 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).

![Scheme S29](image)

The title compound was prepared using an adaptation of the method reported by Wang<sup>26</sup> 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<sub>4</sub>Cl (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<sub>2</sub>; 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\textsubscript{2} atmosphere in ice-bath cooling, LiAlH\textsubscript{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 \textit{in vacuo}. The residue was purified by flash chromatography [SiO\textsubscript{2}; 2-20\% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 0.5\% NH\textsubscript{4}OH] to afford the amine S\textsubscript{46} as a colorless solid (177 mg, 73\%). \textit{\textsuperscript{1}H} NMR (400MHz, CD\textsubscript{3}OD): \(\delta = 2.60-2.65 \text{ (m, 2H, CH\textsubscript{2})}, 2.92-2.96 \text{ (m, 2H, CH\textsubscript{2}}), 7.22-7.31 \text{ (m, 15H, Ph)}. \textit{\textsuperscript{13}C} NMR (100MHz, CD\textsubscript{3}OD): \(\delta = 37.2, 37.4, 55.1, 126.3, 128.0, 128.6, 145.9\). HRMS (ESI+) calcd. for C\textsubscript{21}H\textsubscript{21}N (M+H): 288.17468; found: 288.17465. Analysis calcd. for C\textsubscript{21}H\textsubscript{21}N\cdot H\textsubscript{2}O: 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 (S\textsubscript{48}).

Potassium cyanide (101 mg, 1.56 mmol) was added to a solution of 4,4,4-triphenylbutyl methanesulfonate S\textsubscript{2} (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 \textit{in vacuo}. The crude product was purified by flash chromatography [SiO\textsubscript{2}; 0-12\% EtOAc in hexane] to give nitrile S\textsubscript{47} as a white solid (116 mg, 94\%). 5,5,5-Triphenylpentanenitrile S\textsubscript{47} (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°C and cautiously quenched with saturated Na\textsubscript{2}SO\textsubscript{4} solution (8 mL), concentrated \textit{in vacuo} and the crude product purified by flash chromatography [SiO\textsubscript{2}; 0-10\% MeOH in CH\textsubscript{2}Cl\textsubscript{2} with 0.5\% NH\textsubscript{4}OH] to afford the amine S\textsubscript{48} as a colorless solid (85 mg, 73\%). \textit{\textsuperscript{1}H} NMR(400 MHz, DMSO-\textit{d}_6) \(\delta = 0.95 \text{ (m, 2H, CH\textsubscript{2})}, 1.38-1.44 \text{ (m, 2H, CH\textsubscript{2}}), 2.43-2.56 \text{ (m, 4H, CH\textsubscript{2} and CH\textsubscript{2}}), 3.17-3.40 \text{ (br s, 2H, NH\textsubscript{2}}), 7.21-7.28 \text{ (m, 15H, Ph)}. \textit{\textsuperscript{13}C} NMR (100 MHz, DMSO-\textit{d}_6) \(\delta = 23.4, 29.8, 33.7, 41.8, 56.8, 126.3, 128.4, 129.4, 147.8\). HRMS (ESI+) calcd. for C\textsubscript{23}H\textsubscript{25}N (M+H): 316.20598; found: 316.20667. Analysis calcd. for C\textsubscript{23}H\textsubscript{25}N\cdot 0.5H\textsubscript{2}O: 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).

The title compound was prepared using an adaptation of the method reported by Ōki et al. 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 KMnO₄ (65.5 mg, 0.41 mmol) and NaHCO₃ (65.5 mg, 0.78 mmol) and the mixture stirred at room temperature for 1 h. The reaction was treated with saturated NaHSO₃ solution (5 mL, stir for 1 h) to destroy the excess oxidant. The mixture was extracted with CH₂Cl₂ (20 mL), dried (MgSO₄) and concentrated in vacuo. The crude product was purified by flash chromatography [SiO₂; 10-35% EtOAc in hexane] to give S49 as a white solid (85 mg, 71%). ¹H NMR (400 MHz, DMSO-d₆) δ = 1.85-1.89 (t, 2H, CH₂), 2.81-2.85 (t, 2H, CH₂), 7.21-7.30 (m, 15H, Ph), 12.12 (br s, 1H, COOH). ¹³C NMR (100 MHz, DMSO-d₆) δ = 30.7, 34.5, 55.6, 126.0, 127.9, 128.7, 146.5, 174.1. HRMS (ESI-) calcd. for C₂₂H₂₀O₂ (M−H)⁻: 315.13905; found: 315.13919. Analysis calcd. for C₂₂H₂₀O₂: C, 83.51; H, 6.37. Found: C, 83.06; H, 6.35.

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

The title compound was prepared using an adaptation of the method by Neidigh et al. 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 NH₄OH (20 mL), filtered
and the precipitate washed with CH₂Cl₂. The combined organic washings were concentrated in vacuo and the crude product purified by flash chromatography [SiO₂; 0-10% MeOH in CH₂Cl₂ with 0.5% NH₄OH] to give the secondary amine S50 as a colorless solid (89 mg, 85%). ¹H NMR (500 MHz, DMSO-d₆) δ = 1.07 (m, 2H, CH₂), 2.19 (s, 3H, CH₃), 2.45 (t, 2H, CH₂), 2.56 (t, 2H, CH₂), 7.15-7.29 (m, 15H, Ph). ¹³C NMR (125 MHz, DMSO-d₆) δ = 25.8, 36.4, 37.7, 52.1, 56.6, 126.2, 128.3, 129.3, 147.7. HRMS (ESI+) calcd. for C₂₃H₂₅N · H₂O: M+H⁺: 316.20598; found: 316.20615. Analysis calcd. for C₂₃H₂₅N · H₂O: 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          | ![Decomposition fragments](image1) |
| 7        | 2.9          | ![Decomposition fragments](image2) |
| 8        | 7.0          | ![Decomposition fragments](image3) |
| 9        | stable       | -                       |
| 10       | stable       | -                       |
Table S2: Variation of amino-alkyl chain length with N-trityl and C-trityl series

![Chemical structure](image)

| Cmpd | X    | y | R  | Ligand Efficiency | Inhibition basal ATPase activity $K_{i}^{\text{app}}$ [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 | R₁ | R₂   | Basal ATPase activity |
|--------|---|----|------|-----------------------|
|        |   |    |      | IC<sub>50 [nM]         |
| 55 (FW25) | 0 | CH=CH₂ | 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 | CO₂H | NHBn | >49210                |
| 60 (FW27) | 1 | H   | N₃   | 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 | $\pi$  | $\sigma$ |
|----------------------|--------|----------|
| 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     |

$\pi$ values from *meta*-phenoxyacetic acid series as measured by Fujita *et al*. unless otherwise stated.$^{29}$

$\sigma$ values from Jaffe unless otherwise stated.$^{30}$

* From Craig.$^{31}$
Figure S1: 24-hour acid stability test for nitrogen, oxygen and sulphur analogues.

A)
Figure S2: Enantiomer separation using semipreparative chiral chromatography.

A)

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

1. Will, D. W.; Breipohl, G.; Langner, D.; Knolle, J.; Uhlmann, E. The synthesis of polyamide nucleic acids using a novel monomethoxytrityl protecting-group strategy. *Tetrahedron* **1995**, *51*, 12069-12082.

2. Marvel, C. S.; Dietz, F. C.; Himel, C. M. THE DISSOCIATION OF HEXAARYLETHANES. XIII. HALOGEN SUBSTITUENTS1. *The Journal of Organic Chemistry* **1942**, *07*, 392-396.

3. Zhang, L.; Zhang, W.; Liu, J.; Hu, J. C–F Bond Cleavage by Intramolecular SN2 Reaction of Alkyl Fluorides with O- and N-Nucleophiles. *The Journal of Organic Chemistry* **2009**, *74*, 2850-2853.

4. Deshpande, P. P.; Ellsworth, B. A.; Buono, F. G.; Pullockaran, A.; Singh, J.; Kissick, T. P.; Huang, M.-H.; Lobinger, H.; Denzel, T.; Mueller, R. H. Remarkable $I^2$-Selectivity in the Synthesis of $I^2$-1-C-Arylglucosides: Stereoselective Reduction of Acetyl-Protected Methyl 1-C-Arylglucosides without Acetoxy-Group Participation. *The Journal of Organic Chemistry* **2007**, *72*, 9746-9749.

5. Maltese, M. Reductive Demercuration in Deprotection of Trityl Thioethers, Trityl Amines, and Trityl Ethers. *The Journal of Organic Chemistry* **2001**, *66*, 7615-7625.

6. Carroll, F. I.; Dickson, H. M.; Wall, M. E. Organic Sulfur Compounds. III.1 Synthesis of 2-(Substituted alkylamino)ethanethiols2. *The Journal of Organic Chemistry* **1965**, *30*, 33-38.

7. Keith, D. D.; Tortora, J. A.; Yang, R. Synthesis of L-2-amino-4-methoxy-trans-but-3-enoic acid. *The Journal of Organic Chemistry* **1978**, *43*, 3711-3713.

8. Dubowchik, G. M.; Radia, S. Monomethoxytrityl (MMT) as a versatile amino protecting group for complex prodrugs of anticancer compounds sensitive to strong acids, bases and nucleophiles. *Tetrahedron Letters* **1997**, *38*, 5257-5260.

9. Hatano, M.; Suzuki, S.; Ishihara, K. Highly Efficient Alkylation to Ketones and Aldimines with Grignard Reagents Catalyzed by Zinc(II) Chloride. *Journal of the American Chemical Society* **2006**, *128*, 9998-9999.

10. Gilman, H.; Gorsich, R. D. Some Reactions of o-Halobromobenzenes with n-Butyllithium. *Journal of the American Chemical Society* **1956**, *78*, 2217-2222.

11. DeBonis, S.; Skofias, D. A.; Indorato, R.-L.; Liger, F.; Marquet, B.; Laggner, C.; Joseph, B.; Kozielski, F. Structure–Activity Relationship of S-Trityl-l-Cysteine Analogues as Inhibitors of the Human Mitotic Kinesin Eg5. *Journal of Medicinal Chemistry* **2008**, *51*, 1115-1125.

12. Kumar, S.; Ramachandran, U. Cinchona alkaloid phase-transfer catalysts revisited: influence of substituted aryl groups on the enantioselectivity of glycine ester enolate alkylation. *Tetrahedron* **2005**, *61*, 7022-7028.

13. Chackal-Catoen, S.; Miao, Y.; Wilson, W. D.; Wenzler, T.; Brun, R.; Boykin, D. W. Dicationic DNA-targeted antiprotozoal agents: Naphthalene replacement of benzimidazole. *Bioorganic & Medicinal Chemistry* **2006**, *14*, 7434-7445.

14. Ulrik, S. S.; Erik, F.; Tine, B. S.; Jerzy, W. J.; Ulf, M.; Povl, K.-L. Structural Determinants for AMPA Agonist Activity of Aryl or Heteroaryl Substituted AMPA Analogues. Synthesis and Pharmacology. *Archiv der Pharmazie* **2001**, *334*, 62-68.

15. Katritzky, A. R.; Lue, P. Directed metalation of benzenesulfinamides. A novel route to meta-substituted aromatic compounds. *The Journal of Organic Chemistry* **1990**, *55*, 74-78.

16. Zarkadis, A. K.; Neumann, W. P.; Uzick, W. Über sterisch gehinderte freie Radikale, XIII. Über das Wittig-Radikal 4-Benzoyltriphenylmethyl und analoge mono-4-substituierte Tritylradikale. *Chemische Berichte* **1985**, *118*, 1183-1192.

17. Talley, J. J.; Evans, I. A. Reaction of lithium o-lithiophenoxy with carbonyl compounds. *The Journal of Organic Chemistry* **1984**, *49*, 5267-5269.

18. Bowden, S. T.; Beynon, K. I. 855. Free radicals and radical stability. Part XVII. (m-Hydroxyphenyl)diphenylmethanol and the corresponding free radical. *Journal of the Chemical Society (Resumed)* **1957**, 4253-4256.
19. Luliński, S.; Zajac, K. Selective Generation of Lithiated Benzonitriles: the Importance of Reaction Conditions. *The Journal of Organic Chemistry* **2008**, *73*, 7785-7788.

20. Neumann, W. P.; Penenory, A.; Stewen, U.; Lehning, M. Sterically hindered free radicals. 18. Stabilization of free radicals by substituents as studied by using triphenylmethyls. *Journal of the American Chemical Society* **1989**, *111*, 5845-5851.

21. Parham, W. E.; Jones, L. D. Elaboration of bromoaryl nitriles. *The Journal of Organic Chemistry* **1976**, *41*, 1187-1191.

22. Iso, Y.; Grajkowska, E.; Wroblewski, J. T.; Davis, J.; Goeders, N. E.; Johnson, K. M.; Sanker, S.; Roth, B. L.; Tueckmantel, W.; Kozikowski, A. P. Synthesis and Structure−Activity Relationships of 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine Analogues as Potent, Noncompetitive Metabotropic Glutamate Receptor Subtype 5 Antagonists; Search for Cocaine Medications. *Journal of Medicinal Chemistry* **2006**, *49*, 1080-1100.

23. Hwang, J. Y.; Arnold, L. A.; Zhu, F.; Kosinski, A.; Mangano, T. J.; Setola, V.; Roth, B. L.; Guy, R. K. Improvement of Pharmacological Properties of Irreversible Thyroid Receptor Coactivator Binding Inhibitors. *Journal of Medicinal Chemistry* **2009**, *52*, 3892-3901.

24. Zee-Cheng, K. Y.; Cheng, C. C. Structural modification of S-trityl-L-cysteine. Preparation of some S-(substituted trityl)-L-cysteines and dipeptides of S-trityl-L-cysteine. *Journal of Medicinal Chemistry* **1972**, *15*, 13-16.

25. Creighton, A. M.; Jackman, L. M. 626. Hydrogen transfer. Part XIV. The quinone cyclodehydrogenation of acids and alcohols. *Journal of the Chemical Society (Resumed)* **1960**, 3138-3144.

26. Wang, W.; McMurray, J. S. A selective method for the preparation of primary amides: Synthesis of Fmoc--4-carboxamidophenylalanine and other compounds. *Tetrahedron Letters* **1999**, *40*, 2501-2504.

27. Oki, M.; Taguchi, Y.; Miyasaka, T.; Kitano, M.; Toyota, S.; Tanaka, T.; Yonemoto, K.; Yamamoto, G. Reactivities of Stable Rotamers. XXXV. Diazotization of 2-(1,4-Dimethyl-9-trityl)-2-methylpropylamine Rotamers. *Bulletin of the Chemical Society of Japan* **1995**, *68*, 1485-1496.

28. A. Neidigh, K.; A. Avery, M.; S. Williamson, J.; Bhattacharyya, S. Facile preparation of N-methyl secondary amines by titanium(IV) isopropoxide-mediated reductive amination of carbonyl compounds. *Journal of the Chemical Society, Perkin Transactions 1* **1998**, 2527-2532.

29. Fujita, T.; Iwasa, J.; Hansch, C. A New Substituent Constant, Ê, Derived from Partition Coefficients. *Journal of the American Chemical Society* **1964**, *86*, 5175-5180.

30. Jaffe, H. H. A Rexamination of the Hammett Equation. *Chemical Reviews* **1953**, *53*, 191-261.

31. Craig, P. N. Interdependence between physical parameters and selection of substituent groups for correlation studies. *Journal of Medicinal Chemistry* **1971**, *14*, 680-684.