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Thioarylation of anilines using dual catalysis: two-step synthesis of phenothiazines†

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A two-step synthesis of phenothiazines has been developed using a dual-catalytic *ortho*-thioarylation reaction of anilines as the key step. Activation of *N*-(2-bromophenylthio)succinimide was achieved using the super Lewis acid, iron(III) triflimide and the Lewis base, diphenyl selenide, resulting in an accelerated and efficient *ortho*-thioarylation reaction of various protected aniline derivatives and less reactive, unprotected analogues. The thioarylated adducts were then cyclised to the desired phenothiazines using either an Ullmann–Goldberg or Buchwald–Hartwig coupling reaction. The dual catalytic thioarylation and copper(I)-catalysed cyclisation approach was used for the four-step synthesis of methopromazine, a neuroleptic agent with antipsychotic activity.

Introduction

Phenothiazine heterocycles are an important structural motif, found as the core component of a wide range of pharmaceutically active agents.[1,2] Early analogues such as the parent compound, phenothiazine (Fig. 1) was used as an anthelmintic agent in livestock and humans,[3] while the dye, methylene blue was used for the treatment of malaria.[4] More recently, dimethylaminopropyl analogues such as chlorpromazine have been widely used as antipsychotic drugs for the treatment of mental illnesses such as schizophrenia.[1,5] Thioridazine, a first generation antipsychotic drug, withdrawn due to cardiac arrhythmias, has been shown to be an anti-glioblastoma and anticancer stem cell agent.[6] As well as displaying other medicinal properties,[7] phenothiazine derivatives have also been utilised in applications such as molecular wires,[8] chemiluminescence emitters,[9] sensors for the detection of flavins[10] and as photoredox catalysts.[11]

Due to their importance, particularly as medicinal agents, there have been significant efforts in developing efficient syntheses of phenothiazines. Historically, phenothiazines were prepared by heating diphenylamines with sulfur at high temperatures (250–260 °C).[12] This approach has been improved using microwave heating.[13] For example, a range of phenothiazines with antitubercular activity were prepared in a two-step approach involving a Buchwald–Hartwig reaction for the synthesis of diphenylamines, followed by iodine-catalysed cyclisation with sulfur, using microwave heating (Scheme 1a).[14] Traditionally, phenothiazines have also been prepared *via* a four-step approach, using a based-mediated Smiles rearrangement as the key step.[15] To overcome the regioselectivity issues associated with both approaches, recent strategies have focused on transition metal-catalysed coupling of pre-functionalised anilines and arene partners.[16] Jørgensen and co-workers reported a palladium-catalysed three-component synthesis of phenothiazines using 1-bromo-2-iodobenzenes, primary amines and 2-bromobenzenethiol,[17] while the Ma group developed a sequential copper iodide and L-proline-catalysed process from 2-iodoanilines and 2-bromobenzenethiols (Scheme 1b).[18] A one-pot, rhodium(III)-catalysed C–H thioarylation reaction and copper-catalysed C–N amination of acetanilides and 2-bromobenzenethiols has also been reported (Scheme 1c).[19] In addition to transition metal-catalysed approaches, various base-, enzyme- and iodine-mediated couplings have also recently been described for phenothiazine synthesis.[20]

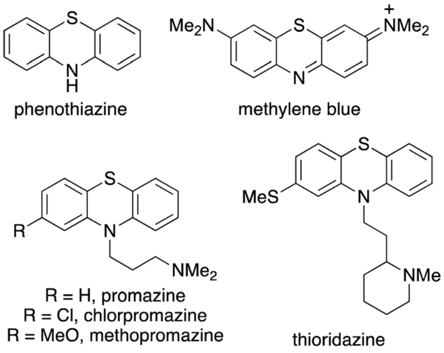

Fig. 1 Structures of medicinally important phenothiazines.

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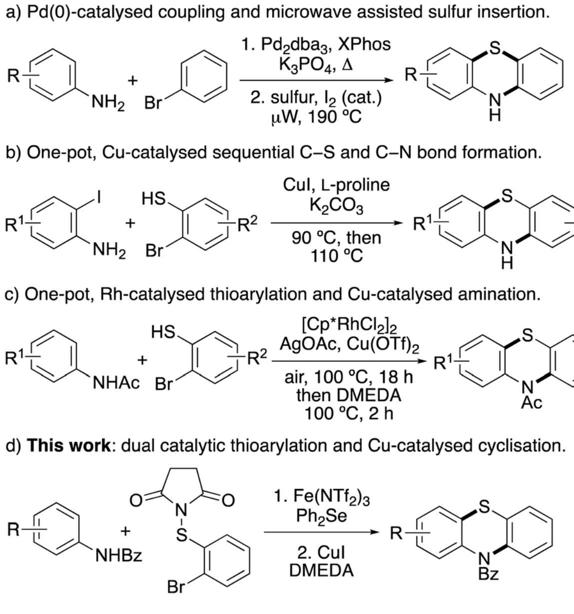
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all compounds. See DOI: **https://doi.org/10.1039/d2ob01082h**



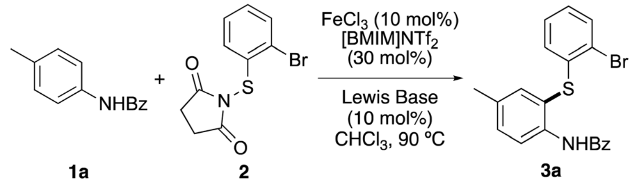
Scheme 1 Methods for the synthesis of phenothiazines.

Several of these methods are elegant and efficient but rely on highly functionalised arenes or the use of precious transition metal catalysis. We have developed catalytic methods for the regioselective halogenation of arenes using the super Lewis acid, iron(III) triflimide to activate *N*-halosuccinimides.[21] More recently, this approach has been extended for aryl C–S bond formation with *N*-thiosuccinimides and used as the key step for the synthesis of phenoxathiins.[22] To address the challenge of phenothiazine synthesis using simple aniline starting materials and non-precious transition metal catalysts, it was proposed that iron(III)-catalysed thioarylation of benzoyl-protected anilines with *N*-(2-bromophenylthio)succinimide would generate intermediates, that following copper-catalysed cyclisation would allow access to phenothiazines (Scheme 1d). Herein, we now report the two-step synthesis of phenothiazines using an accelerated, dual-catalysed thioarylation reaction involving iron(III) triflimide and the Lewis base, diphenyl selenide, followed by copper(I)-catalysed cyclisation. We also describe the use of this two-step approach for the synthesis of the neuroleptic agent, methopromazine.

Results and discussion

Our studies began with the thioarylation of a suitably protected derivative of *p*-toluidine with *N*-(2-bromophenylthio)succinimide (**2**). Although Fu and co-workers showed that uncatalysed thioarylation of unprotected anilines with *N*-(arylthio) succinimides could be achieved using high temperatures (100 °C) and extended reaction times (21–30 h),[23] examples of catalysed methods with activated *N*-thiolation reagents are relatively rare and require the use of protected derivatives.[22a,24,25] Preliminary work in our group demonstrated that iron-catalysed thioarylation of unprotected anilines gave a mixture of thiolated products *via* reaction with either the arene or amine moiety. For this reason, *N*-benzoyl protected *p*-toluidine **1a** was chosen as the model substrate. Using reactions parameters previously optimised (catalyst loading, solvent and temperature),[22] an initial reaction was attempted at 90 °C, using iron(III) triflimide (10 mol%), which was generated *in situ* from iron(III) chloride and the commercially available ionic liquid, [BMIM]NTf$_2$. The transformation was found to be incomplete after 48 h and returned mainly starting material (Table 1, entry 1). This was not surprising as the *ortho*-position of **1a** is more sterically hindered and less activated compared to the parent aniline. Previous work by the Gustafson group has shown that Lewis acid catalysed thioarylations can be accelerated using Lewis bases.[24c] Therefore, a series of commercially available Lewis base catalysts (10 mol%) were screened to determine whether these could improve both the rate and yield of iron(III)-catalysed thioarylation of **1a**. Addition of bis(4-methoxyphenyl)sulfane to the thioarylation reaction of **1a** with thiosuccinimide **2** resulted in significant improvement (entry 2). The reaction was complete after 18 h and gave **3a** in 88% yield. Similar results were observed using 1-methoxy-4-(methylthio)benzene (entry 3). Despite being used as Lewis bases for aryl chlorination,[26] both diaryl thioureas and triphenylphosphine sulfide showed little activity for thioarylation (entries 4 and 5). The best results were observed using the commercially available Lewis base, diphenyl selenide, which allowed complete thioarylation of **1a** after 6 hours and gave **3a** in 91% yield (entry 6). To demonstrate that both iron triflimide and diphenyl selenide were required for the accelerated reaction, the transformation was repeated in the absence of iron(III) triflimide (entry 7). After 20 h, this gave no product, confirming the dual role of both iron(III) triflimide and diphenyl selenide in accelerating the reaction.

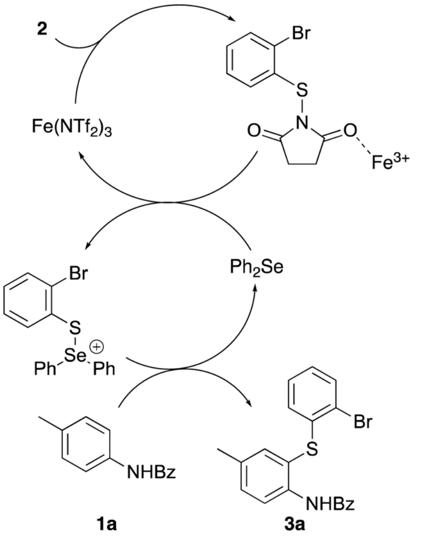
Table 1 Thioarylation of *N*-(4-methylphenyl)benzamide (**1a**)[a]



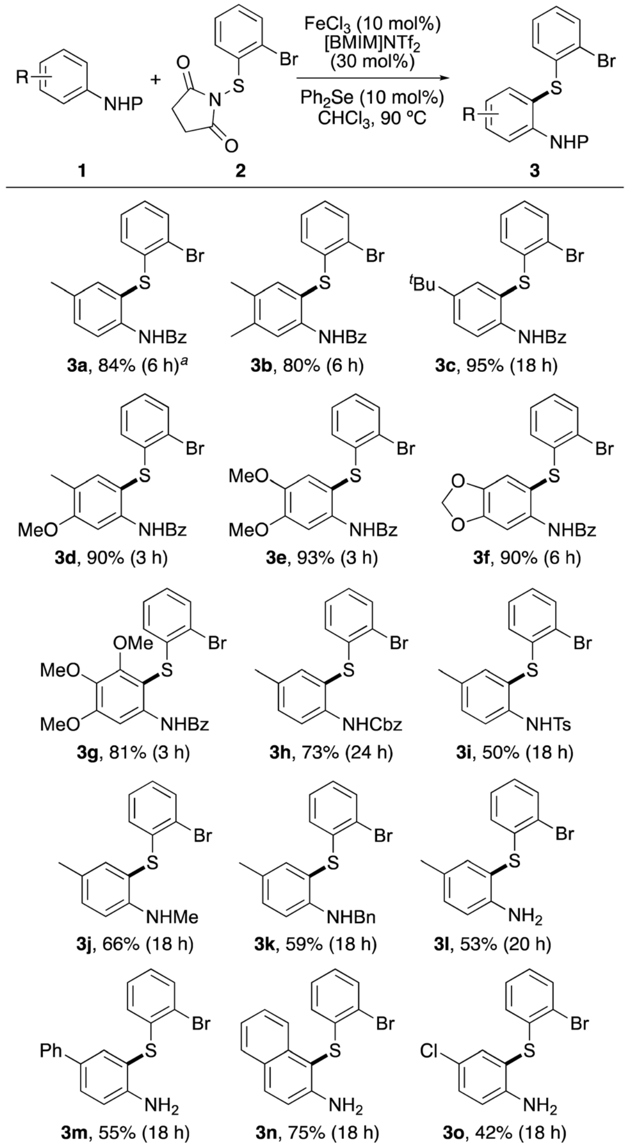
Entry	Lewis base	Time (h)	Yield[b] (%)
1[c]	—	48	—
2	$(4\text{-MeOPh})_2S$	18	88
3	(4-MeOPh)SMe	18	73
4	$(PhNH)_2C{=}S$	24	—
5	$Ph_3P{=}S$	24	—
6	Ph_2Se	6	91
7[d]	Ph_2Se	20	—

[a] Reaction conditions: **1a** (0.29 mmol), **2** (1.2 equiv.), 0.6 M in arene. [b] Isolated yields. [c] Reaction gave a 3.5 : 1 mixture of **1a** : **3a** after 48 h. [d] Reaction performed in the absence of FeCl$_3$ and [BMIM]NTf$_2$.

Using these results, a mechanism for dual-catalysed thioarylation involving both iron(III) triflimide and diphenyl selenide has been proposed (Scheme 2). On activation of *N*-(2-bromo-



Scheme 2 Proposed catalytic pathway for dual catalytic thioarylation.

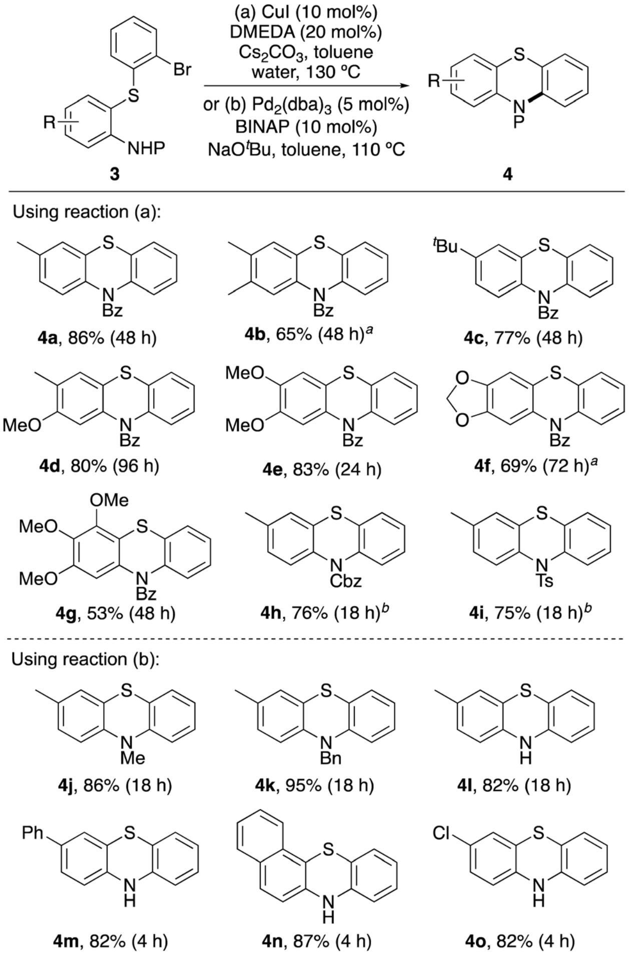


Scheme 3 Reaction scope of anilines. General reaction conditions: **1** (0.29 or 0.58 mmol), **2** (1.2 equiv.), 0.6 M in arene. [a]Reaction performed on a 1.5 mmol scale.

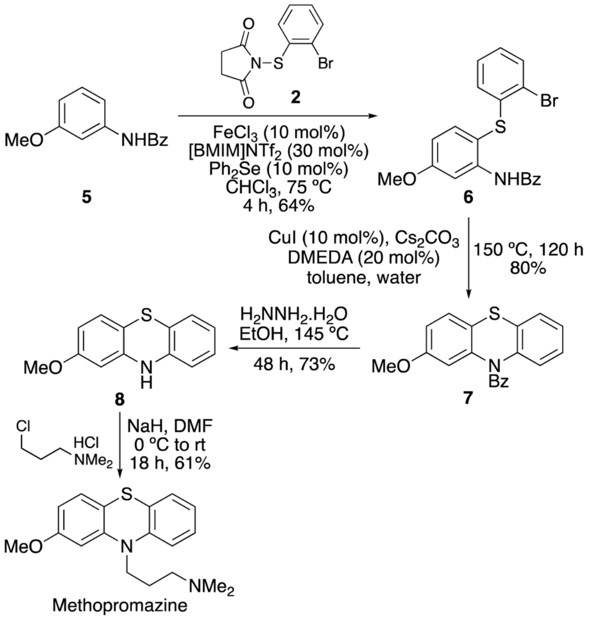
phenylthio)succinimide (**2**) with the strongly Lewis acidic iron(III) cation, the resulting intermediate undergoes rapid reaction with diphenyl selenide to form a cationic intermediate.[27] Due to the charged nature of this intermediate, this undergoes a significantly faster reaction with *N*-benzoyl protected *p*-toluidine **1a** to give thioarylated product **3a**, than using iron(III) triflimide as the only activating agent.

The scope of the dual catalytic thioarylation method was then explored with various *N*-benzoyl protected anilines **1a–1g**, bearing a range of substituent patterns (Scheme 3). The process allowed fast *ortho*-thioarylation of most substrates and gave products **3a–3g** in 80–95% yields. The transformation was also effective for thioarylation at hindered *ortho*, *ortho*-substituted positions, producing **3g** after 3 h, in 81% yield. A larger scale reaction was also performed using *N*-benzoyl protected *p*-toluidine **1a**. At 1.5 mmol scale, this gave thioarylated product **3a** in 84% yield, in a similar manner to that of the small-scale reaction (91%). Using the optimised reaction conditions with diphenyl selenide, the scope of the protecting group was further explored. Successful *ortho*-thioarylation reactions were observed with Cbz-, tosyl- and alkyl-protected *p*-toluidines (**1h–1k**), although longer reaction times were required. Attempted thioarylation with less reactive *N*-benzoyl protected anilines bearing conjugated or deactivating aryl substituents under the optimised conditions showed no reaction or gave low yields (<35%). These results were partly attributed to the low solubility of some of the *N*-benzoyl protected anilines in chloroform. To overcome this issue, it was proposed that a more efficient transformation with these substrates may be possible with the unprotected anilines, which were readily soluble in chloroform. Despite the aforementioned issues associated with reaction of unprotected anilines with activated *N*-thiosuccinimides, treatment of *N*-(2-bromophenylthio)succinimide (**2**) with *p*-toluidine (**1l**), 4-phenylaniline (**1m**), 2-aminonaphthalene (**1n**) and 4-chloroaniline (**1o**) resulted in clean reactions and gave the products in moderate to high yields (42–75%). We believe that a combination of the relatively bulky *N*-thiosuccinimide reagent **2** and the less nucleophilic nature of the amine moiety of substrates **1m–1o** allowed a chemoselective, thioarylation reaction of these anilines. A limitation of this transformation is that anilines with strong electron-withdrawing groups are not substrates for this transformation. For example, 4-aminoacetophenone and 4-aminobenzonitrile showed no reaction under the optimised conditions after 24 h.

Having optimised a dual catalytic thioarylation process to access a range of biaryl sulfides (**3**), cyclisation to the desired phenothiazine targets was then investigated (Scheme 4). For *N*-benzoyl-protected derivatives (**3a–3g**), copper-catalysed Ullmann–Goldberg type cyclisation using a combination of copper(I) iodide and DMEDA under basic conditions proved effective.[28] While in some cases, long reaction times were



Scheme 4 Synthesis of phenothiazines. Reaction conditions for copper-catalysed cyclisation: **3** (0.07 to 0.18 mmol), Cs_2CO_3 (2.0 equiv.), 0.4 M in arene. Reaction conditions for palladium-catalysed cyclisation: **3** (0.10 to 0.39 mmol), NaO^{t}Bu (2.0 equiv.), 0.33 M in arene. [a]Reaction was performed at 150 °C. [b]Reaction was done using *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (10 mol%) instead of DMEDA.



Scheme 5 Synthesis of methopromazine.

required, this gave the majority of phenothiazine products in good yields. These conditions were found to be non-compatible with Cbz- (**3h**) and tosyl-protected derivatives (**3i**), with debrominated and deprotected by-products identified from the crude reaction mixtures. Instead, the use of racemic *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine,[29] to facilitate a ligand-assisted, copper-catalysed cyclisation was more effective. This permitted faster access to phenothiazines **4h** and **4i** in 76% and 75% yields, respectively.

Attempted copper-catalysed cyclisation of *N*-alkyl or unprotected *ortho*-thiolated anilines **3j–3o** returned only starting material. The inability of these compounds to cyclise under these conditions is likely due to strong coordination with the copper catalyst. Instead, substrates **3j–3o** were cyclised to the corresponding phenothiazines using a palladium(0)-catalysed Buchwald–Hartwig reaction (Scheme 4).[30] Under standard conditions,[31] using $Pd_2(dba)_3$ (5 mol%) and BINAP as a ligand, fast and efficient cyclisation to phenothiazines **4j–4o** was observed. In particular, cyclisation of **3m–3o** required reaction times of 4 h and gave phenothiazines **4m–4o** in 82–87% yield.

Finally, the synthetic utility of this two-step approach was demonstrated with a short synthesis of methopromazine, a neuroleptic agent with antipsychotic activity.[32] *N*-Benzoyl protected 3-methoxyaniline **5** was chosen as the starting material for this synthesis (Scheme 5). While both substituents are activating, it was proposed that the stronger electron donating methoxy group would promote reaction at the C6-position.[33,34] Thioarylation of **5** using *N*-(2-bromophenylthio)succinimide (**2**) at 90 °C and a reaction time of 3 h gave **6** in 54% yield. However, the 4,6-dithioarylated product was also observed from the ^{1}H NMR spectrum of the crude reaction mixture and therefore a lower temperature reaction was investigated to minimise side-product formation. At 75 °C, the reaction was completed in a similar reaction time of 4 h and gave **6** in an improved 64% yield. Ullmann–Goldberg cyclisation of **6** using copper(I) iodide and DMEDA gave phenothiazine **7** in 80% yield. The benzoyl protecting was then removed using hydrazine hydrate.[35] Finally, alkylation with the commercially available hydrochloride salt of 3-dimethylaminopropyl chloride using sodium hydride as base completed the four-step synthesis of methopromazine.

Conclusions

In summary, a new approach for the synthesis of phenothiazines has been developed using a dual catalytic thioarylation of anilines as the key step. A combination of the Lewis acid, iron(III) triflimide and the Lewis base, diphenyl selenide permitted rapid and efficient thioarylation of *N*-benzoyl anilines. Ullmann–Goldberg cyclisation of the resulting diaryl sulfides completed the synthesis of a small library of phenothiazines. This straightforward approach was used for a four-step synthesis of the neuroleptic agent, methopromazine. Unprotected anilines and *N*-alkyl derivatives were also substrates for the dual catalytic process and underwent chemoselective thioarylation, rather than *N*-sulfenylation. The products of these reactions were readily cyclised to the corresponding phenothiazines using a Buchwald–Hartwig coupling reaction. Overall, this simple, dual catalytic thioarylation process allowed efficient *ortho*-C–S bond formation of hindered arenes and current work is focused on new applications of this approach for other arene functionalisation reactions.

Experimental

All reagents and starting materials were obtained from commercial sources and used as received. *N*-(2-Bromophenylthio) succinimide (**2**)[22a] and starting materials **1a–1g** and **5**,[36] **1h**,[37] **1i**,[38] **1j** and **1k**,[39] and **1n**[40] were prepared as previously described. Reactions were performed open to air unless otherwise mentioned. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was performed using silica gel 60 (35–70 μm). Aluminium-backed plates pre-coated with silica gel $60F_{254}$ were used for thin layer chromatography and were visualised with a UV lamp or by staining with potassium permanganate. ^1H NMR spectra were recorded on a NMR spectrometer at either 400 or 500 MHz and data are reported as follows: chemical shift in ppm relative to the solvent as internal standard ($CHCl_3$, δ 7.26 ppm; CH_3OH, δ 3.31 ppm; DMSO, δ 2.50), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration). ^{13}C NMR spectra were recorded on a NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as internal standard ($CDCl_3$, δ 77.16 ppm; CD_3OD, δ 49.00 ppm; DMSO-d_6, δ 39.52), multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH_2 or CH_3). Assignment of ^1H and ^{13}C NMR spectra are based on two-dimensional COSY, HSQC, HMBC and DEPT experiments. Infrared spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm^{-1}. Mass spectra were recorded using electron impact or electrospray techniques. HRMS spectra were recorded using dual-focusing magnetic analyser or quadrupole time of flight (Q-TOF) mass spectrometers. Melting points are uncorrected.

General procedure A: preparation of sulfenylated products

Iron(III) trichloride (10 mol%) was dissolved in [BMIM]NTf_2 (30 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (**2**) (1.2 equiv.) in chloroform (0.6 M in arene). The arene (1.0 equiv.) and diphenyl selenide (10 mol%) was then added and the mixture was left to stir at 90 °C, until the reaction was deemed complete. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

(2-Benzoylamino-5-methylphenyl)(2′-bromophenyl)sulfane (3a)

The reaction was performed as described in general procedure A using *N*-(4-methylphenyl)benzamide (**1a**) (61 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 1 : 1) gave (2-benzoylamino-5-methylphenyl) (2′-bromophenyl)sulfane (**3a**) (103 mg, 89%) as a white solid. Mp 105–107 °C; ν_{max}/cm^{-1} (neat) 3379 (NH), 2920 (CH), 1678 (C═O), 1516, 1443, 1304, 1246, 1018, 822; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 6.65 (1H, dd, *J* 7.9, 1.6 Hz, 6′-H), 6.98 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4′-H), 7.10 (1H, ddd, *J* 7.9, 7.4, 1.4 Hz, 5′-H), 7.36–7.44 (3H, m, 4-H, 3″-H and 5″-H), 7.47–7.52 (2H, m, 6-H and 4″-H), 7.54 (1H, dd, *J* 7.9, 1.4 Hz, 3′-H), 7.65–7.69 (2H, m, 2″-H and 6″-H), 8.61 (1H, d, *J* 8.4 Hz, 3-H), 8.95 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 20.8 (CH_3), 119.1 (C), 120.9 (CH), 121.2 (C), 127.1 (2 × CH), 127.3 (CH), 127.4 (CH), 128.4 (CH), 128.9 (2 × CH), 132.0 (CH), 132.6 (CH), 133.1 (CH), 134.7 (C), 134.7 (C), 137.3 (C), 137.5 (CH), 138.0 (C), 165.2 (C); *m*/*z* (ESI) 398.0218 (MH^+. $C_{20}H_{17}{}^{79}BrNOS$ requires 398.0209).

(2-Benzoylamino-4,5-dimethylphenyl)(2′-bromophenyl)sulfane (3b)

The reaction was performed as described in general procedure A using *N*-(3,4-dimethylphenyl)benzamide (**1b**) (66 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 1 : 1) gave (2-benzoylamino-4,5-dimethylphenyl)(2′-bromophenyl)sulfane (**3b**) (96 mg, 80%) as a white solid. Mp 135–140 °C; ν_{max}/cm^{-1} (neat) 3375 (NH), 2916 (CH), 1678 (C═O), 1519, 1442, 1249, 1199, 1018, 752; δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 2.38 (3H, s, CH_3), 6.64 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.97–7.00 (1H, m, 4′-H), 7.08 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5′-H), 7.38–7.43 (3H, m, 6-H, 3″-H and 5″-H), 7.46–7.54 (2H, m, 3′-H and 4″-H), 7.64–7.69 (2H, m, 2″-H and 6″-H), 8.54 (1H, s, 3-H), 8.92 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 19.3 (CH_3), 20.4 (CH_3), 115.8 (C), 121.0 (C), 122.1 (CH), 127.1 (2 × CH), 127.1 (CH), 127.1 (CH), 128.3 (CH), 128.9 (2 × CH), 132.0 (CH), 133.0 (CH), 133.6 (C), 134.8 (C), 137.7 (C), 137.9 (CH), 138.2 (C), 141.3 (C), 165.1 (C); *m*/*z* (ESI) 412.0366 (MH^+. $C_{21}H_{19}{}^{79}BrNOS$ requires 412.0365).

(2-benzoylamino-5-*tert*-butylphenyl)(2′-bromophenyl)sulfane (3c)

The reaction was performed as described in general procedure A using *N*-(4-*tert*-butylphenyl)benzamide (**1c**) (74 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 2) gave (2-benzoylamino-5-*tert*-butylphenyl) (2′-bromophenyl)sulfane (**3c**) (124 mg, 97%) as a white solid. Mp 109–111 °C; ν_{max}/cm^{-1} (neat) 3352 (NH), 2955 (CH), 1678 (C═O), 1505, 1427, 1308, 1022, 841, 752; δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, 3 × CH_3), 6.62 (1H, dd, *J* 8.0, 1.5 Hz, 6′-H), 6.98 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, 4′-H), 7.10 (1H, ddd, *J* 8.0, 7.5, 1.4 Hz, 5′-H), 7.38–7.44 (2H, m, 3″-H and 5″-H), 7.47–7.52 (1H, m, 4″-H), 7.54 (1H, dd, *J* 7.9, 1.4 Hz, 3′-H), 7.60 (1H, dd, *J* 8.7, 2.3

Hz, 4-H), 7.63–7.70 (3H, m, 6-H, 2″-H and 6″-H), 8.63 (1H, d, *J* 8.7 Hz, 3-H), 8.92 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 31.4 (3 × CH_3), 34.7 (C), 118.8 (C), 120.7 (CH), 121.1 (C), 127.1 (2 × CH), 127.1 (CH), 127.2 (CH), 128.4 (CH), 128.9 (2 × CH), 129.1 (CH), 132.0 (CH), 133.1 (CH), 134.1 (CH), 134.8 (C), 137.4 (C), 137.9 (C), 148.2 (C), 165.2 (C); *m*/*z* (ESI) 440.0686 (MH^+. $\text{C}_{23}\text{H}_{23}{}^{79}\text{BrNOS}$ requires 440.0678).

(2-Benzoylamino-4-methoxy-5-methylphenyl)(2′-bromophenyl) sulfane (3d)

The reaction was performed as described in general procedure B using *N*-(3-methoxy-4-methylphenyl)benzamide (**1d**) (70 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 3 h. Purification by flash column chromatography (hexane/dichloromethane, 2 : 3) gave (2-benzoylamino-4-methoxy-5-methylphenyl)(2′-bromophenyl)sulfane (**3d**) (112 mg, 90%) as a white solid. Mp 142–144 °C; ν_max/cm^{-1} (neat) 3379 (NH), 2916 (CH), 1678 (C═O), 1581 (C═C), 1392, 1249, 1168, 1053, 887, 882, 790; δ_H (400 MHz, CDCl_3) 2.22 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 6.61 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.97 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4′-H), 7.09 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5′-H), 7.39–7.45 (3H, m, 3-H, 3″-H and 5″-H), 7.48–7.54 (2H, m, 3′-H and 4″-H), 7.67–7.71 (2H, m, 2″-H and 6″-H), 8.44 (1H, s, 6-H), 9.09 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 15.9 (CH_3), 55.8 (CH_3), 103.0 (CH), 108.3 (C), 120.7 (C), 123.5 (C), 126.9 (CH), 127.0 (CH), 127.1 (2 × CH), 128.3 (CH), 129.0 (2 × CH), 132.1 (CH), 133.0 (CH), 134.7 (C), 138.1 (C), 138.6 (CH), 140.0 (C), 160.5 (C), 165.3 (C); *m*/*z* (ESI) 428.0317 (MH^+. $\text{C}_{21}\text{H}_{19}{}^{79}\text{BrNO}_2\text{S}$ requires 428.0314).

(2-Benzoylamino-4,5-dimethoxyphenyl)(2′-bromophenyl) sulfane (3e)

The reaction was performed as described in general procedure A using *N*-(3,4-dimethoxyphenyl)benzamide (**1e**) (75 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 3 h. Purification by flash column chromatography (hexane/ethyl acetate, 4 : 1) gave (2-benzoylamino-4,5-dimethoxyphenyl)(2′-bromophenyl)sulfane (**3e**) (120 mg, 93%) as a pale-yellow solid. Mp 119–120 °C; ν_max/cm^{-1} (neat) 3329 (NH), 2943 (CH), 1659 (CO), 1586 (C═C), 1516, 1439, 1250, 1204, 1045, 868; δ_H (400 MHz, CDCl_3) 3.89 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.61 (1H, dd, *J* 8.0, 1.5 Hz, 6′-H), 6.98 (1H, td, *J* 7.7, 1.5 Hz, 4′-H), 7.08–7.13 (2H, m, 6-H and 5′-H), 7.40–7.45 (2H, m, 3″-H and 5″-H), 7.48–7.52 (1H, m, 4″-H), 7.54 (1H, dd, *J* 7.7, 1.3 Hz, 3′-H), 7.66–7.70 (2H, m, 2″-H and 6″-H), 8.52 (1H, s, 3-H), 8.97 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 56.3 (CH_3), 56.4 (CH_3), 104.7 (CH), 108.6 (C), 118.9 (CH), 120.7 (C), 126.8 (CH), 127.0 (2 × CH), 127.2 (CH), 128.4 (CH), 129.0 (2 × CH), 132.1 (CH), 133.1 (CH), 134.7 (C), 135.6 (C), 137.8 (C) 145.8 (C), 151.7 (C), 165.2 (C); *m*/*z* (ESI) 444.0273 (MH^+. $\text{C}_{21}\text{H}_{19}{}^{79}\text{BrNO}_3\text{S}$ requires 444.0264).

(2-Benzoylamino-4,5-methylenedioxyphenyl)(2′-bromophenyl) sulfane (3f)

The reaction was performed as described in general procedure A using *N*-(3,4-methylenedioxyphenyl)benzamide (**1f**) (70 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 7) gave (2-benzoylamino-4,5-methylenedioxyphenyl)(2′-bromophenyl)sulfane (**3f**) (99 mg, 79%) as a white solid. Mp 160–161 °C; ν_max/cm^{-1} (neat) 3375 (NH), 1670 (C═O), 1516 (C═C), 1465 (C═C), 1238, 1176, 1030, 933, 879; δ_H (400 MHz, CDCl_3) 6.07 (2H, s, OCH_2O), 6.69 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.99 (1H, ddd, *J* 8.0, 7.5, 1.6 Hz, 4′-H), 7.09 (1H, s, 6-H), 7.12 (1H, ddd, *J* 8.0, 7.5, 1.4 Hz, 5′-H), 7.39–7.44 (2H, m, 3″-H and 5″-H), 7.48–7.55 (2H, m, 3′-H and 4″-H), 7.65–7.70 (2H, m, 2″-H and 6″-H), 8.36 (1H, s, 3-H), 9.00 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 102.2 (CH_2), 102.9 (CH), 110.2 (C), 115.8 (CH), 121.0 (C), 127.0 (CH), 127.1 (2 × CH), 127.3 (CH), 128.4 (CH), 128.9 (2 × CH), 132.1 (CH), 133.1 (CH), 134.6 (C), 136.3 (C), 137.5 (C), 144.3 (C), 150.6 (C), 165.0 (C); *m*/*z* (ESI) 427.9950 (MH^+. $\text{C}_{20}\text{H}_{15}{}^{79}\text{BrNO}_3\text{S}$ requires 427.9951).

(2-Benzoylamino-4,5,6-trimethoxyphenyl)(2′-bromophenyl) sulfane (3g)

The reaction was performed as described in general procedure A using *N*-(3,4,5-trimethoxyphenyl)benzamide (**1g**) (84 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 3 h. Purification by flash column chromatography (hexane/ethyl acetate, 4 : 1) gave (2-benzoylamino-4,5,6-trimethoxyphenyl)(2′-bromophenyl)sulfane (**3g**) (112 mg, 81%) as a white solid. Mp 134–137 °C; ν_max/cm^{-1} (neat) 3352 (NH), 2936 (CH), 1663 (C═O), 1582 (C═C), 1512, 1442, 1288, 1111, 1015, 930; δ_H (400 MHz, CDCl_3) 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 6.65 (1H, dd, *J* 8.0, 1.5 Hz, 6′-H), 6.98 (1H, ddd, *J* 7.9, 7.4, 1.5 Hz, 4′-H), 7.10 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5′-H), 7.40–7.46 (2H, m, 3″-H and 5″-H), 7.49–7.55 (2H, m, 3′-H and 4″-H), 7.70–7.75 (2H, m, 2″-H and 6″-H), 8.36 (1H, s, 3-H), 9.28 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 56.3 (CH_3), 61.3 (CH_3), 62.0 (CH_3), 100.3 (CH), 104.5 (C), 121.1 (C), 126.8 (CH), 127.1 (2 × CH), 127.1 (CH), 128.3 (CH), 129.0 (2 × CH), 132.2 (CH), 133.1 (CH), 134.6 (C), 137.6 (C), 137.6 (C), 139.1 (C), 155.8 (C), 156.4 (C), 165.4 (C); *m*/*z* (ESI) 474.0377 (MH^+. $\text{C}_{22}\text{H}_{20}{}^{79}\text{BrNO}_4\text{S}$ requires 474.0369).

[2-(Benzyloxycarbonyl)amino-5-methylphenyl](2′-bromophenyl)sulfane (3h)

The reaction was performed as described in general procedure A using benzyl-*p*-tolylcarbamate (**1h**) (70 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 7 : 3) gave [2-(benzyloxycarbonyl)amino-5-methylphenyl](2′-bromophenyl)sulfane (**3h**) (91 mg, 73%) as a yellow solid. Mp 84–86 °C; ν_max/cm^{-1} (neat) 3381 (NH), 2945 (CH), 1732 (C═O), 1519 (C═C), 1443, 1219, 1049, 824, 740; δ_H (400 MHz, CDCl_3) 2.24 (3H, s, CH_3), 5.07 (2H, s, $\text{PhC}H_2$), 6.45 (1H, dd, *J* 7.7, 1.5 Hz, 6′-H), 6.91 (1H, td, *J* 7.7, 1.5 Hz, 4′-H), 7.00 (1H, td, *J* 7.7, 1.4 Hz, 5′-H), 7.17–7.29 (6H, m, 4-H and Ph), 7.31 (1H, d, *J* 1.6 Hz, 6-H), 7.44 (1H, dd, *J* 7.7, 1.4 Hz, 3′-H), 7.56 (1H, br s, NH), 8.10 (1H, d, *J* 8.4 Hz, 3-H); δ_C (101 MHz, CDCl_3) 20.6 (CH_3), 67.1 (CH_2), 118.1 (C), 119.6 (CH), 121.2 (C), 126.9 (CH), 127.0 (CH), 128.2 (CH), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 132.6 (CH), 133.1 (CH), 133.9 (C), 136.1 (C), 137.6 (CH), 137.8 (C), 138.3 (C), 153.4 (C); *m*/*z* (ESI) 428.0312 (MH^+. $C_{21}H_{19}{}^{79}BrNO_2S$ requires 428.0314).

[2(4″-Methylphenylsulfonyl)amino-5-methylphenyl](2′-bromophenyl)sulfane (3i)

The reaction was performed as described in general procedure A using *N*-(4-methylphenyl)-*p*-toluenesulfonamide (**1i**) (76 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 2) gave [2-(4-methylphenylsulfonyl)amino-5-methylphenyl](2′-bromophenyl)sulfane (**3i**) (65 mg, 50%) as a white solid. Mp 108–110 °C; ν_{max}/cm^{-1} (neat) 3212 (NH), 2918 (CH), 1486, 1340, 1185, 1019, 806, 677; δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, CH_3), 2.35 (3H, s, CH_3), 6.23 (1H, dd, *J* 7.8, 1.6 Hz, 6′-H), 6.92 (1H, ddd, *J* 7.8, 7.4, 1.5 Hz, 5′-H), 6.98 (1H, dd, *J* 7.8, 7.4, 1.6 Hz, 4′-H), 7.09–7.13 (2H, m, 3″-H and 5″-H), 7.20–7.26 (2H, m, 4-H and 6-H), 7.49 (1H, br s, NH), 7.51 (1H, dd, *J* 7.8, 1.5 Hz, 3′-H), 7.55–7.60 (2H, m, 2″-H and 6″-H), 7.70 (1H, d, *J* 8.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 21.7 (CH_3), 120.4 (CH), 121.4 (C), 127.0 (CH), 127.2 (CH), 127.2 (C), 127.4 (2 × CH), 128.1 (CH), 129.7 (2 × CH), 132.6 (CH), 133.1 (CH), 135.4 (C), 136.0 (C), 137.3 (C), 137.4 (C), 137.9 (CH), 144.0 (C); *m*/*z* (ESI) 469.9852 (MNa^+. $C_{20}H_{18}{}^{79}BrNNaO_2S_2$ requires 469.9855).

(2-Methylamino-5-methylphenyl)(2′-bromophenyl)sulfane (3j)

The reaction was performed as described in general procedure A using *N*-methyl-*p*-toluidine (**1j**) (35 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 9 : 1) gave (2-methylamino-5-methylphenyl)(2′-bromophenyl)sulfane (**3j**) (59 mg, 66%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3395 (NH), 2909 (CH), 1605 (C=C), 1512, 1443, 1312, 1169, 1018, 745; δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 2.81 (3H, d, *J* 4.9 Hz, $NHCH_3$), 4.73 (1H, q, *J* 4.9 Hz, $NHCH_3$), 6.56 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.63 (1H, d, *J* 8.3 Hz, 3-H), 6.95 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4′-H), 7.08 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5′-H), 7.21 (1H, dd, *J* 8.3, 2.1 Hz, 4-H), 7.30 (1H, d, *J* 2.1 Hz, 6-H), 7.51 (1H, dd, *J* 7.9, 1.4 Hz, 3′-H); δ_C (101 MHz, $CDCl_3$) 20.2 (CH_3), 30.8 (CH_3), 110.5 (CH), 112.4 (C), 120.7 (C), 126.2 (CH), 126.2 (CH), 126.4 (C), 127.9 (CH), 132.8 (CH), 132.9 (CH), 138.3 (CH), 138.5 (C), 148.9 (C); *m*/*z* (ESI) 329.9929 (MNa^+. $C_{14}H_{14}{}^{79}BrNNaS$ requires 329.9923).

(2-Benzylamino-5-methylphenyl)(2′-bromophenyl)sulfane (3k)

The reaction was performed as described in general procedure A using *N*-benzyl-*p*-toluidine (**1k**) (57 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 9 : 1) gave (2-benzylamino-5-methylphenyl)(2′-bromophenyl)sulfane (**3k**) (66 mg, 59%) as a yellow solid. Mp 72–75 °C; ν_{max}/cm^{-1} (neat) 3403 (NH), 2897 (CH), 1605 (C=C), 1508, 1443, 1316, 1015, 806, 748; δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 4.34 (2H, d, *J* 5.8 Hz, $PhCH_2$), 5.24 (1H, t, *J* 5.8 Hz, NH), 6.56 (1H, d, *J* 8.3 Hz, 3-H), 6.64 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.98 (1H, ddd, *J* 7.8, 7.4, 1.6 Hz, 4′-H), 7.07–7.29 (7H, m, 4-H, 5′-H and Ph), 7.32 (1H, d, *J* 1.8 Hz, 6-H), 7.51 (1H, dd, *J* 7.8, 1.3 Hz, 3′-H); δ_C (101 MHz, $CDCl_3$) 20.2 (CH_3), 47.8 (CH_2), 111.4 (CH), 112.9 (C), 121.0 (C), 126.4 (CH), 126.7 (CH), 126.8 (C), 127.0 (2 × CH), 127.2 (CH), 127.8 (CH), 128.7 (2 × CH), 132.8 (CH), 132.9 (CH), 138.3 (CH), 138.4 (C), 139.3 (C), 147.4 (C); *m*/*z* (ESI) 406.0239 (MNa^+. $C_{20}H_{18}{}^{79}BrNNaS$ requires 406.0236).

(2-Amino-5-methylphenyl)(2′-bromophenyl)sulfane (3l).[25f]

The reaction was performed as described in general procedure A using *p*-toluidine (**1l**) (31 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 7 : 3) gave (2-amino-5-methylphenyl)(2′-bromophenyl)sulfane (**3l**) (46 mg, 53%) as a white solid. Mp 83–86 °C (lit.[25f] 82–84 °C); δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 4.16 (2H, br s, NH_2), 6.63 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.75 (1H, d, *J* 8.2 Hz, 3-H), 6.97 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4′-H), 7.08–7.12 (2H, m, 4-H and 5′-H), 7.29 (1H, d, *J* 2.0 Hz, 6-H), 7.52 (1H, dd, *J* 7.9, 1.4 Hz, 3′-H); δ_C (101 MHz, $CDCl_3$) 20.3 (CH_3), 113.2 (C), 115.7 (CH), 120.8 (C), 126.3 (CH), 126.4 (CH), 127.9 (CH), 128.5 (C), 132.7 (CH), 132.9 (CH), 138.0 (CH), 138.3 (C), 146.9 (C); *m*/*z* (ESI) 294 (MH^+. 100%).

(2-Amino-5-biphenyl)(2′-bromophenyl)sulfane (3m)

The reaction was performed as described in general procedure A using 4-aminobiphenyl (**1m**) (99 mg, 0.58 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 2) gave (2-amino-5-biphenyl)(2′-bromophenyl)sulfane (**3m**) (113 mg, 55%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3371 (NH), 3024 (CH), 1613 (C=C), 1477, 1443, 1157, 1018, 745; δ_H (400 MHz, $CDCl_3$) 4.37 (2H, br s, NH_2), 6.72 (1H, dd, *J* 8.0, 1.6 Hz, 6′-H), 6.91 (1H, d, *J* 8.4 Hz, 3-H), 6.99 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4′-H), 7.12 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5′-H), 7.27–7.32 (1H, m, 4″-H), 7.39–7.44 (2H, m, 3″-H and 5″-H), 7.53–7.59 (4H, m, 4-H, 3′-H, 2″-H and 6″-H), 7.77 (1H, d, *J* 2.2 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 113.7 (C), 115.9 (CH), 120.9 (C), 126.4 (2 × CH), 126.4 (CH), 126.5 (CH), 126.8 (CH), 128.0 (CH), 128.9 (2 × CH), 130.5 (CH), 132.2 (C), 133.0 (CH), 136.3 (CH), 138.0 (C), 140.1 (C), 148.6 (C); *m*/*z* (ESI) 356.0109 (MH^+. $C_{18}H_{15}{}^{79}BrNS$ requires 356.0103).

1-(2′-Bromophenylthio)-2-aminonaphthalene (3n)[41]

The reaction was performed as described in general procedure A using 2-aminonaphthalene (**1n**) (83 mg, 0.58 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 7 : 3) gave 1-(2′-bromophenylthio)-2-aminonaphthalene (**3n**) (142 mg, 75%) as an orange solid. Mp 125–127 °C; Spectroscopic data were consistent with the literature.[41] δ_H (400 MHz, $CDCl_3$) 4.72 (2H, br s, NH_2), 6.37–6.46 (1H, m, 8-H), 6.90–6.98 (2H, m, 6-H and 7-H), 7.07 (1H, d, *J* 8.7 Hz, 3-H), 7.29 (1H, ddd, *J* 8.0, 6.9, 1.2 Hz, 5′-H), 7.45 (1H, ddd, *J* 8.4, 6.9, 1.3 Hz, 4′-H), 7.50–7.57 (1H, m, 5-H), 7.74 (1H, dd, *J* 8.0, 1.3 Hz, 6′-H), 7.80 (1H, d, *J* 8.7 Hz, 4-H), 8.19 (1H, dd, *J* 8.4, 1.2 Hz, 3′-H); δ_C (101 MHz, $CDCl_3$) 103.7 (C), 117.8 (CH), 121.1 (C), 122.9 (CH), 124.1 (CH), 126.1 (CH), 126.2 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 128.6 (C), 132.4 (CH), 132.9 (CH), 136.6 (C), 137.7 (C), 148.8 (C); *m*/*z* (ESI) 330 (MH^+. 100%).

(2-Amino-5-chloro)(2′-bromophenyl)sulfane (3o)

The reaction was performed as described in general procedure A using 4-chloroaniline (**1o**) (37 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 7 : 3) gave (2-amino-5-chloro)(2′-bromophenyl)sulfane (**3o**) (38 mg, 42%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3372 (NH), 3055 (CH), 1609 (C=C), 1474, 1442, 1296, 1103, 1018, 745; δ_H (400 MHz, $CDCl_3$) 4.30 (2H, br s, NH_2), 6.65 (1H, dd, *J* 8.0, 1.5 Hz, 6′-H), 6.75 (1H, d, *J* 8.6 Hz, 3-H), 7.00 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, 4′-H), 7.13 (1H, ddd, *J* 8.0, 7.5, 1.3 Hz, 5′-H), 7.23 (1H, dd, *J* 8.6, 2.5 Hz, 4-H), 7.45 (1H, d, *J* 2.5 Hz, 6-H), 7.53 (1H, dd, *J* 7.9, 1.3 Hz, 3′-H); δ_C (101 MHz, $CDCl_3$) 114.7 (C), 116.5 (CH), 121.1 (C), 122.8 (C), 126.6 (CH), 126.8 (CH), 128.0 (CH), 131.8 (CH), 133.1 (CH), 136.8 (CH), 137.2 (C), 147.9 (C); *m*/*z* (ESI) 313.9401 (MH^+. $C_{12}H_{10}{}^{79}BrClNS$ requires 313.9400).

General procedure B: copper catalysed synthesis of phenothiazines

To a solution of biaryl sulfide (1.0 equiv.) in toluene (0.4 M in arene) was added copper(I) iodide (10 mol%), cesium carbonate (2.0 equiv.), *N*,*N*′-dimethylethylenediamine (20 mol%) and water (1 M in arene). The mixture was purged with nitrogen and then heated to 130 °C or 150 °C, until the reaction was deemed complete. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous solution of sodium thiosulfate solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting material was purified by flash column chromatography.

N-Benzoyl-3-methylphenothiazine (4a)

The reaction was performed as described in general procedure B using (2-benzoylamino-5-methylphenyl)(2′-bromophenyl) sulfane (**3a**) (32 mg, 0.080 mmol). The reaction mixture was stirred at 130 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 2 : 3) gave *N*-benzoyl-3-methylphenothiazine (**4a**) (22 mg, 86%) as a white solid. Mp 123–125 °C; ν_{max}/cm^{-1} (neat) 2916 (CH), 1667 (C=O), 1462, 1319, 1258, 1111, 810, 760; δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, 3-CH_3), 6.95 (1H, dd, *J* 8.2, 1.9 Hz, 2-H), 7.11–7.17 (2H, m, 6-H and 8-H), 7.19–7.33 (5H, m, 1-H, 4-H, 3′-H, 4′-H and 5′-H), 7.35–7.46 (4H, m, 7-H, 9-H, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.0 (CH_3), 126.5 (CH), 126.8 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CH), 127.8 (CH), 128.1 (2 × CH), 128.2 (CH), 129.0 (2 × CH), 130.4 (CH), 132.0 (C), 132.4 (C), 135.5 (C), 136.6 (C), 137.1 (C), 139.8 (C), 169.0 (C); *m*/*z* (ESI) 318.0954 (MH^+. $C_{20}H_{16}NOS$ requires 318.0947).

N-Benzoyl-2,3-dimethylphenothiazine (4b)

The reaction was performed as described in general procedure B using (2-benzoylamino-4,5-dimethylphenyl)(2′-bromophenyl) sulfane (**3b**) (30 mg, 0.072 mmol). The reaction mixture was stirred at 150 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 2) gave *N*-benzoyl-2,3-dimethylphenothiazine (**4b**) (15 mg, 65%) as a white solid. Mp 170–171 °C; ν_{max}/cm^{-1} (neat) 2916 (CH), 1678 (C=O), 1492, 1392, 1246, 1014, 883, 794; δ_H (400 MHz, $CDCl_3$) 2.14 (3H, s, CH_3), 2.21 (3H, s, CH_3), 7.05–7.13 (2H, m, 6-H and 8-H), 7.19–7.22 (3H, m, 4-H, 3′-H and 5′-H), 7.26–7.31 (3H, m, 1-H, 7-H and 4′-H), 7.35–7.37 (2H, m, 2′-H and 6′-H), 7.42 (1H, dd, *J* 7.6, 1.8 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 19.5 (CH_3), 19.6 (CH_3), 126.4 (CH), 126.8 (CH), 127.2 (CH), 127.8 (CH), 128.0 (2 × CH), 128.1 (CH), 128.4 (CH), 128.8 (C), 128.9 (2 × CH), 130.3 (CH), 132.9 (C), 135.3 (C), 135.6 (C), 135.8 (C), 137.1 (C), 140.0 (C), 169.0 (C); *m*/*z* (ESI) 332.1111 (MH^+. $C_{21}H_{18}NOS$ requires 332.1104).

N-Benzoyl-3-*tert*-butylphenothiazine (4c)

The reaction was performed as described in general procedure B using (2-benzoylamino-5-*tert*-butylphenyl)(2′-bromophenyl)sulfane (**3c**) (80 mg, 0.18 mmol). The reaction mixture was stirred at 130 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 1 : 1) gave *N*-benzoyl-3-*tert*-butylphenothiazine (**4c**) (50 mg, 77%) as a white solid. Mp 123–124 °C; ν_{max}/cm^{-1} (neat) 2963 (CH), 1651 (C=O), 1462, 1323, 1258, 1115, 880, 756; δ_H (400 MHz, $CDCl_3$) 1.30 (9H, s, 3 × CH_3), 7.07–7.16 (2H, m, 7-H and 8-H), 7.18–7.24 (3H, m, 2-H, 3′-H and 5′-H), 7.26–7.33 (2H, m, 6-H and 4′-H), 7.36–7.40 (2H, m, 2′-H and 6′-H), 7.42–7.47 (3H, m, 1-H, 4-H and 9-H); δ_C (101 MHz, $CDCl_3$) 31.4 (3 × CH_3), 34.8 (C), 124.3 (CH), 124.6 (CH), 126.4 (CH), 126.6 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CH), 128.0 (2 × CH), 129.0 (2 × CH), 130.4 (CH), 131.6 (C), 132.6 (C), 135.5 (C), 136.8 (C), 139.9 (C), 150.0 (C), 169.0 (C); *m*/*z* (ESI) 360.1425 (MH^+. $C_{23}H_{22}NOS$ requires 360.1417).

N-Benzoyl-2-methoxy-3-methylphenothiazine (4d)

The reaction was performed as described in general procedure B using (2-benzoylamino-4-methoxy-5-methylphenyl)(2′-bromophenyl)sulfane (**3d**) (60 mg, 0.14 mmol). The reaction mixture was stirred at 130 °C for 96 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 7) gave *N*-benzoyl-2-methoxy-3-methylphenothiazine (**4d**) (52 mg, 80%) as a white solid. Mp 180–181 °C; ν_{max}/cm^{-1} (neat) 3050 (CH), 1654 (C=O), 1462, 1338, 1249, 1057, 756, 706; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, 3-CH_3), 3.62 (3H, s, 2-OCH_3), 6.91 (1H, s, 4-H), 7.10–7.17 (3H, m, 1-H, 7-H and 8-H), 7.21–7.25 (2H, m, 3′-H and 5′-H), 7.29–7.34 (1H, m, 4′-H), 7.37–7.44 (4H, m, 6-H, 9-H, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 16.0 (CH_3), 55.7 (CH_3), 109.9 (CH), 122.1 (C), 125.7 (C), 126.4 (CH), 126.7 (CH), 127.1 (CH), 127.7 (CH), 128.1 (2 × CH), 128.8 (CH) 128.8 (2 × CH), 130.4 (CH), 133.2 (C), 135.6 (C), 138.3 (C), 139.7 (C), 156.9 (C), 169.1 (C); *m*/*z* (ESI) 348.1060 (MH^+. $C_{21}H_{18}NO_2S$ requires 348.1053).

N-Benzoyl-2,3-dimethoxyphenothiazine (4e)

The reaction was performed as described in general procedure B using (2-benzoylamino-4,5-dimethoxyphenyl)(2′-bromophenyl)sulfane (**3e**) (50 mg, 0.11 mmol). The reaction mixture was stirred at 130 °C for 24 h. Purification by flash column chromatography (hexane/diethyl ether, 3 : 2) gave *N*-benzoyl-2,3-dimethoxyphenothiazine (**4e**) (34 mg, 83%) as a white solid. Mp 112–114 °C; ν_{max}/cm^{-1} (neat) 2936 (CH), 1663 (C═O), 1501, 1443, 1308, 1261, 1026, 849; δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.89 (1H, s, 4-H), 6.92 (1H, s, 1-H), 7.12–7.18 (2H, m, 6-H and 8-H), 7.20–7.25 (2H, m, 3′-H and 5′-H), 7.29–7.33 (1H, m, 4′-H), 7.35–7.46 (4H, m, 7-H, 9-H, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 56.2 (CH_3), 56.3 (CH_3), 109.9 (CH), 111.1 (CH), 123.0 (C), 126.4 (CH), 126.9 (CH), 127.1 (CH), 127.7 (CH), 128.2 (2 × CH), 128.8 (2 × CH), 130.4 (CH), 132.7 (C), 132.8 (C), 135.6 (C), 139.8 (C), 147.6 (C), 148.1 (C), 169.1 (C); *m*/*z* (ESI) 364.1011 (MH^+. $C_{21}H_{18}NO_3S$ requires 364.1002).

N-Benzoyl-2,3-methylenedioxyphenothiazine (4f)

The reaction was performed as described in general procedure B using (2-benzoylamino-4,5-methylenedioxyphenyl)(2′-bromophenyl)sulfane (**3f**) (79 mg, 0.18 mmol). The reaction mixture was stirred at 150 °C for 72 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 7) gave *N*-benzoyl-2,3-methylenedioxyphenothiazine (**4f**) (44 mg, 69%) as a white solid. Mp 185–187 °C; ν_{max}/cm^{-1} (neat) 3055 (CH), 1647 (C═O), 1462, 1327, 1238, 1030, 922, 860, 806; δ_H (400 MHz, $CDCl_3$) 5.95 (2H, s, OCH_2O), 6.87 (1H, s, 4-H), 7.03 (1H, s, 1-H), 7.09 (1H, td, *J* 7.6, 1.4 Hz, 8-H), 7.14 (1H, td, *J* 7.6, 1.4 Hz, 7-H), 7.21–7.25 (3H, m, 6-H, 3′-H and 5′-H), 7.32 (1H, tt, *J* 7.4, 1.2 Hz, 4′-H), 7.35–7.38 (2H, m, 2′-H and 6′-H), 7.43 (1H, dd, *J* 7.6, 1.4 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 102.1 (CH_2), 107.4 (CH), 108.6 (CH), 124.8 (C), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.7 (CH), 128.2 (2 × CH), 128.9 (2 × CH), 130.5 (CH), 133.2 (C), 133.6 (C), 135.3 (C), 140.1 (C), 146.3 (C), 147.3 (C), 169.0 (C); *m*/*z* (ESI) 348.0691 (MH^+. $C_{20}H_{14}NO_3S$ requires 348.0689).

N-Benzoyl-2,3,4-trimethoxyphenothiazine (4g)

The reaction was performed as described in general procedure B using (2-benzoylamino-4,5,6-trimethoxyphenyl)(2′-bromophenyl)sulfane (**3g**) (50 mg, 0.11 mmol). The reaction mixture was stirred at 130 °C for 48 h. Purification by flash column chromatography (hexane/ethyl acetate, 4 : 1) gave *N*-benzoyl-2,3,4-trimethoxyphenothiazine (**4g**) (22 mg, 53%) as a white solid. Mp 111–113 °C; ν_{max}/cm^{-1} (neat) 2936 (CH), 1659 (C═O), 1447, 1308, 1242, 1107, 926, 745; δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.86 (1H, s, 1-H), 7.08–7.16 (2H, m, 7-H and 8-H), 7.20–7.39 (6H, m, 6-H and Ph), 7.46 (1H, dd, *J* 7.5, 1.6 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 56.4 (CH_3), 61.3 (CH_3), 61.4 (CH_3), 107.5 (CH), 118.0 (C), 126.5 (CH), 126.9 (CH), 127.1 (CH), 128.0 (CH), 128.1 (2 × CH), 128.8 (2 × CH), 130.5 (CH), 132.5 (C), 134.7 (C) 135.5 (C), 139.7 (C), 140.8 (C), 149.6 (C), 152.5 (C), 169.2 (C); *m*/*z* (ESI) 394.1117 (MH^+. $C_{22}H_{20}NO_4S$ requires 394.1108).

N-Benzyloxycarbonyl-3-methylphenothiazine (4h)

The reaction was performed as described in general procedure B using ([2-(benzyloxycarbonyl)amino-5-methylphenyl](2′-bromophenyl)sulfane (**3h**) (50 mg, 0.12 mmol) and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (3.7 μL, 23 mol%) instead of *N*,*N*′-dimethylethylenediamine. The reaction mixture was stirred at 130 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 2) gave *N*-benzyloxycarbonyl-3-methylphenothiazine (**4h**) (31 mg, 76%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2952 (CH), 1711 (C═O), 1469, 1318, 1216, 1093, 748; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, 3-CH_3), 5.26 (2H, s, PhCH_2), 7.08 (1H, dd, *J* 8.2, 1.3 Hz, 2-H), 7.14–7.20 (2H, m, 4-H and 7-H), 7.27 (1H, ddd, *J* 8.0, 7.5, 1.5 Hz, 8-H), 7.30–7.39 (6H, m, 6-H and Ph), 7.42 (1H, d, *J* 8.2 Hz, 1-H) 7.54 (1H, dd, *J* 8.0, 1.0 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 21.0 (CH_3), 68.1 (CH_2), 126.5 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 127.7 (CH), 127.8 (CH), 127.9 (2 × CH), 128.0 (CH), 128.2 (CH), 128.6 (2 × CH), 132.0 (C), 132.4 (C), 135.8 (C), 136.1 (C), 136.6 (C), 138.6 (C), 153.8 (C); *m*/*z* (ESI) 348.1052 (MH^+. $C_{21}H_{18}NO_2S$ requires 348.1053).

N-(4′-Methylphenylsulfonyl)-3-methylphenothiazine (4i)

The reaction was performed as described in general procedure B using [2-(4-methylphenylsulfonyl)amino-5-methylphenyl](2′-bromophenyl)sulfane (**3i**) (39 mg, 0.087 mmol) and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (2.7 μL, 20 mol%) instead of *N*,*N*′-dimethylethylenediamine. The reaction mixture was stirred at 130 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3 : 2) gave *N*-(4′-methylphenylsulfonyl)-3-methylphenothiazine (**4i**) (24 mg, 75%) as a yellow solid. Mp 146–148 °C; ν_{max}/cm^{-1} (neat) 2920 (CH), 1597 (C═C), 1447, 1354, 1165, 922, 760; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, 3-CH_3), 2.37 (3H, s, 4′-CH_3), 6.92 (1H, d, *J* 1.1 Hz, 4-H), 7.05 (2H, d, *J* 8.1 Hz, 3′-H and 5′-H), 7.08–7.16 (4H, m, 2-H, 6-H, 2′-H and 6′-H), 7.20 (1H, td, *J* 7.5, 1.3 Hz, 7-H), 7.32 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, 8-H), 7.61 (1H, d, *J* 8.2 Hz, 1-H), 7.73 (1H, dd, *J* 7.9, 1.3 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 21.1 (CH_3), 21.8 (CH_3), 127.0 (CH), 127.2 (CH), 127.3 (CH), 127.7 (CH), 127.8 (2 × CH), 128.2 (CH), 129.4 (2 × CH), 129.8 (CH), 130.1 (CH), 132.8 (C), 133.3 (C), 133.5 (C), 136.2 (C), 136.3 (C), 138.0 (C), 144.1 (C); *m*/*z* (ESI) 402.0395 (MCl^-. $C_{20}H_{17}{}^{35}ClNO_2S_2$ requires 402.0395).

General procedure C: palladium catalysed synthesis of phenothiazines

To a solution of biaryl sulfide (1.0 equiv.) in toluene (0.33 M in arene) was added $Pd_2(dba)_3$ (5 mol%) and (*S*)-BINAP (10 mol%). The reaction mixture was purged with nitrogen and sodium *tert*-butoxide (2.0 equiv.) was added. The mixture was then heated at 110 °C, until the reaction was deemed complete. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added before being filtered through Celite and washed with dichloromethane (10 mL). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The resulting material was purified by flash column chromatography.

3,10-Dimethylphenothiazine (4j).[20c]

The reaction was performed as described in general procedure C using (2-methylamino-5-methylphenyl)(2′-bromophenyl) (**3j**) (48 mg, 0.16 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 9 : 1) gave 3,10-dimethylphenothiazine (**4j**) (30 mg, 86%) as a white solid. Mp 143–145 °C (lit.[20c] 145–146 °C); δ_H (400 MHz, CDCl$_3$) 2.26 (3H, s, 3-CH$_3$), 3.35 (3H, s, NCH$_3$), 6.71 (1H, d, *J* 8.1 Hz, 1-H), 6.80 (1H, dd, *J* 8.0, 1.2 Hz, 9-H), 6.92 (1H, td, *J* 7.6, 1.2 Hz, 7-H), 6.95–7.01 (2H, m, 2-H and 4-H), 7.11–7.21 (2H, m, 6-H and 8-H); δ_C (101 MHz, CDCl$_3$) 20.4 (CH$_3$), 35.4 (CH$_3$), 114.0 (CH), 114.0 (CH), 122.3 (CH), 123.3 (C), 123.5 (C), 127.3 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 132.1 (C), 143.5 (C), 146.2 (C); *m*/*z* (ESI) 228 (MNa$^+$. 100%).

N-Benzyl-3-methylphenothiazine (4k)

The reaction was performed as described in general procedure C using (2-benzylamino-5-methylphenyl)(2′-bromophenyl) sulfane (**3k**) (46 mg, 0.12 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 1 : 1) gave *N*-benzyl-3-methylphenothiazine (**4k**) (34 mg, 95%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2916 (CH), 1578 (C=C), 1466, 1358, 1254, 871, 729; δ_H (400 MHz, CDCl$_3$) 2.21 (3H, s, 3-CH$_3$), 5.07 (2H, s, PhC*H*$_2$), 6.53 (1H, d, *J* 8.3 Hz, 1-H), 6.62 (1H, dd, *J* 8.2, 1.1 Hz, 9-H), 6.77 (1H, dd, *J* 8.3, 1.6 Hz, 2-H), 6.85 (1H, td, *J* 7.5, 1.1 Hz, 7-H), 6.92 (1H, d, *J* 1.6 Hz, 4-H), 6.97 (1H, ddd, *J* 8.2, 7.5, 1.6 Hz, 8-H), 7.09 (1H, dd, *J* 7.5, 1.6 Hz, 6-H), 7.22–7.38 (5H, m, Ph); δ_C (101 MHz, CDCl$_3$) 20.4 (CH$_3$), 52.7 (CH$_2$), 115.3 (CH), 115.4 (CH), 122.3 (CH), 123.0 (C), 123.1 (C), 126.7 (2 × CH), 126.9 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.8 (2 × CH), 132.2 (C), 137.0 (C), 142.1 (C), 144.8 (C); *m*/*z* (ESI) 326.0982 (MNa$^+$. C$_{20}$H$_{17}$NNaS requires 326.0974).

3-Methyl-10*H*-phenothiazine (4l).[42]

The reaction was performed as described in general procedure C using (2-amino-5-methylphenyl)(2′-bromophenyl)sulfane (**3l**) (30 mg, 0.10 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification by flash column chromatography (hexane/ethyl acetate, 9 : 1) gave 3-methyl-10*H*-phenothiazine (**4l**) (18 mg, 82%) as a white solid. Mp 166–169 °C (lit.[42] 169–170 °C); δ_H (400 MHz, DMSO-d_6) 2.12 (3H, s, 3-CH$_3$), 6.58 (1H, d, *J* 8.0 Hz, 1-H), 6.66 (1H, dd, *J* 7.9, 1.1 Hz, 9-H), 6.68–6.75 (2H, m, 4-H and 7-H), 6.79 (1H, dd, *J* 8.0, 1.8 Hz, 2-H), 6.89 (1H, dd, *J* 7.7, 1.3 Hz, 6-H), 6.97 (1H, td, *J* 7.9, 1.3 Hz 8-H), 8.45 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 19.9 (CH$_3$), 114.3 (CH), 114.3 (CH), 116.2 (C), 116.2 (C), 121.4 (CH), 126.2 (CH), 126.5 (CH), 127.5 (CH), 128.0 (CH), 130.7 (C), 139.5 (C), 142.4 (C); *m*/*z* (ESI) 214 (MH$^+$. 100%).

3-Phenyl-10*H*-phenothiazine (4m).[43]

The reaction was performed as described in general procedure C using (2-amino-5-biphenyl)(2′-bromophenyl)sulfane (**3m**) (100 mg, 0.28 mmol). The reaction mixture was stirred at 110 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 5 : 1) gave 3-phenyl-10*H*-phenothiazine (**4m**) (63 mg, 82%) as a yellow solid. Mp 220–222 °C (lit.[43] 216–218 °C); δ_H (400 MHz, DMSO-d_6) 6.69 (1H, dd, *J* 7.9, 1.1 Hz, 9-H), 6.73–6.79 (2H, m, 1-H and 7-H), 6.93 (1H, dd, *J* 7.7, 1.4 Hz, 6-H), 7.00 (1H, td, *J* 7.9, 1.4 Hz, 8-H), 7.22 (1H, d, *J* 2.1 Hz, 4-H), 7.25–7.32 (2H, m, 2-H and 4′-H), 7.37–7.43 (2H, m, 3′-H and 5′-H), 7.54–7.59 (2H, m, 2′-H and 6′-H), 8.70 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 114.4 (CH), 114.7 (CH), 116.1 (C), 117.0 (C), 121.8 (CH), 124.1 (CH), 125.7 (2 × CH), 125.8 (CH), 126.2 (CH), 126.8 (CH), 127.6 (CH), 128.8 (2 × CH), 133.7 (C), 139.1 (C), 141.3 (C), 141.7 (C); *m*/*z* (ESI) 299 (MNa$^+$. 100%).

Benzo[*a*]phenothiazine (4n).[44]

The reaction was performed as described in general procedure C using 1-(2′-bromophenylthio)-2-aminonaphthalene (**3n**) (100 mg, 0.39 mmol). The reaction mixture was stirred at 110 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 5 : 1) gave benzo[*a*]phenothiazine (**4n**) (85 mg, 87%) as a yellow solid. Mp 184–186 °C (lit.[44] 185 °C); δ_H (400 MHz, DMSO-d_6) 6.74 (1H, dd, *J* 8.3, 1.3 Hz, 13-H), 6.80 (1H, td, *J* 7.5, 1.3 Hz, 11-H), 7.00–7.05 (3H, m, 1-H, 10-H and 12-H), 7.31 (1H, ddd, *J* 8.0, 6.9, 1.1 Hz, 4-H), 7.49 (1H, ddd, *J* 8.3, 6.9, 1.3 Hz, 5-H), 7.63 (1H, d, *J* 8.6 Hz, 2-H), 7.70 (1H, dd, *J* 8.3, 1.1 Hz, 6-H), 7.76 (1H, dd, *J* 8.0, 1.3 Hz, 3-H), 8.80 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 107.0 (C), 114.5 (CH), 116.0 (C), 116.8 (CH), 121.4 (CH), 122.3 (CH), 123.3 (CH), 126.6 (CH), 127.0 (CH), 127.4 (CH), 127.8 (CH), 128.4 (CH), 129.6 (C), 129.9 (C), 139.8 (C), 142.4 (C); *m*/*z* (ESI) 288 (MK$^+$. 100%).

3-Chloro-10*H*-phenothiazine (4o).[16b]

The reaction was performed as described in general procedure C using (2-amino-5-chloro)(2′-bromophenyl)sulfane (**3o**) (60 mg, 0.19 mmol). The reaction mixture was stirred at 110 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 5 : 1) gave 3-chloro-10*H*-phenothiazine (**4o**) (85 mg, 87%) as a white solid. Mp 201–203 °C (lit.[16b] 200–201 °C); δ_H (400 MHz, DMSO-d_6) 6.63–6.68 (2H, m, 1-H and 9-H), 6.77 (1H, td, *J* 7.7, 1.3 Hz, 7-H), 6.91 (1H, dd, *J* 7.7, 1.4 Hz, 6-H), 6.97–7.05 (3H, m, 2-H, 4-H and 8-H), 8.71 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 114.6 (CH), 115.4 (CH), 115.5 (C), 118.6 (C), 122.1 (CH), 124.9 (C), 125.4 (CH), 126.3 (CH), 127.2 (CH), 127.8 (CH), 141.1 (C), 141.6 (C); *m*/*z* (EI) 233 (M$^+$. 100%).

(2-Benzoylamino-4-methoxyphenyl)(2′-bromophenyl)sulfane (6)

The reaction was performed as described in general procedure A using *N*-(3-methoxyphenyl)benzamide (**5**) (66 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 4 h. Purification by flash column chromatography (hexane/ethyl acetate, 9 : 1) gave (2-benzoylamino-4-methoxyphenyl)(2′-bromophenyl)sulfane (**6**) (78 mg, 66%) as a white solid. Mp 78–81 °C; $\nu_{\max}$/cm^{-1} (neat) 3360 (NH), 2936 (CH), 1678 (C═O), 1574 (C═C), 1443, 1250, 1169, 1018, 748; δ_H (400 MHz, CDCl$_3$) 3.93 (3H, s, OCH$_3$), 6.61 (1H, dd, *J* 8.0, 1.5 Hz, 6′-H), 6.77 (1H, dd, *J* 8.6, 2.8 Hz, 5-H), 6.98 (1H, td, *J* 7.7, 1.5 Hz, 4′-H), 7.10 (1H, ddd, *J* 8.0, 7.7, 1.4 Hz, 5′-H), 7.40–7.45 (2H, m, 3″-H and 5″-H), 7.48–7.55 (2H, m, 3′-H and 4″-H), 7.56 (1H, d, *J* 8.6 Hz, 6-H), 7.67–7.71 (2H, m, 2″-H and 6″-H), 8.47 (1H, d, *J* 2.8 Hz, 3-H), 9.13 (1H, br s, NH); δ_C (101 MHz, CDCl$_3$) 55.8 (CH$_3$), 105.6 (CH), 109.4 (C), 111.7 (CH), 120.8 (C), 126.8 (CH), 127.1 (2 × CH), 127.1 (CH), 128.3 (CH), 129.0 (2 × CH), 132.2 (CH), 133.1 (CH), 134.6 (C), 137.9 (C), 138.4 (CH), 141.9 (C), 162.7 (C), 165.4 (C); *m*/*z* (ESI) 414.0160 (MH$^+$. $C_{20}H_{17}{}^{79}BrNO_2S$ requires 414.0158).

N-Benzoyl-2-methoxyphenothiazine (7)

The reaction was performed as described in general procedure B using (2-benzoylamino-4-methoxyphenyl)(2′-bromophenyl) sulfane (**6**) (250 mg, 0.60 mmol). The reaction mixture was stirred at 150 °C for 120 h. Purification by flash column chromatography (hexane/ethyl acetate, 9 : 1) gave *N*-benzoyl-2-methoxyphenothiazine (**7**) (160 mg, 80%) as a white solid. Mp 156–157 °C; $\nu_{\max}$/cm^{-1} (neat) 2920 (CH), 1655 (C═O), 1578 (C═C), 1442, 1335, 1246, 1022, 756; δ_H (400 MHz, CDCl$_3$) 3.65 (3H, s, OCH$_3$), 6.74 (1H, dd, *J* 8.6, 2.7 Hz, 3-H), 7.01 (1H, d, *J* 2.7 Hz, 1-H), 7.10–7.17 (2H, m, 7-H and 8-H), 7.21–7.25 (2H, m, 3′-H and 5′-H), 7.29–7.44 (6H, m, 4-H, 6-H, 9-H, 2′-H, 4′-H and 6′-H); δ_C (101 MHz, CDCl$_3$) 55.7 (CH$_3$), 112.8 (CH), 113.6 (CH), 123.0 (C), 126.5 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CHCH), 128.2 (CH), 128.2 (2 × CH), 128.9 (2 × CH), 130.5 (CH), 133.0 (C), 135.4 (C), 139.7 (C), 140.8 (C), 159.1 (C), 169.1 (C); *m*/*z* (ESI) 334.0902 (MH$^+$. $C_{20}H_{16}NO_2S$ requires 334.0896).

2-Methoxyphenothiazine (8).[18]

To a solution of *N*-benzoyl-2-methoxyphenothiazine (**7**) (100 mg, 0.30 mmol) in ethanol (5.3 mL) was added hydrazine monohydrate (11 mL) under an atmosphere of argon. The reaction mixture was stirred at 145 °C for 48 h. The resulting residue was cooled and poured onto ice-water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 4 : 1) gave 2-methoxyphenothiazine (**8**) (50 mg, 73%) as a white solid. Mp 183–185 °C (lit.[18] 184–185 °C); δ_H (400 MHz, DMSO-*d*$_6$) 3.68 (3H, s, OCH$_3$), 6.32 (1H, d, *J* 2.7 Hz, 1-H), 6.38 (1H, dd, *J* 8.4, 2.7 Hz, 3-H), 6.67 (1H, dd, *J* 8.0, 1.3 Hz, 6-H), 6.75 (1H, ddd, *J* 7.7, 7.4, 1.3 Hz, 8-H), 6.82 (1H, d, *J* 8.4 Hz, 4-H), 6.91 (1H, dd, *J* 7.7, 1.5 Hz, 9-H), 6.98 (1H, ddd, *J* 8.0, 7.4, 1.5 Hz, 7-H), 8.59 (1H, br s, NH); δ_C (101 MHz, DMSO-*d*$_6$) 55.0 (CH$_3$), 100.7 (CH), 107.1 (C), 107.2 (CH), 114.4 (CH), 117.0 (C), 121.8 (CH), 126.2 (CH), 126.8 (CHCH), 127.4 (CH), 141.8 (C), 143.3 (C), 159.3 (C); *m*/*z* (EI) 229 (M$^+$. 100%).

Methopromazine[45]

Sodium hydride (7.5 mg, 0.43 mmol) was slowly added to DMF (0.4 mL) under an atmosphere of argon and the resulting suspension was cooled to 0 °C. 3-Dimethylamino-1-propyl chloride hydrochloride (41 mg, 0.26 mmol) and 2-methoxyphenothiazine (**8**) (30 mg, 0.13 mmol) were subsequently added. The reaction mixture was stirred at room temperature for 18 h. The resulting residue was diluted with dichloromethane (20 mL) and washed with 5% aqueous lithium chloride (30 mL). The aqueous layer was further extracted with dichloromethane (2 × 20 mL) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane/methanol, 19 : 1) gave methopromazine (25 mg, 61%) as a brown oil. Spectroscopic data were consistent with the literature.[45] δ_H (400 MHz, CDCl$_3$) 1.98 (2H, pent, *J* 7.1 Hz, 2′-H$_2$), 2.23 (6H, s, 2 × CH$_3$), 2.44 (2H, t, *J* 7.1 Hz, 3′-H$_2$), 3.78 (3H, s, OCH$_3$), 3.90 (2H, t, *J* 7.1 Hz, 1′-H$_2$), 6.43–6.52 (2H, m, 1-H and 3-H), 6.86–6.94 (2H, m, 6-H and 8-H), 7.03 (1H, d, *J* 8.4 Hz, 4-H), 7.09–7.17 (2H, m, 7-H and 9-H); δ_C (101 MHz, CDCl$_3$) 24.6 (CH$_2$), 45.1 (2 × CH$_3$), 45.3 (CH$_2$), 55.7 (CH$_3$), 57.0 (CH$_2$), 103.6 (CH), 107.3 (CH), 115.9 (CH), 116.5 (C), 122.8 (CH), 126.1 (C), 127.3 (CH), 127.6 (CH), 127.9 (CH), 145.0 (C), 146.7 (C), 160.0 (C); *m*/*z* (ESI) 315 (MH$^+$. 100%).

Conflicts of interest

There are no conflicts to declare.

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