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PAPER

Versatile synthesis of functionalised dibenzothiophenes *via* Suzuki coupling and microwave-assisted ring closure†

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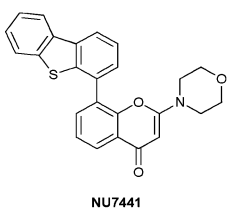
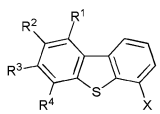
Amino-substituted biphenyls were obtained by Suzuki cross-coupling of 2,6-dibromoaniline with a phenylboronic acid (substituted with Me, NO_2, OH, OMe or Cl) preferably assisted by microwave irradiation. Conversion of the amino group into a thiol preceded a base-induced intramolecular substitution, also facilitated by microwave heating, to generate the second C–S bond of the target dibenzothiophene. The 1-, 2-, 3- or 4-substituted 6-halodibenzothiophenes obtained were subjected to a palladium-mediated coupling with 2-morpholin-4-yl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4*H*-chromen-4-one to give the respective 6-, 7-, 8- or 9-substituted dibenzothiophen-4-ylchromenones. These compounds were evaluated as inhibitors of DNA-dependent protein kinase (DNA-PK) and compared to the parent 8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholin-4-yl-4*H*-chromen-4-one. Notably, derivatives bearing hydroxy or methoxy substituents at C-8 or C-9 retained activity, whereas substitution at C-7 lowered activity. Substitution with chloro at C-6 was not detrimental to activity, but a chloro group at C-7 or C-8 reduced potency. The data indicate permissive elaboration of hydroxyl at C-8 or C-9, enabling the possibility of improved pharmaceutical properties, whilst retaining potency against DNA-PK.

Introduction

We report the synthesis of selectively functionalised dibenzothiophene derivatives **1**, **2a–f**, **3a–c** and **4** by cyclisation of intermediate halo-biarylthiophenols, prepared *via* Suzuki[1,2] cross-coupling.[3,4] Our interest in substituted dibenzothiophenes arose from the preparation of 8-(dibenzothiophen-4-yl)chromen-4-ones as inhibitors of DNA-dependent protein kinase (DNA-PK), as exemplified by 8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholin-4-yl-4*H*-chromen-4-one (NU7441, IC_{50} = 28 nM).[5,6] DNA-PK participates in the repair of mammalian DNA double-strand breaks (DSBs).[7] ATP-competitive DNA-PK inhibitors, by impeding DNA DSB repair, have potential application as radio- and chemo-potentiators in the treatment of cancer.[8,9] We required access to a range of substituted dibenzothiophenes with a view to optimising the biological and pharmaceutical properties of lead compounds (*e.g.* NU7441) and to expand structure–activity relationships (SARs).



NU7441



1	R^1 = H	R^2 = H	R^3 = Me	R^4 = H	X = Br
2a	R^1 = OMe	R^2 = H	R^3 = H	R^4 = H	X = Br
2b	R^1 = H	R^2 = OMe	R^3 = H	R^4 = H	X = Br
2c	R^1 = H	R^2 = H	R^3 = OMe	R^4 = H	X = Br
2d	R^1 = H	R^2 = Cl	R^3 = H	R^4 = H	X = Br
2e	R^1 = H	R^2 = H	R^3 = Cl	R^4 = H	X = Br
2f	R^1 = H	R^2 = H	R^3 = H	R^4 = Cl	X = Br
3a	R^1 = OH	R^2 = H	R^3 = H	R^4 = H	X = Br
3b	R^1 = H	R^2 = OH	R^3 = H	R^4 = H	X = Br
3c	R^1 = H	R^2 = H	R^3 = OH	R^4 = H	X = Br
4	R^1 = H	R^2 = NO_2	R^3 = H	R^4 = H	X = Cl

The synthesis of functionalised dibenzothiophenes is of interest because such structural motifs are potentially useful for the design of new therapeutic agents. A number of methods for the synthesis of dibenzothiophenes have been reviewed.[10,11] However, many of the routes are only useful for the synthesis of specific compounds. More recently, cyclisation routes to regioselectively functionalised dibenzothiophenes and related heterocycles have been developed. For dibenzothiophenes, the anionic cyclisation of benzyne-tethered aryllithiums[12] and the ring-closure of biphenyl dithiocarbamates with potassium *tert*-butoxide have been utilised.[13] Palladium-mediated cyclisation of benzylphenyl sulfoxides to substituted dibenzothiophenes has recently been reported.[14] The synthesis of the structurally related fused benzo[4,5]furo-heterocycles has been achieved by copper(I) thiophene-2-carboxylate mediated intramolecular cyclisation of a

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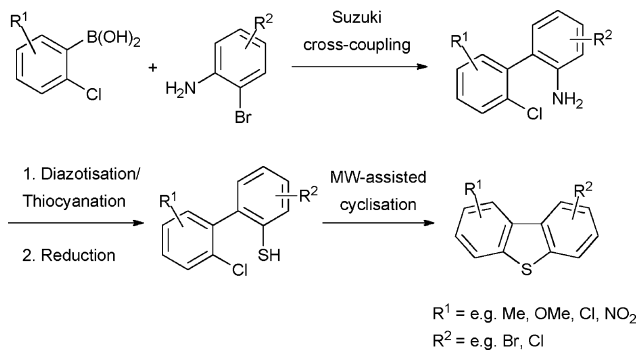
† Electronic supplementary information (ESI) available: Experimental procedures for compounds **11b–f**, **12b–f**, **13c–f**, **2c–f**, **3c**, **22b–f**, **23a–c**, **24**. See DOI: 10.1039/c1ob05282a

diphenyl intermediate derived by Suzuki cross-coupling.[15] Similarly, substituted phenanthridin-6(5*H*)-ones have been obtained by cross-coupling followed by an anionic ring closure.[16]

We conceived a route to substituted dibenzothiophenes *via* the coupling of appropriately substituted boronic acids with bromoanilines, leading to a biphenyl intermediate that was converted into a thiol by functional group interconversions. Finally, microwave-assisted ring closure gave the desired substituted dibenzothiophenes (Scheme 1).



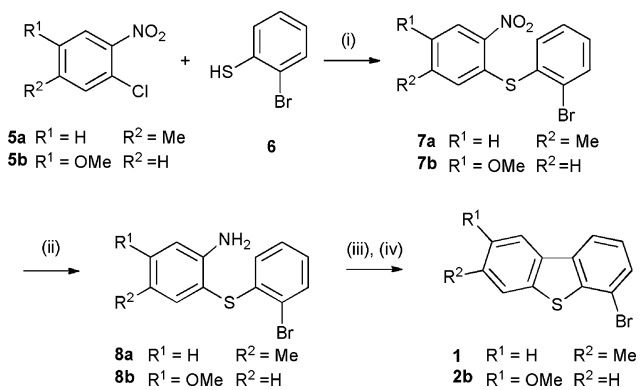
Scheme 1 Preparation of dibenzothiophene derivatives *via* Suzuki coupling and microwave-assisted ring closure (*e.g.* R_1 = OMe; R_2 = Br).

In these studies, 2,6-dibromoaniline was employed in order to retain one bromo substituent for subsequent manipulation facilitating the synthesis of functionalised dibenzothiophen-4-yl chromenones. The use of a variety of boronic acids enabled structural diversity in the final 8-(dibenzothiophen-4-yl)chromen-4-ones, and identified positions on the dibenzothiophenyl ring that were tolerant to substitution without detriment to DNA-PK inhibitory activity.

Results and discussion

Synthesis of 6-bromo-3-methyldibenzo[*b*,*d*]thiophene (1) and 6-bromo-2-methoxydibenzo[*b*,*d*]thiophene (2b)

Initially we employed the classical route to substituted dibenzothiophenes whereby a 2-(phenylthio)aniline was diazotised to give a diazonium intermediate that was cyclised following treatment with iron(II) sulfate (Scheme 2).[17–20] Two derivatives (**1** and **2b**) were prepared using this synthetic pathway. The principal disadvantages of this synthetic approach were the poor yields obtained for the two key steps, namely thiobridge and C–C bond formation (*e.g.* 46% and 13%, respectively for **2b**) in agreement with prior literature.[17–20] There were also limitations with respect to the substitution pattern. As a consequence, utilising this strategy for functionalising other positions on the dibenzothiophene ring was deemed impractical.



Scheme 2 *Reagents and conditions*: (i) NaOMe, MeOH, reflux, 18 h, **7a** 84%, **7b** 46%; (ii) Zn, NH_4Cl, THF, reflux, 18 h, **8a** 93%, **8b** 100%; (iii) HBF_4, 5 M HCl, $NaNO_2$, 5 °C, 15 min; (iv) $FeSO_4$, H_2O, 100 °C, 1 h, **1** 31%, **2b** 13%.

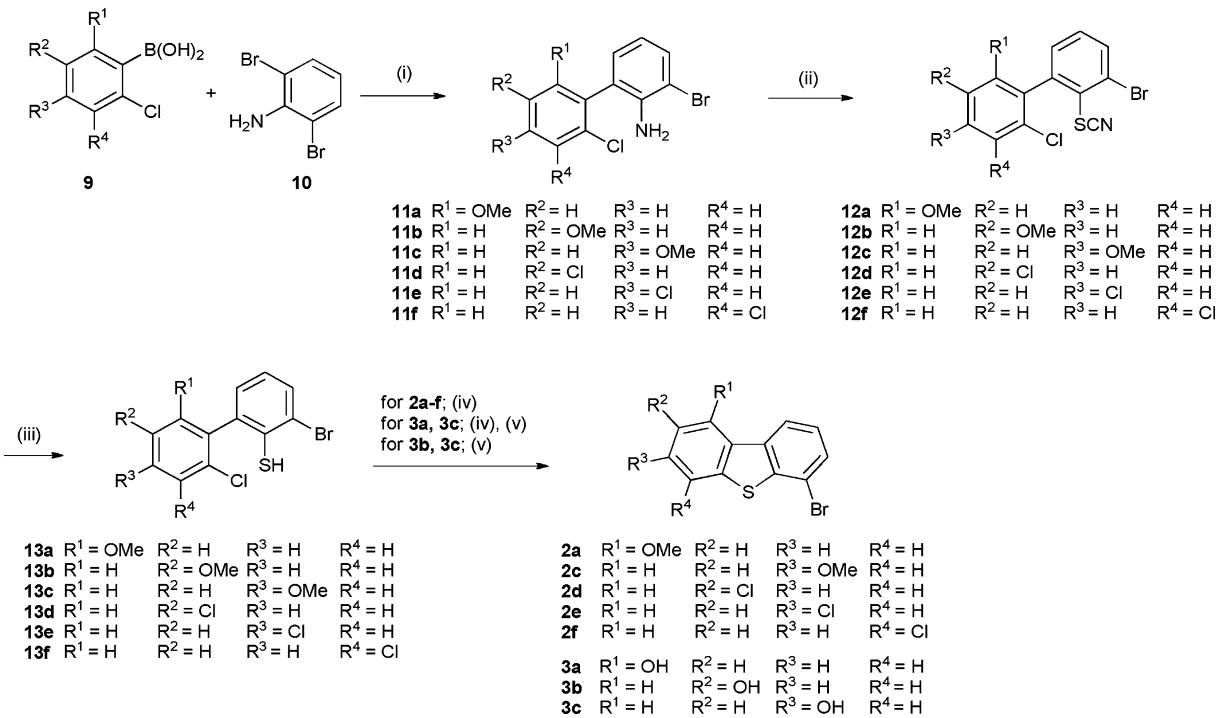
Synthesis of 1-, 2-, 3- and 4-substituted 6-bromodibenzo-[*b*,*d*]thiophene derivatives (2a, 2c–f, 3a–c)

An alternative strategy was sought whereby the traditional sequence of reactions for the formation of the dibenzothiophene core was reversed. Thus, a Suzuki cross-coupling reaction was employed to generate the C–C bond of an intermediate amino-substituted biphenyl. Functional group interconversion (NH_2 → SH) was followed by a putative intramolecular nucleophilic aromatic substitution (S_NAr) to form the second C–S bond of the target dibenzothiophene (Scheme 3). This order of events was necessary because thiols and thiolates are known to poison palladium-catalysed reactions. Hence, a functional group was introduced that could be converted later into the desired thiol. For this reason, we chose to cross-couple 2,6-dibromoaniline with an arylboronic acid under standard cross-coupling conditions ($Pd(PPh_3)_4$, Na_2CO_3, DME, MW heating).[21] Owing to the wide availability of substituted arylboronic acids, a range of functionalised halobiphenyls could be prepared using this protocol in up to *ca.* 80% yields. The cross-coupling of 2-chloro-6-methoxyphenylboronic acid with **10** was much poorer yielding (49%), presumably due to the sterically hindered nature of both coupling partners.

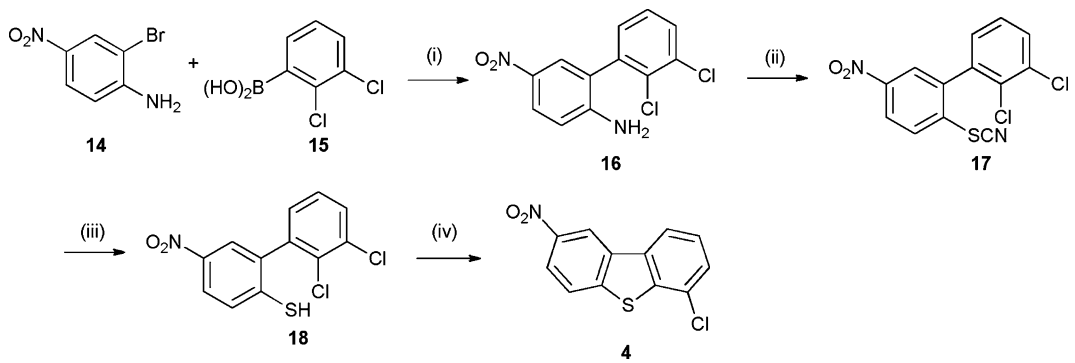
The biphenylamines **11a–f** were diazotised and treated with a thiocyanate nucleophile. The resultant thiocyanates **12a–f** (50–79%) were reduced with lithium aluminium hydride (87–99%) or hydrolysed with potassium hydroxide in ethanol (91%). The final base-induced cyclisation step utilised caesium carbonate in acetonitrile to obtain compounds **2a**, **2c–f** (70–96%). Microwave irradiation was essential for the achievement of high yields (*e.g.* synthesis of **2d** under conventional heating for 6 h, 74% yield, under microwave irradiation for 5 min, 95% yield) and short reaction times. Upon deprotection of **2a** and **2c** with pyridine hydrochloride at 150 °C, the hydroxy-substituted dibenzothiophenes **3a** and **3c** were isolated in 71% and 70% yield, respectively. The cyclisation of **13b** failed with caesium carbonate employing the conditions used in the preparation of **2b**. It was intended to examine the ring closure on the free hydroxyl derivative. However, serendipitously, it was found that on treating **13b** with pyridine hydrochloride at 150 °C, the product isolated was **3b** (63%). This surprising result, *i.e.* deprotection and cyclisation in one step, was also observed when **13c** was treated with pyridine hydrochloride, leading to the synthesis of **3c** (35%) in a one-pot reaction.

Synthesis of 6-chloro-2-nitrodibenzo[*b*,*d*]thiophene (4)

Due to the availability of the appropriate starting materials, the synthesis of 6-chloro-2-nitrodibenzo[*b*,*d*]thiophene **4** was performed by coupling 2-bromo-4-nitroaniline (**14**) and 2,3-dichlorophenylboronic acid (**15**) (Scheme 4) to give aminobiphenyl



Scheme 3 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, $Na_2CO_{3(aq)}$, DME, MW, 175 °C, 50–80 min, 40–77%; (ii) $NaNO_2$, c. HCl, MeOH, 0 °C, 10 min then KSCN, $FeCl_3$, RT, 4–5 h, 62–79% or $NaNO_2$, c. HCl, TFE, −5 °C, 20 min, then KSCN, CuSCN, RT, 5.5 h, 66%; (iii) $LiAlH_4$, THF, 0 °C, 4 h, 87–99% or $KOH_{(s)}$, $EtOH/H_2SO_4$, 0 °C then RT, 30 min, 91%; (iv) $Cs_2CO_{3(s)}$, CH_3CN, MW, 130 °C, 8–10 min, 70–98%; (v) pyridine hydrochloride, 150 °C, 18 h, 35–70%.



Scheme 4 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, $Na_2CO_{3(aq)}$, DME, MW, 175 °C, 85 min, 66%; (ii) $NaNO_2$, c. HCl, MeOH, 0 °C, 10 min then KSCN, $FeCl_3$, RT, 4–5 h, 52%; (iii) $KOH_{(s)}$, $EtOH/H_2SO_4$, 10 °C, 1 h, 80%; (iv) $Cs_2CO_{3(s)}$, CH_3CN, MW, 130 °C, 8 min, 91%.

16, *i.e.* in the alternative manner to that described above. Conversion of **16** to thiol **18** and ring closure as before using caesium carbonate under microwave heating gave **4** in 91% yield.

Synthesis of substituted dibenzothiophen-4-yl chromenone derivatives

Our previous studies have utilised the chromenone triflate **19**[22] or chromenone boronate **20** as building blocks for the preparation of 8-substituted chromenones, employing Suzuki cross-coupling.[23–25] Initially, **1** and **2b** were converted into the boronate derivatives, using bis(pinacolato)diboron, $PdCl_2$(dppf) and Cs_2CO_3 in THF, and subsequently coupled with **19** to prepare the desired dibenzothiophen-4-yl chromenones **21** and **22b**, respectively (Scheme 5). Subsequently, a better strategy was found to entail coupling of **20** with the 6-bromo-dibenzo[*b*,*d*]thiophene derivatives **2a**, **2c–f** and **3a–c** to afford **22a**, **22c–f**, **23a–c** (30–75%).

All new compounds described in this paper were characterised by ^1H and ^{13}C NMR, high resolution mass spectrometry and/or combustion analysis and liquid chromatography mass spectrometry. The dibenzothiophenes **2d**, **2e**, **2f**, **3a**, **4** and the thiocyanate **12d** were additionally characterised by crystal structure analysis, the data for which will be published elsewhere.

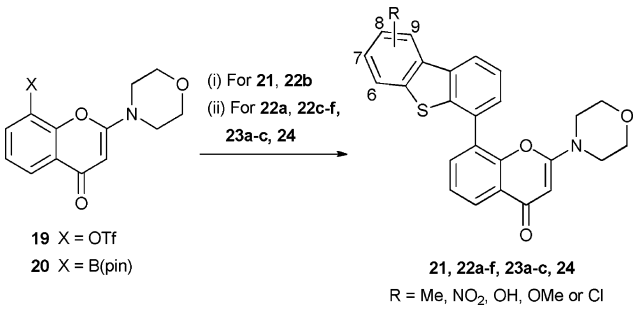
Biological evaluation

The effect upon DNA-PK inhibitory activity of substitution at the 6-, 7-, 8- and 9- position of the dibenzothiophen-4-yl moiety was investigated. The structures and inhibitory activities of compounds **21**, **22a–f**, **23a–c**, **24** are summarised in Table 1. The

Table 1 Inhibition of DNA-PK by substituted 8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholin-4-yl-4*H*-chromen-4-ones (**21**, **22a–f**, **23a–c**, **24**)

	R	DNA-PK inhibitory activity (IC_{50})/nM[a]
NU7441	H	28
21	7-Me	117
22a	9-OMe	91
22b	8-OMe	11
22c	7-OMe	2900
22d	8-Cl	690
22e	7-Cl	1430
22f	6-Cl	30
23a	9-OH	81
23b	8-OH	43
23c	7-OH	687
24	8-NO_2	814

[a] IC_{50} values were determined in accordance with reference 24 and are the mean of at least two determinations.



Scheme 5 *Reagents and conditions*: (i) **1** or **2b**, $PdCl_2$(dppf), $K_2CO_{3(s)}$, bis(pinacolato)diboron, THF, reflux, 16 h; then **19**, $PdCl_2$(dppf), $Cs_2CO_{3(s)}$, THF, reflux, 16 h, **21** 58%, **22b** 30%; (ii) **20** and **2a**, **2c–f** or **3a–c**, $Pd(PPh_3)_4$, $Na_2CO_{3(aq)}$, DME, MW, 175 °C, 35–70 min, 30–75%.

activity of the parent 8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholin-4-yl-4*H*-chromen-4-one (NU7441) is included for comparative purposes. The results show that for hydroxy and methoxy substituents the order of potency is C-8 > C-9 ≫ C-7. Notably, the 8-methoxy compound **22b** is even more active than the benchmark NU7441. For chloro, activity is retained for substitution at C-6 but attenuated at both C-7 and C-8. Single examples for methyl and nitro showed a small loss of activity for substitution at C-7 (Me) and a significant loss at C-8 (NO_2). Further studies focussed on elaboration of hydroxyl groups at C-8 and C-9 to improve the pharmaceutical properties of the inhibitors will be reported.

Conclusions

We have shown that a variety of functionalised dibenzothiophenes can be conveniently obtained from biphenyl precursors. The ring closure of these precursors was achieved by microwave-assistance in which a sulfide on one ring attacked the carbon atom linked to a halogen on the other in a S_NAr-like process. The biphenyl intermediates were obtained by Suzuki coupling. The method is potentially scaleable and should be applicable to a wide range of substituent patterns beyond those described. The dibenzothiophenes were further modified by palladium-catalysed cross-coupling with a chromenone boronate leading to dibenzothiophen-4-yl chromenones that were tested as inhibitors of DNA-PK. These results indicate those regions of the distal benzo ring that could be further elaborated without compromising inhibitory activity.

Experimental

Materials and methods

Chemicals and solvents were obtained from reputable suppliers. Solvents were either dried by standard techniques or purchased as anhydrous. Reactions needing microwave irradiation were carried out in an Initiator™ Sixty Biotage apparatus. Petrol refers to petroleum ether (bp 40–60 °C, reagent grade, Aldrich). All reactions that required inert or dry atmosphere were carried out under a blanket of nitrogen, which was dried by passage through a column of phosphorus pentoxide. Glassware was dried in an oven prior to use. Column chromatography was carried out using 40–60 μm mesh silica in glass columns under medium pressure or with a Biotage SP4 flash purification system using KP-Sil™ silica. Thin layer chromatography (TLC) was performed on 20 mm precoated plates of silica gel (Merck, silica gel 60F254); visualisation was made using ultraviolet light (254 nm). NMR spectra were recorded on a Bruker Spectrospin AC 300E 300 MHz (for ^{1}H and ^{13}C) NMR Spectrometer or Bruker BioSpin UltraShield Plus 500 MHz (for some ^{1}H) using deuterated solvent as a lock. The abbreviation, ap t, when listing NMR spectra, refers to apparent triplet. IR spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR. UV analysis was performed using a Hitachi U-2000 spectrophotometer. LCMS was carried out on a Micromass Platform instrument operating in positive and negative ion electrospray mode, employing a 50 × 4.6 mm C18 column (Supelco Discovery or Waters Symmetry) and a 15 min gradient elution of 0.05% formic acid and methanol (10–90%). HRMS were measured using a Finnigan MAT 95 XP or a Finnigan MAT 900 XLT by the EPSRC National Mass Spectrometry Service Centre (Swansea).

(2-Bromophenyl)(5-methyl-2-nitrophenyl)sulfane (7a)

To a solution of sodium methoxide (1.17 g, 21.6 mmol) and methanol (25 mL) were added 2-chloro-4-methyl-1-nitrobenzene (2.04 g, 11.9 mmol) and 2-bromobenzenethiol (1.3 mL, 10.8 mmol). The reaction mixture was heated at reflux overnight and a yellow precipitate appeared. The precipitate was filtered, washed with cold methanol and dried, yielding the title compound as a yellow solid (2.94 g, 84%): R_f 0.42 (petrol/EtOAc 4 : 1); mp: 114–116 °C; IR (cm^{-1}) 3428, 2361, 2159, 1577, 1497; λ_{max} (EtOH)/nm 279, 363; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (3H, s, Me), 6.43 (1H, s, H-Ar), 6.94 (1H, d, J = 8.4 Hz, H-Ar), 7.28 (1H, ap t, J = 7.5 Hz, H-Ar), 7.32 (1H, d, J = 7.5 Hz, H-Ar), 7.65 (1H, d, J = 7.5 Hz, H-Ar), 7.67 (1H, d, J = 7.7 Hz, H-Ar), 8.10 (1H, d, J = 8.4 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 126.4, 126.8, 128.4, 129.2, 131.4, 132.0, 132.9, 134.6, 137.6, 138.4, 143.2, 145.4; MS (ES+) m/z = 324.2 [M(^{79}Br) + H]$^+$, 326.1 [M(^{81}Br) + H]$^+$; HRMS calcd for $C_{13}H_{11}BrNO_2S$ [M(^{79}Br) + H]$^+$ 323.9688, found 323.9687.

(2-Bromophenyl)(4-methoxy-2-nitrophenyl)sulfane (7b)

Prepared following the same procedure as for **7a** with 1-chloro-4-methoxy-2-nitrobenzene (8.21 g, 44.0 mmol), 2-bromobenzenethiol (5.8 mL, 48.0 mmol), sodium methoxide

(4.75 g, 88.0 mmol) and MeOH (150 mL). The crude product was purified by medium pressure chromatography (petrol/EtOAc 98 : 2) to give the title compound as a yellow solid (6.82 g, 46%): R_f 0.35 (petrol/EtOAc 4 : 1); mp: 68–70 °C; IR (cm^{-1}) 3101, 2941, 2837, 2159, 1609, 1558, 1514, 1432; λ_{max} (EtOH)/nm 227, 396; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (3H, s, OMe), 6.78 (1H, d, J = 8.9 Hz, H-Ar), 7.02 (1H, dd, J = 2.8 and 8.9 Hz, H-Ar), 7.28 (1H, ap td, J = 1.6 and 7.7 Hz, H-Ar), 7.33 (1H, ap td, J = 1.3 and 7.5 Hz, H-Ar), 7.63 (1H, dd, J = 1.6 and 7.7 Hz, H-Ar), 7.74–7.76 (2H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.3, 109.7, 122.1, 127.4, 129.0, 130.3, 130.6, 131.4, 133.9, 134.5, 137.3, 147.1, 158.2; MS (ES+) m/z = 340.2 [M(^{79}Br) + H]$^+$, 342.1 [M(^{81}Br) + H]$^+$; HRMS calcd for $C_{13}H_{11}BrNO_3S$ [M(^{79}Br) + H]$^+$ 339.9638, found 339.9635.

2-((2-Bromophenyl)thio)-4-methylaniline (8a)

A suspension of (2-bromophenyl)(5-methyl-2-nitrophenyl)sulfane **7a** (2.0 g, 6.17 mmol), NH_4Cl (3.30 g, 61.7 mmol) and zinc powder (4.0 g, 61.7 mmol) in THF (40 mL) was heated at reflux overnight. The reaction mixture was filtered, rinsed with hot THF and the filtrate was evaporated to dryness *in vacuo*. The crude product was purified by medium pressure chromatography (petrol/EtOAc 4 : 1) to give the title compound as a white solid (1.69 g, 93%): R_f 0.51 (petrol/EtOAc 4 : 1); mp: 85–87 °C; IR (cm^{-1}) 3467, 3369, 2155, 2014, 1976, 1608, 1495, 1444; λ_{max} (EtOH)/nm 315; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (3H, s, Me), 4.01 (2H, br. s, NH_2), 6.51 (1H, d, J = 7.9 Hz, H-Ar), 6.67 (1H, d, J = 8.2 Hz, H-Ar), 6.89 (1H, d, J = 7.8 Hz, H-Ar), 6.95–7.01 (2H, m, H-Ar), 7.20 (1H, s), 7.43 (1H, d, J = 7.9 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 116.0, 120.9, 125.7, 126.5, 128.2, 128.5, 128.8, 129.4, 133.0, 138.3, 147.2, 162.7; MS (ES+) m/z = 294.2 [M(^{79}Br) + H]$^+$, 296.2 [M(^{81}Br) + H]$^+$; HRMS calcd for $C_{13}H_{13}BrNS$ [M(^{79}Br) + H]$^+$ 293.9947, found 293.9951.

2-((2-Bromophenyl)thio)-5-methoxyaniline (8b)

Prepared following the same procedure as for **8a** with (2-bromophenyl)(4-methoxy-2-nitrophenyl)sulfane **7b** (6.7 g, 19.8 mmol), NH_4Cl (10.6 g, 197.8 mmol), zinc powder (12.9 g, 197.8 mmol) and THF (200 mL). This mixture yielded the title compound as a grey solid (6.73 g, 100%): R_f 0.37 (petrol/EtOAc 4 : 1); mp: 78–81 °C; IR (cm^{-1}) 3383, 2159, 2019, 1979, 1597, 1442; λ_{max} (EtOH)/nm 245, 299; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s, OMe), 4.32 (2H, br. s, NH_2), 6.41–6.45 (2H, m, H-Ar), 6.60 (1H, d, J = 7.9 Hz, H-Ar), 6.98 (1H, ap t, J = 7.4 Hz, H-Ar), 7.12 (1H, ap t, J = 7.4 Hz, H-Ar), 7.38 (1H, s, H-Ar), 7.52 (1H, d, J = 7.8 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 68.6, 101.1, 105.3, 106.5, 120.7, 126.3, 128.1, 129.4, 133.1, 139.3, 150.5, 163.2; MS (ES+) m/z = 310.2 [M(^{79}Br) + H]$^+$, 312.2 [M(^{81}Br) + H]$^+$; HRMS calcd for $C_{13}H_{13}BrNOS$ [M(^{79}Br) + H]$^+$ 309.9896, found 309.9892.

6-Bromo-3-methyldibenzo[*b*,*d*]thiophene (1)

A suspension of 2-((2-bromophenyl)thio)-4-methylaniline **8a** (0.742 g, 2.5 mmol) in HBF_4 (50% in water, 2.2 g, 1.6 mL) was cooled to 5 °C. 5 M Hydrochloric acid (2.5 mL) was added and the reaction mixture was stirred vigorously. Sodium nitrite (0.191 g, 2.8 mmol) in water was added dropwise and the reaction mixture was stirred at 5 °C for 15 min. Water was added and the yellow precipitate was filtered and dried to afford 2-((2-bromophenyl)thio)-4-methylbenzenediazonium tetrafluoroborate [**CARE!** *Although no problems were encountered handling this compound*, *diazonium salts are potentially explosive and so the scale described here should not be exceeded without a risk assessment*]. A heated solution of $FeSO_4$ (1.4 g, 5.0 mmol) in water was added dropwise to a solution of the diazonium salt in water at 100 °C. The reaction mixture was heated at 100 °C for 1 h, cooled and extracted into DCM. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by medium pressure chromatography (petrol) to give the title compound as a white solid (0.218 g, 31%): R_f 0.63 (petrol/EtOAc 4 : 1); mp: 79–80 °C; IR (cm^{-1}) 3423, 2921, 2360, 1925, 1682, 1542, 1439, 1384; λ_{max} (EtOH)/nm 284, 325; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (3H, s, Me), 7.23 (1H, d, J = 7.3 Hz, H-Ar), 7.26 (1H, ap t, J = 7.8 Hz, H-Ar), 7.51 (1H, d, J = 7.8 Hz, H-Ar), 7.62 (1H, s, H-Ar), 7.93 (1H, d, J = 8.0 Hz, H-Ar), 8.00 (1H, d, J = 7.8 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 56.1, 84.8, 105.0, 116.1, 123.6, 123.9, 124.7, 134.5, 136.5, 147.2, 157.8; MS (EI) m/z = 276.0 [M(^{79}Br)]$^+$, 278.0 [M(^{81}Br)]$^+$; HRMS calcd for $C_{13}H_9BrS$ [M(^{79}Br)]$^+$ 275.9607, found 275.9603.

6-Bromo-2-methoxydibenzo[*b*,*d*]thiophene (2b)

2-((2-Bromophenyl)thio)-5-methoxyaniline **8b** (0.505 g, 1.6 mmol), in HBF_4 (50% in water, 0.660 g) and ethanol (50 mL) was cooled to 0 °C. *tert*-Butyl nitrite (0.191 g, 2.8 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Diethyl ether (50 mL) was added to the reaction mixture and the precipitate was filtered and dried to afford 2-((2-bromophenyl)thio)-5-methoxybenzenediazonium tetrafluoroborate [**CARE!** *See note above for* **1**]. A heated solution of $FeSO_4$ (7.0 g, 25.2 mmol) in water was added dropwise to a solution of the diazonium salt in water at 100 °C. The reaction mixture was heated at 100 °C for 1 h, cooled and extracted into DCM, the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by medium pressure chromatography (petrol/EtOAc 95 : 5) to give the title compound as a white solid (0.041 g, 13%): R_f 0.52 (petrol/EtOAc 4 : 1); mp: 138–140 °C; IR (cm^{-1}) 2925, 2838, 1601, 1544, 1472, 1425, 1384; λ_{max} (EtOH)/nm 342, 293, 231; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (3H, s, OMe), 7.12 (1H, dd, J = 2.4 and 8.7 Hz, H-Ar), 7.32 (1H, ap t, J = 7.8 Hz, H-Ar), 7.55 (1H, d, J = 2.4 Hz, H-Ar), 7.59 (1H, d, J = 7.8 Hz, H-Ar), 7.74 (1H, d, J = 8.7 Hz, H-Ar), 8.04 (1H, d, J = 7.8 Hz, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.8, 105.5, 116.5, 116.6, 120.4, 123.7, 125.6, 129.5, 131.2, 136.8, 137.2, 142.5, 157.9; MS (ES+) m/z = 292.1 [M(^{79}Br) + H]$^+$, 294.1 [M(^{81}Br) + H]$^+$; HRMS calcd for $C_{13}H_{10}BrOS$ 292.9630 [M(^{79}Br) + H]$^+$, found 292.9623.

Chloro- and methoxy-substituted 3-bromo-biphenyl-2-amines (11a–f)

Typical procedure. A mixture of a substituted aryl bromide (1.0 eq.), phenylboronic acid (1.3 eq.), $Pd(PPh_3)_4$ (5 mol%), 2 M aqueous Na_2CO_3 and DME or 1,4-dioxane was heated under microwave irradiation at 175 °C for 50–80 min. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl

and the product was extracted into EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product that was purified by medium pressure chromatography.

3-Bromo-2′-chloro-6′-methoxy-[1,1′-biphenyl]-2-amine (11a)

2,6-Dibromoaniline (0.50 g, 2 mmol), 2-chloro-6-methoxyphenylboronic acid (0.45 g, 2.4 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol), 2 M Na_2CO_3 (4 mL) and 1,4-dioxane (5 mL). The reaction mixture was heated under microwave irradiation at 150 °C for 40 min. The crude product was purified by medium pressure chromatography (DCM/petrol 3 : 2) to give the title compound as a colourless oil (0.35 g, 57%): R_f 0.25 (DCM/petrol 2 : 3); IR (cm^{-1}) 3049, 1609, 1449, 1270, 1255, 1118, 1064, 1033, 907, 850, 769; λ_{max} (EtOH)/nm 285; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (3H, s, OMe), 3.75 (2H, s, NH_2), 6.57 (1H, ap t, J = 7.6 Hz, H-Ar), 6.78 (1H, d, J = 8.2 Hz, H-Ar), 6.84 (1H, d, J = 7.6 Hz, H-Ar), 7.01 (1H, d, J = 8.2 Hz, H-Ar), 7.17 (1H, ap t, J = 8.2 Hz, H-Ar), 7.33 (1H, d, J = 7.6 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.9, 110.4, 110.7, 119.2, 122.8, 123.2, 127.1, 130.4, 130.8, 132.8, 136.1, 142.8, 159.3; MS (EI) m/z = 311.0 [M(^{35}Cl,^{79}Br)]$^+$, 313.0 [M(^{35}Cl,^{81}Br; ^{37}Cl,^{79}Br)]$^+$, 315.1 [M(^{37}Cl,^{81}Br)]$^+$; HRMS calcd for $C_{13}H_{12}NClBrO$ [M(^{35}Cl,^{79}Br) + H]$^+$ 311.9783, found 311.9783.

Chloro- and methoxy-substituted 3-bromo-2-thiocyanatobiphenyls (12a–f)

Typical procedure. Method A: To a solution of the substituted aniline (**11a–f**, 1.0 eq.) in MeOH was added dropwise conc. hydrochloric acid over 15 min at 0 °C. A cooled (0 °C) solution of sodium nitrite (1.0 eq.) in water was added dropwise, maintaining the temperature below 0 °C. The resulting solution was stirred for 10 min. A mixture of potassium thiocyanate (3.2 eq.) and iron(III) chloride (0.7 eq.) in water was added to the reaction mixture at 0 °C. The mixture was stirred for 4–5 h at room temperature. Upon neutralisation with 2 M aqueous NaOH the reaction mixture was extracted into DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting thiocyanate was purified by medium pressure chromatography.

Method B: To a solution of the substituted aniline (**11b**, 1.0 eq.) in 2,2,2-trifluoroethanol was added dropwise conc. hydrochloric acid at −5 °C. To this mixture a cooled (0 °C) solution of sodium nitrite (1.0 eq.) in water was added dropwise, maintaining the temperature < −5 °C. Copper thiocyanate (1.6 eq.) and potassium thiocyanate (20.0 eq.) in water was pre-cooled and added dropwise to the reaction mixture maintaining the temperature < −5 °C. The reaction mixture was warmed to room temperature and stirred for 5.5 h. Upon neutralisation with 2 M aqueous NaOH the reaction mixture was extracted into DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by medium pressure chromatography.

3-Bromo-2′-chloro-6′-methoxy-2-thiocyanato-1,1′-biphenyl (12a)

Following Method A: 3-bromo-6′-chloro-2′-methoxybiphenyl-2-amine **11a** (2.1 g, 6.7 mmol), MeOH (30 mL), conc. hydrochloric acid (15 mL), sodium nitrite (0.46 g, 6.7 mmol), potassium thiocyanate (3.47 g, 21.4 mmol), iron(III) chloride (0.775 g, 4.7 mmol) and water (20 mL). The crude product was purified by medium pressure chromatography (DCM/petrol 1 : 1) to give the title compound as a colourless oil which crystallised on standing (1.84 g, 77%): R_f 0.44 (DCM/petrol 1 : 1); mp: 101–103 °C; IR (cm^{-1}) 2152, 1587, 1570, 1456, 1429, 1392, 1257, 1188, 1033, 848, 783, 736; λ_{max} (EtOH)/nm 286; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (3H, s, OMe), 6.96 (1H, d, J = 8.2 Hz, H-Ar), 7.15 (1H, d, J = 8.2 Hz, H-Ar), 7.32 (1H, d, J = 7.7 Hz, H-Ar), 7.38 (1H, ap t, J = 8.2 Hz, H-Ar), 7.45 (1H, ap t, J = 7.7 Hz, H-Ar), 7.80 (1H, d, J = 7.7 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4, 110.0, 122.2, 122.3, 129.2, 129.4, 129.6, 129.7, 130.8, 133.7, 134.6, 138.0, 158.3; MS (EI) m/z = 353.0 [M(^{35}Cl,^{79}Br)]$^+$, 355.0 [M(^{35}Cl,^{81}Br; ^{37}Cl,^{79}Br)]$^+$, 357.0 [M(^{37}Cl,^{81}Br)]$^+$; HRMS calcd for $C_{14}H_9NSClBrO$ [M(^{35}Cl,^{79}Br)]$^+$ 352.9271, found 352.9276.

Chloro- and methoxy-substituted 3-bromo-biphenyl-2-thiols (13a–f)

Typical procedure. Method C: A solution of the thiocyanate (**12a–f**, 1.0 eq.) in dry THF was added dropwise to a solution of $LiAlH_4$ (1.1 eq.) in THF at 0 °C. The reaction mixture was stirred for 4 h, and the unreacted $LiAlH_4$ was destroyed by the cautious addition of water. The resulting mixture was acidified with 2 M aqueous HCl and the product was extracted into EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting product was used without further purification.

Method D: Potassium hydroxide (20.0 eq.) in EtOH was cooled to 0 °C and, the thiocyanate (**12b**, 1.0 eq.) was added portion-wise to the solution. The reaction mixture was stirred at room temperature for 30 min. Conc. H_2SO_4 in EtOH was added slowly, followed by water. The reaction mixture was extracted into DCM, the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by medium pressure chromatography.

3-Bromo-2′-chloro-6′-methoxy-[1,1′-biphenyl]-2-thiol (13a)

Following Method C: 3-bromo-6′-chloro-2′-methoxy-2-thiocyanatobiphenyl **12a** (1.8 g, 5 mmol), $LiAlH_4$ (1 M in THF, 5.5 mL, 5.5 mmol) and THF (10 mL). The title compound was obtained as an oil, which solidified on standing and was used without further purification (1.6 g, 96%): R_f 0.43 (DCM/petrol 1 : 4); mp: 112–113 °C; IR (cm^{-1}) 1569, 1456, 1423, 1396, 1255, 1186, 1039, 850, 772; λ_{max} (EtOH)/nm 284; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (3H, s, OMe), 3.77 (1H, s, SH), 6.82 (1H, d, J = 8.2 Hz, H-Ar), 6.95–6.98 (2H, m, H-Ar), 7.04 (1H, d, J = 8.2 Hz, H-Ar), 7.24 (1H, ap t, J = 8.2 Hz, H-Ar), 7.46–7.49 (1H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6, 122.4, 122.8, 126.1, 129.2, 130.0, 130.4, 132.7, 135.1, 135.4, 136.4, 158.5; MS (EI) m/z = 328.0 [M(^{35}Cl,^{79}Br)]$^+$, 330.0 [M(^{35}Cl,^{81}Br; ^{37}Cl,^{79}Br)]$^+$, 332.0 [M(^{37}Cl,^{81}Br)]$^+$; HRMS calcd for $C_{13}H_{10}BrClSO$ [M(^{35}Cl,^{79}Br)]$^+$ 327.9319, found 327.9320.

1-, 2-, 3-, 4-Chloro or methoxy-6-bromo-dibenzo[*b*,*d*]thiophene derivatives (2a–f)

Typical procedure. A mixture of the substituted thiol (**13a**, **13c–f**, 1.0 eq.), and Cs_2CO_3 (1.5 eq.) in acetonitrile was heated by microwave irradiation at 130 °C for 10 min. The mixture was diluted with DCM and washed with water. The organic layer was

dried over $MgSO_4$ and concentrated *in vacuo* to give the required compound.

4-Bromo-1-methoxydibenzo[*b*,*d*]thiophene (2a)

3-Bromo-6′-chloro-2′-methoxybiphenyl-2-thiol **13a** (0.100 g, 0.30 mmol), Cs_2CO_3 (0.144 g, 0.44 mmol) and acetonitrile (2 mL). The reaction mixture was heated by microwave irradiation at 130 °C for 8 min. The crude product was purified by medium pressure chromatography (petrol/DCM 95 : 5) to give the title compound as a white solid (0.070 g, 80%): R_f 0.47 (DCM/petrol 5 : 95); mp 112–113 °C; IR (cm^{-1}) 1590, 1566, 1539, 1475, 1455, 1384, 1325, 1257, 1185, 1037, 1012, 785; λ_{max} (EtOH)/nm 283, 317, 330; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (3H, s, OMe), 6.94 (1H, d, J = 7.7 Hz, H-Ar), 7.35 (1H, ap t, J = 7.7 Hz, H-Ar), 7.41–7.51 (2H, m, H-Ar), 7.59 (1H, d, J = 7.7 Hz, H-Ar), 8.62 (1H, d, J = 8.0 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 106.3, 115.3, 115.8, 124.9, 125.6, 126.0, 128.0, 128.8, 136.9, 140.8, 141.0, 158.0; MS (EI) m/z = 292.0 $[M(^{79}Br)]^+$, 294.0 $[M(^{81}Br)]^+$; HRMS calcd for $C_{13}H_9SBrO$ $[M(^{79}Br)]^+$ 291.9552, found 291.9551.

6-Bromodibenzo[*b*,*d*]thiophenols (3a–c)

Typical procedure for the deprotection of 2a, 2c and the 'one-pot' cyclisation and deprotection of 13b, 13c. The substituted methoxydibenzothiophene (**2a**, **2b**, 1.0 eq.) or substituted thiol (**13b**, **13c**, 1.0 eq.) and pyridine hydrochloride (10.0 eq.) were placed in a Schlenk tube. The mixture was heated at 150 °C for 16–28 h, cooled to 80 °C and quenched with water. The resulting mixture was extracted with DCM, the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by medium pressure chromatography.

6-Bromo-dibenzo[*b*,*d*]thiophen-1-ol (3a)

4-Bromo-1-methoxydibenzothiophene **2a** (0.658 g, 2.2 mmol), and pyridine hydrochloride (5.0 g, 42.5 mmol) were heated in a sealed tube at 150 °C for 18 h. The crude product was purified by medium pressure chromatography (DCM/petrol 1 : 1) to give the title compound as a white solid (0.490 g, 79%): R_f 0.30 (DCM/petrol 1 : 1); mp 145–146 °C; IR (cm^{-1}) 3150, 1609, 1543, 1436, 1382, 1310, 1242, 1119, 1109, 945, 779; λ_{max} (EtOH)/nm 319, 332; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (1H, br. s, OH), 6.80 (1H, d, J = 7.7 Hz, H-Ar), 7.31–7.39 (2H, m, H-Ar), 7.48 (1H, d, J = 8.0 Hz, H-Ar), 7.60 (1H, d, J = 7.7 Hz, H-Ar), 8.61 (1H, d, J = 8.0 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 115.7, 115.9, 124.7, 124.9, 126.1, 127.8, 129.0, 136.6, 140.9, 141.4, 153.6; MS (EI) m/z = 278.1 $[M(^{79}Br)]^+$, 279.9 $[M(^{81}Br)]^+$; HRMS calcd for $C_{12}H_7BrS$ $[M(^{79}Br)]^+$ 277.9395, found 277.9394.

6-Bromo-dibenzo[*b*,*d*]thiophen-2-ol (3b)

3-Bromo-2′-chloro-5′-methoxy-biphenyl-2-thiol **13b** (2.13 g, 6.5 mmol) and pyridine hydrochloride (5 g, 43.3 mmol) were heated in a sealed tube at 150 °C for 18 h. Trituration from toluene yielded the title compound as a beige solid (1.14 g, 63%): R_f 0.31 (petrol/DCM 1 : 9); mp 173–175 °C; IR (cm^{-1}) 3257, 1610, 1571, 1539, 1427, 1393, 1334, 1307, 1244, 1180, 1095, 1014, 977, 862; λ_{max} (EtOH)/nm 184, 193, 344; ^1H NMR (300 MHz, d_4-MeOD) δ 6.94 (1H, d, J = 8.6 Hz, H-Ar), 7.26 (1H, ap t, J = 7.8 Hz, H-Ar), 7.47–7.52 (2H, m, H-Ar), 7.60 (1H, d, J = 8.6 Hz, H-Ar), 8.01 (1H, d, J = 7.8 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.7, 117.2, 117.3, 120.9, 124.2, 126.1, 130.1, 132.1, 137.1, 138.0, 154.2; MS (EI) m/z = 278.0 $[M(^{79}Br)]^+$, 280.0 $[M(^{81}Br)]^+$; HRMS calcd for $C_{12}H_7BrOS$ $[M(^{79}Br)]^+$ 277.9401, found 277.9401.

2′,3′-Dichloro-5-nitro-[1,1′-biphenyl]-2-amine (16)

A mixture of a 2-bromo-4-nitroaniline (0.6 g, 2.7 mmol), 2,3-dichlorophenylboronic acid (0.640 g, 3.3 mmol), $Pd(PPh_3)_4$ (0.1 g, 0.13 mmol), 2 M aqueous Na_2CO_3 (5 mL) and DME (6 mL) was heated under microwave irradiation at 175 °C, for 85 min. The resulting mixture was poured into a saturated solution of NH_4Cl and the product was extracted into EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product that was purified by medium pressure chromatography (DCM/petrol 1 : 4), to give the title compound as a yellow solid (0.52 g, 66%): R_f 0.47 (petrol/DCM 1 : 4); mp 118–120 °C; IR (cm^{-1}) 3341, 3222, 1631, 1605, 1573, 1472, 1451, 1301, 1265, 1188, 1120, 820, 785; λ_{max} (EtOH)/nm 268, 372; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (2H, s, NH_2), 6.76 (1H, d, J = 8.9 Hz, H-Ar), 7.26 (1H, d, J = 8.0 Hz, H-Ar), 7.35 (1H, ap t, J = 7.9 Hz, H-Ar), 7.58 (1H, d, J = 7.9 Hz, H-Ar), 8.00 (1H, s, H-Ar), 8.14 (1H, d, J = 8.9 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.5, 124.0, 126.2, 127.2, 128.3, 130.2, 131.2, 132.9, 134.7, 138.7, 139.6, 150.0; MS (EI) m/z = 282.0 $[M(^{35}Cl)]^+$, 284.0 $[M(^{37}Cl)]^+$; HRMS calcd for $C_{12}H_8N_2O_2Cl_2$ $[M(^{35}Cl)]^+$ 281.9957, found 281.9958.

2,3-Dichloro-5′-nitro-2′-thiocyanato-1,1′-biphenyl (17)

To a solution of the substituted aniline 2′,3′-dichloro-5-nitro-[1,1′-biphenyl]-2-amine **16** (0.20 g, 0.7 mmol) in MeOH (8 mL) was added dropwise conc. hydrochloric acid (3 mL) over 15 min at 0 °C. To this mixture a cooled (0 °C) solution of sodium nitrite (0.06 g, 0.77 mmol) in water was added dropwise maintaining the temperature below 0 °C. The resulting solution was stirred for 10 min. A mixture of potassium thiocyanate (0.217 g, 2.24 mmol) and iron(III) chloride (0.08 g, 0.05 mmol) in water (15 mL) was added to the reaction mixture at 0 °C. The mixture was stirred for 4–5 h at room temperature. Upon neutralisation with 2 M NaOH the reaction mixture was extracted into DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting thiocyanate was purified by medium pressure chromatography (DCM/petrol 1 : 1) to give the title compound as a colourless oil (0.120 g, 52%): R_f 0.43 (DCM/petrol 1 : 1); IR (cm^{-1}) 2160, 1570, 1521, 1444, 1409, 1194, 1026, 894, 829, 789; λ_{max} (EtOH)/nm 291; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, d, J = 7.9 Hz, H-Ar), 7.30 (1H, ap t, J = 7.9 Hz, H-Ar), 7.56 (1H, d, J = 8.0 Hz, H-Ar), 7.90 (1H, d, J = 8.8 Hz, H-Ar), 8.07 (1H, s, H-Ar), 8.29 (1H, d, J = 8.8 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.2, 124.9, 125.9, 128.3, 129.3, 129.6, 129.9, 132.4, 134.3, 135.0, 137.1, 140.0, 148.5; MS (EI) m/z = 324.0 $[M(^{35}Cl)]^+$, 326.0 $[M(^{37}Cl)]^+$; HRMS calcd for $C_{13}H_6N_2O_2SCl_2$ $[M(^{35}Cl)]^+$ 323.9522, found 323.9527.

2′,3′-Dichloro-5-nitro-[1,1′-biphenyl]-2-thiol (18)

To a solution of KOH (0.5 g, 15.3 mmol) in EtOH (8 mL), was added 2,3-dichloro-5′-nitro-2′-thiocyanato-1,1′-biphenyl **17** in

EtOH (5 mL). The reaction mixture was stirred for 1 h at 10 °C. A solution of 5% H_2SO_4 in EtOH was added dropwise, the mixture was poured on water (20 mL) extracted into EtOAc, washed with brine (15 mL) and dried over $MgSO_4$. The title compound was obtained as a white solid and used without further purification (0.130 g, 80%): R_f 0.81 (MeOH/DCM 1 : 99); mp 183–185 °C; IR (cm^{-1}) 2559, 1600, 1568, 1505, 1445, 1407, 1334, 1245, 1191, 1116, 1151, 1074, 1018, 894; λ_{max} (EtOH)/nm 314, 438; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (1H, s, SH), 7.21 (1H, d, J = 7.9 Hz, H-Ar), 7.36 (1H, ap t, J = 7.9 Hz, H-Ar), 7.52 (1H, d, J = 8.6 Hz, H-Ar), 7.61 (1H, d, J = 7.9 Hz, H-Ar), 8.05 (1H, s, H-Ar), 8.14 (1H, d, J = 8.6 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.8, 125.5, 128.1, 129.4, 129.7, 131.5, 132.7, 134.7, 138.4, 139.6, 142.2, 146.1; MS (EI) m/z = 299.0 [M(^{35}Cl)]$^+$, 301.0 [M(^{37}Cl)]$^+$; HRMS calcd for $C_{12}H_7NO_2Cl_2$ [M(^{35}Cl)]$^+$ 298.9569, found 298.9569.

6-Chloro-2-nitrodibenzo[*b*,*d*]thiophene (4)

A mixture of 2′,3′-dichloro-5-nitro-[1,1′-biphenyl]-2-thiol (1.40 g, 4.6 mmol) and Cs_2CO_3 (2.30 g, 6.9 mmol) in acetonitrile (10 mL) was heated by microwave irradiation at 130 °C for 8 min. The mixture was diluted with DCM and washed with water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as cream needles which were used without further purification (1.10 g, 91%): R_f 0.78 (DCM/petrol 1 : 4); mp 199–201 °C; IR (cm^{-1}) 1570, 1504, 1398, 1338, 1243, 1192, 1192, 1147, 1112, 1022, 896, 815, 781; λ_{max} (EtOH)/nm 254, 271, 304, 328; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.61 (2H, m, H-Ar), 8.04 (1H, d, J = 8.8 Hz, H-Ar), 8.19 (1H, d, J = 7.5 Hz, H-Ar), 8.38 (1H, d, J = 8.8 Hz, H-Ar), 9.04 (1H, s, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.9, 120.7, 122.0, 123.7, 126.9, 127.0, 128.1, 128.3, 129.0, 130.2, 136.6, 146.1; MS (EI) m/z = 263.0 [M(^{35}Cl)]$^+$, 265.0 [M(^{37}Cl)]$^+$; HRMS calcd for $C_{12}H_6NClSO_2$ [M(^{35}Cl)]$^+$ 262.9802, found 262.9802.

Substituted dibenzothiophen-4-yl chromenone derivatives (21, 22a–f, 23a–c, 24)

Typical procedure. Method E: A mixture of the substituted 6-bromo-dibenzo[*b*,*d*]thiophene (**1**, **2b**, 1.0 eq.), bis(pinacolato)diboron (1.5 eq.), $PdCl_2$(dppf) (10 mol%), KOAc (6.0 eq.) and THF was heated at reflux for 16 h. EtOAc was added and the combined organic phase was washed with water and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product that was purified by medium pressure chromatography. In a Schlenk tube, a degassed solution of the boronate (1.0 eq.), 2-morpholin-4-yl-4-oxo-4*H*-chromen-8-yl trifluoromethanesulfonate **19** (1.05 eq.), $PdCl_2$(dppf) (10 mol%), Cs_2CO_3 (3.0 eq.) in THF (5 mL) was heated to reflux for 16 h. Water (10 mL) was added and the reaction mixture was extracted into DCM. the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by medium pressure chromatography.

Method F: A mixture of the substituted halo dibenzothiophenes (**2a**, **2c–f**, **3a–c**, 1.0 eq.), 2-morpholin-4-yl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4*H*-chromen-4-one **20** (1.0 eq.), $Pd(PPh_3)_4$ (5 mol%), 2 M aqueous Na_2CO_3 and DME was heated under microwave irradiation at 175 °C for 45–60 min. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl and the product was extracted into EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product that was purified by medium pressure chromatography.

8-(7-Methyldibenzo[*b*,*d*]thiophen-4-yl)-2-morpholin-4-yl-4*H*-chromen-4-one (21)

Following Method E: 6-bromo-3-methyldibenzo[*b*,*d*]thiophene (0.072 g, 0.259 mmol), $PdCl_2$(dppf) (0.021 g, 0.026 mmol), KOAc (0.153 g, 1.56 mmol) and bis(pinacolato)diboron (0.099 g, 0.389 mmol) in THF (7 mL) at reflux for 24 h. The crude product was purified by medium pressure chromatography (EtOAc/MeOH 95 : 5) to yield 4,4,5,5-tetramethyl-2-(7-methyldibenzo[*b*,*d*]thiophen-4-yl)-1,3,2-dioxaborolane. The boronate (0.030 g, 0.093 mmol), **19** (0.037 g, 0.097 mmol), $PdCl_2$(dppf) (8.0 mg, 0.009 mmol) and Cs_2CO_3 (0.091 g, 0.279 mmol) in THF (5 mL) was heated at reflux for 16 h. The crude product was purified by medium pressure chromatography (DCM/MeOH 9 : 1) to yield the title compound as a white solid (0.027 g, 58%): R_f 0.12 (EtOAc); mp 258–260 °C; IR (cm^{-1}) 2853, 1618, 1560, 1405, 1244, 1116, 985, 780; λ_{max} (EtOH)/nm 237; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (3H, s, Me), 3.03 (4H, m, morpholine-CH_2), 3.44 (4H, m, morpholine-CH_2), 5.23 (1H, s, H-3), 7.22 (1H, ap t, J = 7.6 Hz, H-Ar), 7.28–7.53 (4H, m, H-Ar), 7.74 (1H, d, J = 7.4 Hz, H-Ar), 8.01 (1H, d, J = 8.1 Hz, H-Ar), 8.09 (1H, d, J = 8.1 Hz, H-Ar), 8.21 (1H, d, J = 7.8 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1; 31.3; 44.9; 66.2; 87.4; 121.4; 121.9; 124.9; 125.3; 126.6; 126.9; 127.5; 127.9; 129.0; 131.6; 133.5; 133.9; 136.5; 137.9; 139.8; 150.9; 162.5; MS (ES+) m/z 428.61 [M+H]$^+$; Anal. Calcd for $3C_{26}H_{21}NO_3S{\cdot}2CH_2Cl_2$: C, 66.16, H, 4.65, N, 2.89. Found: C, 66.20, H, 4.60, N, 2.62%.

8-(9-Methoxydibenzo[*b*,*d*]thiophen-4-yl)-2-morpholin-4-yl-4*H*-chromen-4-one (22a)

Following Method F: 2-morpholin-4-yl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4*H*-chromen-4-one **20** (0.10 g, 0.28 mmol), 4-bromo-1-methoxydibenzo[*b*,*d*]thiophene **2a** (0.09 g, 0.28 mmol), $Pd(PPh_3)_4$ (5.0 mg, 0.002 mmol), 2 M Na_2CO_3 (0.6 mL) and DME (4 mL). The reaction mixture was heated under microwave irradiation at 175 °C for 1 h. The crude product was purified using medium pressure chromatography (MeOH/DCM 5 : 95) to give the title compound as a white solid (0.040 g, 40%): R_f 0.45 (MeOH/DCM 3 : 97); mp 266–267 °C; λ_{max} (EtOH)/nm 282, 316; IR (cm^{-1}) 1641, 1579, 1428, 1260, 1124, 1053, 992, 795; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08–3.11 (4H, m, morpholine-CH_2), 3.49–3.53 (4H, m, morpholine-CH_2), 4.14 (3H, s, OMe), 5.54 (1H, s, H-3), 6.93–7.00 (1H, m, H-Ar), 7.40–7.60 (5H, m, H-Ar), 7.79 (1H, d, J = 7.7 Hz, H-Ar), 8.28 (1H, d, J = 8.5 Hz, H-Ar), 8.75 (1H, d, J = 8.5 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.0, 55.8, 66.0, 87.3, 106.2, 115.2, 124.0, 124.9, 125.0, 125.5, 125.9, 126.2, 127.3, 127.9, 129.2, 130.9, 133.6, 136.1, 139.4, 141.2, 151.1, 157.1, 162.5, 177.2; MS (ES+) m/z = 444.2 [M + H]$^+$; HRMS calcd for $C_{26}H_{21}NO_4S$ [M + H]$^+$ 444.1264, found 444.1262. Anal. Calcd for $C_{26}H_{21}NO_4S$: C, 69.35, H, 4.73, N, 3.10. Found: C, 69.43, H, 4.72, N, 3.04%.

Enzyme inhibition assay

Compounds **21**, **22a–f**, **23a–c** and **24** were measured for inhibition of the DNA-PK enzyme as detailed in reference 26. Mammalian

DNA-PK (500 ng μL^{-1}) was isolated from HeLa cell nuclear extract by Q-Sepharose, followed by S-Sepharose chromatography and a final step of heparin-agarose chromatography. DNA-PK (250 ng) activity was measured at 30 °C, in a final volume of 40 μL, in buffer containing 25 mM Hepes, pH 7.4, 12.5 mM $MgCl_2$, 50 mM KCl, 1 mM DTT, 10% glycerol, 0.1% NP-40, and 1 μg of the substrate GST-p53N66 (the amino-terminal 66 amino acid residues of human wild-type p53 fused to glutathione S-transferase) in polypropylene 96-well plates. To the assay mix were added varying concentrations of inhibitor (in DMSO at a final concentration of 1%). After 10 min of incubation, ATP was added to give a final concentration of 50 μM along with a 30mer double-stranded DNA oligonucleotide (final concentration of 0.5 ng mL^{-1}) to initiate the reaction. After 1 h with shaking, 150 μL of phosphate-buffered saline (PBS) was added to the reaction and 5 μL was then transferred to a 96-well opaque white plate containing 45 μL of PBS per well, where the GSTp53N66 substrate was allowed to bind to the wells for 1 h at room temperature. To detect the phosphorylation event on the serine-15 residue of p53 elicited by DNA-PK, a rabbit phosphoserine-15 antibody (Cell Signaling Technology) was used in a basic ELISA procedure. An anti-rabbit HRP conjugated secondary antibody (Pierce) was then employed in the ELISA before the addition of chemiluminescence reagent (NEN Renaissance) to detect the signal as measured by chemiluminescent counting *via* a TopCount NXT (Packard). IC_{50} was derived from a sigmoidal plot using the graphic package Prism, in which the DNA-PK activity in the varying concentrations of compounds was plotted against the concentration of compound.

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