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An efficient synthetic route to biologically relevant 2-phenylbenzothiazoles substituted on the benzothiazole ring

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ABSTRACT

Certain 2-phenylbenzothiazoles containing substituents on the benzothiazole ring possess important biological properties, yet the majority of synthetic methods to 2-phenylbenzothiazoles described to date focus on their unsubstituted ring counterparts. Here we describe a new concise and efficient synthetic route to biologically relevant 2-phenylbenzothiazoles in high yield from the reaction of substituted 2-aminothiophenol disulfides and benzaldehydes, promoted by the inexpensive and non-toxic inorganic oxidant sodium metabisulfite in DMSO at 120 °C. Our new method is tolerant of a range of substituents on both the benzothiazole and phenyl ring, and affords efficient access to substituted 2-phenylbenzothiazoles without the need for column chromatography.

1. Introduction

Certain substituted 2-phenylbenzothiazoles have emerged as agents of considerable biological importance in recent years in a variety of diagnostic and therapeutic settings.[1] Particularly noteworthy applications have come in the fields of the potential diagnosis of Alzheimer's disease[2] and cancer therapy.[3]

An important milestone in the development of substituted 2-phenylbenzothiazoles as non-invasive diagnostic imaging agents came with the development of the ^{11}C-labelled 2-(4-methylamino phenyl)-6-hydroxybenzothiazole (known as Pittsburgh compound B; PiB; **1**; Fig. 1).[2a–d] PiB is currently in clinical trials for diagnostic imaging of Alzheimer's disease by Positron Emission Tomography (PET), through selective binding to Aβ (amyloid) plaques, a hallmark pathological feature of Alzheimer's.[2e] The potential application of fluorinated 2-(4-aminophenyl)benzothiazoles as potential PET imaging agents in this context has also been described.[2f]

2-(4-Amino-3-methylphenyl)-5-fluorobenzothiazole (5F 203; **2**; Fig. 1) is a potent and selective member of the 2-(4-aminophenyl)benzothiazole class of antitumour agents[3a,b] with a novel cellular mechanism of action involving induction of the cytochrome P450 isoform CYP1A1 in selected cancer cells.[3c,d] The presence of a fluorine atom on the benzothiazole ring was found to be crucial in subverting metabolic deactivation, when compared to its non-fluorinated counterpart.[3e] The water-soluble lysyl amide prodrug of 5F 203[3f] (known as Phortress) is currently in Phase 1 clinical trials for cancer in the U.K. Further potent and selective fluorinated benzothiazole-based antitumour agents that have been identified including 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610; **3**; Fig. 1)[3g] and fluorinated benzothiazole-substituted hydroxycyclohexa-2,5-dienones ('quinols' **4**; Fig. 1).[3h]

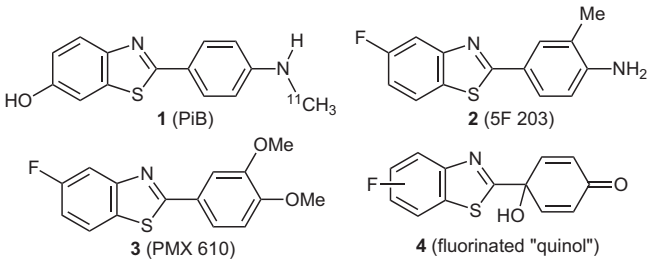

Fig. 1. Biologically relevant 2-phenylbenzothiazole derivatives substituted on the benzothiazole ring.

A range of synthetic approaches to 2-phenylbenzothiazoles unsubstituted on the benzothiazole ring are available, and have recently been reviewed.[1] Most commonly these routes involve the condensation between commercially available 2-aminothiophenol and either benzoic acids/benzoic acid derivatives (esters/acyl chlorides etc.);[4a–c] or benzaldehydes (Scheme 1).[5a,b] In the case of benzaldehydes as condensation partners, the initial formation of

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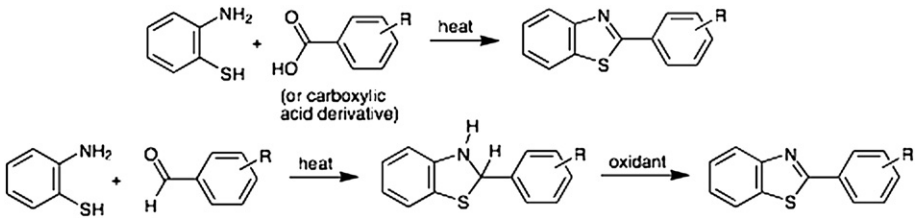
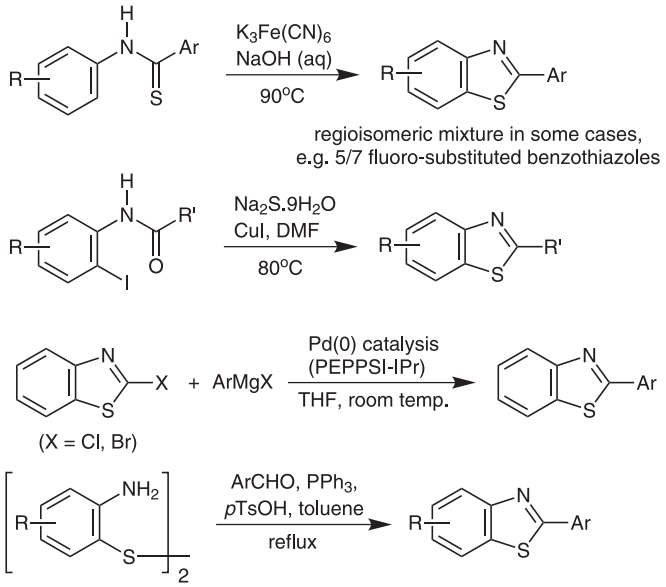
a putative dihydrobenzothiazole product has necessitated the further addition of an external oxidant in a number of cases (Scheme 1), under both thermal[5a] and microwave-promoted conditions.[5b] Although 2-aminothiophenol is readily available, the synthesis of ring-substituted 2-aminothiophenols presents particular difficulties due to their instability and propensity towards oxidation/degradation.



Scheme 1. General synthetic routes to 2-phenylbenzothiazole from *o*-aminothiophenol.

Alternative synthetic routes to 2-phenylbenzothiazoles have been developed. For example thioanilide (Jacobsen) cyclisation has been commonly used (Scheme 2), particularly where substituents on the benzothiazole ring are required, such as in the antitumour 2-(4-aminophenyl)benzothiazole series.[3c,e] However, this thioamide cyclisation reaction onto the *ortho*-position gives rise to regioisomeric product mixtures in certain cases (such as the 5-fluoro-2-phenylbenzothiazole antitumour agents), necessitating installation of an *ortho*-halide group to direct thioanilide cyclisation.[6] The necessity to synthesise thioamides using agents such as the toxic and malodorous Lawesson's reagent is a further limitation of this method, which is generally not applicable to substrates containing other carbonyl functionalities.



Scheme 2. Alternative synthetic routes to 2-phenylbenzothiazoles, including products containing benzothiazole-ring substituents.

Ma and co-workers have recently described an attractive alternative route to 2-substituted benzothiazoles from 2-haloanilides using sodium sulfide ($Na_2S\cdot 9H_2O$) as coupling partner under copper (I)-catalysed conditions (Scheme 2).[7] Reports of transition metal-catalysed carbon–carbon bond forming reactions between 2-halobenzothiazoles and leaving group-containing aryl rings (e.g., aryl Grignards in the Kumada–Tamao–Coriu reaction)[8] have also been increasing in recent years (Scheme 2).

We have previously described the regiospecific synthesis of 2-phenylbenzothiazoles in moderate yields from the reaction of stable *ortho*-aminothiophenol disulfides with benzaldehydes, using triphenylphosphine to reduce the disulfide bond in situ prior to reaction with the benzaldehyde (Scheme 2).[3g] This method has required the use of column chromatography for final purification to remove the triphenylphosphine by-product. We now report an operationally simple and concise route to substituted 2-phenylbenzothiazoles from *ortho*-aminothiophenol disulfides and benzaldehydes, using sodium metabisulfite as an oxidant[9] to give a range of benzothiazole products in high yield and without the need for column chromatography. Remarkably these new reaction conditions allow clean synthesis of benzothiazole product in just a few hours without the need for a reducing agent to initiate reaction.

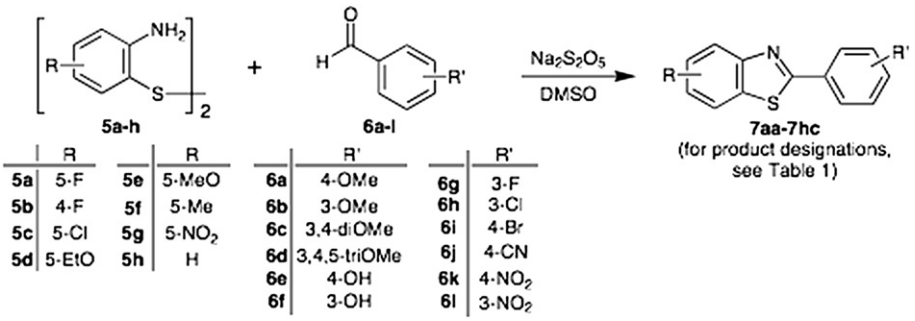
2. Results and discussion

2.1. Synthesis of 2-phenylbenzothiazoles containing benzothiazole-ring substituents

The starting point for our new benzothiazole synthesis was the substituted 2-aminothiophenol disulfides **5a**–**h**. The required 5-substituted 2-aminothiophenol disulfides (**5a**, **5c**–**g**) can be synthesised as stable solid products from the corresponding commercially available 2-amino-6-substituted benzothiazoles via potassium hydroxide-mediated hydrolytic cleavage followed by air oxidation, according to previously published methods.[3e,10,11] 2-Amino-5-fluorobenzothiazole was synthesised from 3-fluoroaniline as previously described, and was converted to 2-amino-4-fluorothiophenol disulfide (**5b**) by the basic hydrolysis/oxidation method.[3e] Unsubstituted 2-aminothiophenol disulfide (**5h**) is commercially available (Sigma–Aldrich, U.K; 97% purity). It is noteworthy that the 2-aminothiophenol disulfide substrates prepared by this method exist as stable powders that are easily handled. In comparison unsubstituted 2-aminothiophenol (substituted 2-aminothiophenols are not generally commercially available) is a harmful and corrosive liquid with toxic effects in the aquatic environment. In this respect 2-aminothiophenol disulfide represents an environmentally attractive alternative for benzothiazole synthesis.

The key step in the synthesis involves reaction of substituted 2-aminothiophenol disulfides (**5a**–**h**) with benzaldehydes **6a**–**l** containing both electron-donating (e.g., OMe) and electron-withdrawing (e.g., CN, NO_2) groups, promoted by the non-toxic and inexpensive oxidant sodium metabisulfite ($Na_2S_2O_5$) in DMSO at 120 °C. Reaction progress was monitored by TLC, with complete formation of benzothiazole product in 40–90 min. Product isolation and purification was straightforward, involving addition of water to precipitate the product with further aqueous washing to remove traces of inorganic by-products derived from sodium metabisulfite. This simple workup procedure gave pure benzothiazole products (**7aa**–**7hc**) without the need for purification by column chromatography; although recrystallisation of product was necessary in some cases (Scheme 3). Isolated product yields in the

majority of cases were >80% (Table 1). A further notable feature of this method is the ability to synthesise phenolic benzothiazoles without the need for phenol protecting groups (products **7ae**, **7af**, **7cf**, **7de**, **7df**, **7fe** and **7ff**).



	R		R		R'		R'
5a	5-F	5e	5-MeO	6a	4-OMe	6g	3-F
5b	4-F	5f	5-Me	6b	3-OMe	6h	3-Cl
5c	5-Cl	5g	5-NO_2	6c	3,4-diOMe	6i	4-Br
5d	5-EtO	5h	H	6d	3,4,5-triOMe	6j	4-CN
				6e	4-OH	6k	4-NO_2
				6f	3-OH	6l	3-NO_2

Scheme 3. Synthesis of substituted 2-phenylbenzothiazoles using sodium metabisulfite as oxidant.

Table 1
Substituted 2-phenylbenzothiazole product designations and yields

Cpd.	R	R′	Yield (%)	Cpd.	R	R′	Yield (%)
7aa	6-F	4-OMe	88	**7db**	6-OEt	3-OMe	92
7ab	6-F	3-OMe	84	**7dc**	6-OEt	3,4-DiOMe	91
7ac	6-F	3,4-DiOMe	83	**7dd**	6-OEt	3,4,5-TriOMe	82
7ad	6-F	3,4,5-TriOMe	97	**7de**	6-OEt	4-OH	91
7ae	6-F	4-OH	91	**7df**	6-OEt	3-OH	93
7af	6-F	3-OH	93	**7dg**	6-OEt	3-F	84
7ag	6-F	3-F	91	**7dh**	6-OEt	3-Cl	67
7ah	6-F	3-Cl	91	**7di**	6-OEt	4-Br	93
7ai	6-F	4-Br	89	**7dj**	6-OEt	4-CN	82
7aj	6-F	4-CN	86	**7dk**	6-OEt	4-NO_2	86
7ak	6-F	4-NO_2	96	**7dl**	6-OEt	3-NO_2	80
7bc	5-F	3,4-DiOMe	87	**7ec**	6-OMe	3,4-DiOMe	93
7bk	5-F	4-NO_2	90	**7fa**	6-Me	4-OMe	94
7ca	6-Cl	4-OMe	83	**7fc**	6-Me	3,4-DiOMe	81
7cb	6-Cl	3-OMe	89	**7fd**	6-Me	3,4,5-TriOMe	84
7cc	6-Cl	3,4-DiOMe	88	**7fe**	6-Me	4-OH	90
7cd	6-Cl	3,4,5-TriOMe	84	**7ff**	6-Me	3-OH	86
7cf	6-Cl	3-OH	90	**7fh**	6-Me	3-Cl	90
7ci	6-Cl	4-Br	85	**7fi**	6-Me	4-Br	83
7cj	6-Cl	4-CN	95	**7gc**	6-NO_2	3,4-DiOMe	91
7ck	6-Cl	4-NO_2	90	**7gd**	6-NO_2	3,4,5-TriOMe	88
7cl	6-Cl	3-NO_2	91	**7hc**	H	3,4-DiOMe	72
7da	6-OEt	4-OMe	88				

2.2. Mechanistic considerations

Our previously reported protocol for substituted 2-phenylbenzothiazole synthesis made use of triphenylphosphine, a reagent previously reported for the reduction of disulfides to the corresponding thiols.[3g,12] Reduction of the substituted thiophenol disulfide to the corresponding thiophenol using triphenylphosphine was assumed to be a necessary pre-requisite to the condensation/cyclisation reaction with benzaldehydes to form 2-phenylbenzothiazoles. Intriguingly, in our new protocol we were able to efficiently react substituted thiophenol disulfides with benzaldehydes to form 2-phenylbenzothiazoles within an apparent oxidising environment ($Na_2S_2O_5$ in DMSO). The 'oxidised' nature of our disulfide starting materials was confirmed by analytical methods (NMR and mass spectrometry, by comparison to previously reported compounds[3g]), and by their physical appearance as pale yellow solids (disulfide) rather than oils (thiol). Furthermore the commercially available unsubstituted thiophenol disulfide (**5h**), supplied in 97% purity (Sigma–Aldrich, U.K.), reacted smoothly with 3,4-dimethoxybenzald ehyde (**6c**) to give 2-(3,4-dimethoxyphenyl)benzothiazole (**7hc**) in 72% yield within 2 h.

Our new method describes the synthesis of substituted 2-phenylbenzothiazoles from thiophenol disulfides and benzaldehydes under oxidising reaction conditions; our working hypothesis for the possible reaction mechanism(s) is overviewed in Scheme 4. We assume that the amino group of substituted 2-aminothiophenol disulfide (A) initially reacts with the benzaldehyde to form the imine disulfide compound denoted (B). Cyclisation of the disulfide onto the imine would then lead to intermediate (C), followed by spontaneous disulfide bond cleavage to give (D), the tautomer of the 2-phenylbenzothiazole product, and iminothiophenol (E). The iminothiophenol (E) could then either cyclise onto the imine to generate dihydrobenzothiazole (G), or be re-oxidised to intermediate (B), which would then cyclise to further benzothiazole product via (C) and (D). An alternative mechanistic explanation involves the exchange of disulfide and thiol forms in equilibrium in DMSO, although it should be noted that the unsubstituted thiophenol disulfide (**5h**) was found to be entirely stable in DMSO-d_6 by NMR, even upon heating. It is known that the interchange between alkyl disulfides and thiolates is dependent on choice of solvent, and that solvents with high dielectric constants, such as DMSO and DMF increase the rate of interchange.[13] It is also possible that a small amount of water present in the 'anhydrous' DMSO used would react with sodium metabisulfite to produce SO_2, which would act as a reductant to facilitate formation of thiophenol, either before or after initial reaction with substituted benzaldehyde. Such disulfide–thiol interchange would lead to the formation of intermediates such as (E) and (F), which could then cyclise to the dihydrobenzothiazole (G) and subsequently to product under the oxidising conditions of the reaction.

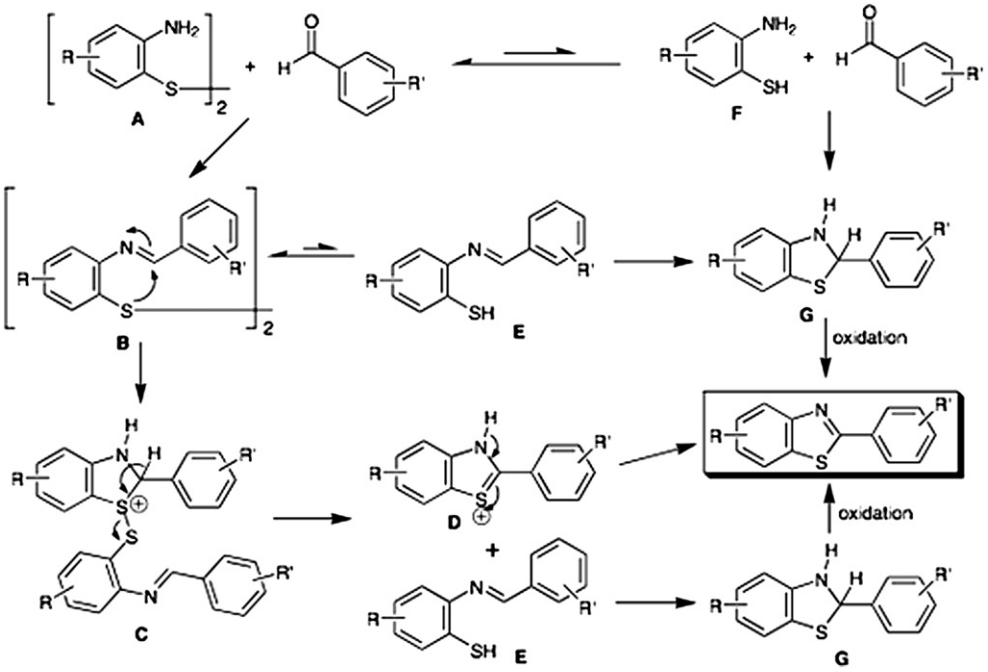
3. Conclusion

Substituted 2-phenylbenzothiazoles containing benzothiazole-ring substituents are an important class of molecules from both a disease diagnostic and therapeutic standpoint. There are relatively few reported methods for the synthesis of 2-phenylbenzothiazoles containing benzothiazole-ring substituents compared to their non-substituted counterparts. Here we present an operationally simple route to substituted 2-phenylbenzothiazoles containing a diversity of ring substituents, through heating thiophenol disulfides with commercially available benzaldehydes in the presence of sodium metabisulfite in DMSO. Our method features short reaction times (<2 h) and simple workup leading to the isolation of pure benzothiazole products without the need for column chromatographic purification, and is applicable to the synthesis of a wide range of substituted 2-phenylbenzothiazoles.

4. Experimental

4.1. General methods

Melting points were measured on a Griffin melting point apparatus and are uncorrected. ^{1}H (500 MHz), ^{13}C NMR (125 MHz)



Scheme 4. Postulated mechanism for formation of substituted 2-phenylbenzothiazoles under 'oxidising' conditions.

and ^{19}F NMR (471 MHz) spectra were recorded on a Bruker AVANCE 500 MHz instrument; chemical shift values are in parts per million and coupling constants (*J* values) are in hertz. Mass spectra were recorded on a Bruker MicroTOF LC instrument or at the EPSRC National Mass Spectrometry Centre (Swansea, U.K.). All commercially available starting materials were used without further purification, and synthesis of the required 2-aminothiophenol disulfide starting materials (**5a**–**g**) was carried out according to well established literature methods as described in the chemistry results section. Compound **5h** is commercially available (Sigma–Aldrich).

4.2. General procedure for the synthesis of substituted 2-phenylbenzothiazoles

The appropriate 4- or 5-substituted 2-aminothiophenol disulfide (0.86 mmol), substituted benzaldehyde (0.88 mmol) and sodium metabisulfite (0.88 mmol) were dissolved in anhydrous DMSO (5 mL). The resulting reaction mixture was stirred at 120 °C and the formation of the desired compound monitored by TLC analysis. On completion of reaction (in most cases between 40 and 90 min) the mixture was cooled to room temperature, water was added and the resulting precipitate was collected by vacuum filtration. The precipitate was then washed with excess water, re-dissolved in dichloromethane (25 mL) and the remaining traces of sodium metabisulfite were removed by washing with brine (25 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. In a minority of cases further purification was required, and the product was either recrystallised or washed through a plug of silica (using dichloromethane as eluent) and reduced to dryness.

4.3. Spectroscopic and characterisation data for selected representative new substituted 2-phenylbenzothiazoles

*4.3.1. 6-Fluoro-2-(3-methoxyphenyl)benzothiazole (**7ab**).* Bis(2-amino-5-fluorophenyl)disulfide and *m*-anisaldehyde were reacted to give the *title compound* **7ab** (190 mg, 84%) as a pale green solid, mp 84–86 °C; [Found: C, 64.8; H, 4.0; N, 5.6. $C_{14}H_{10}FNOS$ requires C, 64.85; H, 3.89; N, 5.40%]; δ_H (500 MHz, $CDCl_3$) 8.04 (1H, dd, *J* 9.0, 5.0 Hz, H-4), 7.66–7.58 (3H, m, H-7, H-2′, H-6′), 7.42 (1H, t, *J* 8.2 Hz, H-5′), 7.25 (1H, dt, *J* 9.0, 2.5 Hz, H-5), 7.08–7.06 (1H, m, H-4′), 3.94 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 167.7, 161.5, 159.7 (d, *J* 270 Hz), 150.7, 136.1 (d, *J* 10.0 Hz), 134.6, 130.1, 124.2 (d, *J* 10.0 Hz), 120.1, 117.4, 115.0 (d, *J* 25.0 Hz), 112.0, 107.8 (d, *J* 26.3 Hz), 55.5; δ_F (471 MHz, $CDCl_3$) 115.76; *m*/*z* (EI) 259 (100, M^+).

*4.3.2. 6-Fluoro-2-(3-fluorophenyl)benzothiazole (**7ag**).* Bis(2-amino-5-fluorophenyl)disulfide and 3-fluorobenzaldehyde were reacted to give the *title compound* **7ag** (196 mg, 91%) as a yellow solid, mp 102–104 °C; [Found: C, 63.0; H, 2.8; N, 5.6. $C_{13}H_6F_2NS$ requires C, 63.15; H, 2.85; N, 5.66%]; δ_H (500 MHz, $CDCl_3$) 8.05 (1H, dd, *J* 7.5, 4.5 Hz, ArH), 7.84–7.81 (2H, m, ArH), 7.62 (1H, dd, *J* 8.0, 2.5 Hz, ArH), 7.51–7.47 (1H, m, ArH), 7.27–7.20 (2H, m, ArH). δ_C (125 MHz, $CDCl_3$) 165.7 (d, *J* 250 Hz), 163.4, 161.2 (d, *J* 265 Hz), 159.0, 150.2, 134.8 (d, *J* 8.8 Hz), 131.6 (d, *J* 8.8 Hz), 124.4 (d, *J* 10.0 Hz), 123.5, 118.3 (d, *J* 21.3 Hz), 115.4 (d, *J* 23.8 Hz), 113.5 (d, *J* 23.8 Hz), 108.8 (d, *J* 27.5 Hz); δ_F (471 MHz, $CDCl_3$) 115.37, 111.92; *m*/*z* (EI) 247 (100, M^+).

*4.3.3. 2-(3-Chlorophenyl)-6-fluorobenzothiazole (**7ah**).* Bis(2-amino-5-fluorophenyl)disulfide and 3-chlorobenzaldehyde were reacted to give the *title compound* **7ah** (210 mg, 91%) as a pale green solid, mp 101–103 °C; [Found: C, 59.2; H, 2.8; N, 5.4. $C_{13}H_7ClFNS$ requires C, 59.21; H, 2.68; N, 5.31%]; δ_H (500 MHz, $CDCl_3$) 8.11 (1H, t, *J* 1.5 Hz, H-2′), 8.05 (1H, dd, *J* 9.0, 5.0 Hz, H-7), 7.93 (1H, dt, *J* 7.5, 1.5 Hz, H-4), 7.62 (1H, dd, *J* 8.0, 2.5 Hz, H-6′), 7.50–7.40 (2H, m, H-4′, H-5′), 7.35–7.28 (1H, m, H-5); δ_C (125 MHz, $CDCl_3$) 166.0, 161.7, 159.7, 150.6, 136.1 (d, *J* 11.3 Hz), 135.1 (d, *J* 28.8 Hz), 130.9, 130.3, 127.3, 125.6, 124.4 (d, *J* 8.8 Hz), 115.3 (d, *J* 23.8 Hz), 107.9 (d, *J* 26.3 Hz); δ_F (471 MHz, $CDCl_3$) 115.10; *m*/*z* (EI) 263 (100, M^+).

*4.3.4. 2-(4-Bromophenyl)-6-fluorobenzothiazole (**7ai**).* Bis(2-amino-5-fluorophenyl)disulfide and 4-bromobenzaldehyde were reacted to give the *title compound* **7ai** (240 mg, 89%) as a pale green solid, mp 144–146 °C; δ_H (500 MHz, $CDCl_3$) 8.04 (1H, dd, *J* 9.0, 4.5 Hz, H-4), 7.96 (2H, d, *J* 8.5 Hz, H-3′, H-5′), 7.66 (2H, d, *J* 8.5 Hz, H-2′, H-6′), 7.61 (1H, dd, *J* 7.5, 2.5 Hz, H-7), 7.27 (1H, dt, *J* 7.5, 2.5 Hz, H-5); δ_C (125 MHz, $CDCl_3$) 166.4 (d, *J* 3.8 Hz), 161.6, 159.6, 150.7, 136.0 (d, *J* 11.3 Hz), 132.3,

128.8, 125.5, 124.3 (d, *J* 8.8 Hz), 115.2 (d, *J* 25.0 Hz), 107.9 (d, *J* 26.3 Hz); δ_F (471 MHz, $CDCl_3$) 115.31; *m*/*z* (EI) 307/309 (100, M^+); HRMS (EI): M^+, found 306.9461. $C_{13}H_7BrFNS$ requires 306.9467.

*4.3.5. 4-(6-Fluorobenzothiazol-2-yl)benzonitrile (**7aj**).* Bis(2-amino-5-fluorophenyl)disulfide and 4-cyanobenzaldehyde were reacted to give the *title compound* **7aj** (190 mg, 86%) as a yellow solid, mp 218–220 °C; δ_H (500 MHz, $CDCl_3$) 8.38 (2H, d, *J* 9.0 Hz, H-2′, H-6′), 8.26 (2H, d, *J* 9.0 Hz, H-3′, H-5′), 8.10 (1H, dd, *J* 8.5, 5.0 Hz, H-4), 7.66 (1H, dd, *J* 8.5, 2.5 Hz, H-7), 7.32 (1H, td, *J* 8.5, 2.5 Hz, H-5); δ_C (125 MHz, DMSO-d_6) 165.0, 161.2, 159.3, 150.4, 148.8, 138.1, 136.4 (d, *J* 12.5 Hz), 128.3, 124.9 (d, *J* 10.0 Hz), 124.6, 115.8 (d, *J* 25.0 Hz), 109.0 (d, *J* 27.5 Hz); δ_F (471 MHz, $CDCl_3$) 113.79. *m*/*z* (EI) 254 (100, M^+); HRMS (EI): M^+, found 254.0312. $C_{14}H_7FN_2S$ requires 254.0314.

*4.3.6. 2-(4-Bromophenyl)-6-ethoxybenzothiazole (**7di**).* Bis(2-amino-5-ethoxyphenyl)disulfide and 4-bromobenzaldehyde were reacted to give the *title compound* **7di** (270 mg, 93%) as a white solid, mp 130–133 °C; δ_H (500 MHz, $CDCl_3$) 7.92 (1H, d, *J* 9.0 Hz, H-4), 7.91 (2H, d, *J* 8.5 Hz, H-3′, H-5′), 7.61 (2H, d, *J* 8.5 Hz, H-2′, H-6′), 7.34 (1H, d, *J* 2.5 Hz, H-7), 7.10 (1H, dd, *J* 8.5, 2.5 Hz, H-5), 4.13 (2H, q, *J* 7.0 Hz, OCH_2), 1.49 (3H, t, *J* 7.0 Hz, CH_3). δ_C (125 MHz, $CDCl_3$) 164.03, 157.34, 148.56, 136.44, 132.76, 132.16, 128.59, 124.83, 123.80, 116.30, 104.87, 64.15, 14.82; *m*/*z* (EI) 333/335 (100, M^+); HRMS (EI): M^+, found 332.9822. $C_{15}H_{12}BrNOS$ requires 332.9823.

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Supplementary data

Characterisation data (mp, NMR, MS) for previously reported substituted 2-phenylbenzothiazole products (**7aa**, **7ac**–**af**, **7ak**, **7bc**–**bk**, **7ca**–**cl**, **7da**–**ah**, **7dj**–**l**, **7ec**, **7fa**–**fi**, **7gc**–**gd**). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.004.

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