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SYNTHESIS AND REACTIVITY OF DIMETHOXY ACTIVATED BENZOTHIAZOLES

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Abstract – A range of 2-substituted-5,7-dimethoxybenzothiazoles and 2-substituted-4,6-dimethoxybenzothiazoles have been synthesized by oxidative cyclization of the corresponding thioamides. These activated benzothiazoles display nucleophilic reactivity at C4 and C7 respectively and undergo formylation, acetylation and related reactions. Some 5,7-dimethoxybenzothiazoles with functionalization in a 2-aryl substituent are also reported as potential precursors for so far unsuccessful formation of macrocycles containing two benzothiazoles and two benzimidazoles.

INTRODUCTION

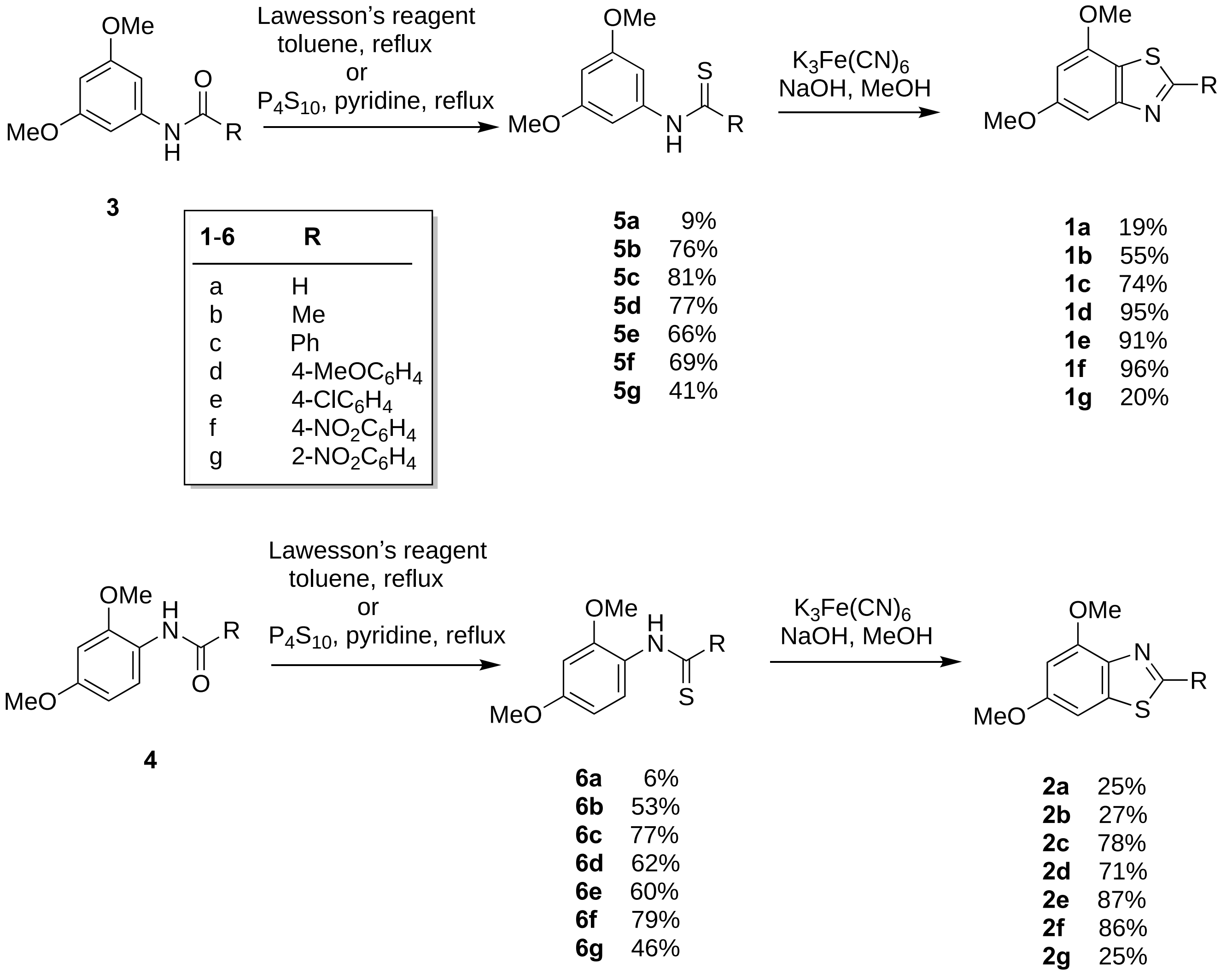
Benzothiazoles are precursors of natural products, pharmaceutical agents and other compounds that exhibit a wide spectrum of biological activity such as antitumor, immunosuppressive, immunomodulatory and antiviral properties.[1-3] Previous work in our group has established that strategically positioned 4,6-dimethoxy groups on indoles,[4,5] benzofurans,[6,7] and benzimidazoles[8,9] specifically activate the chemical reactivity of these heterocyclic systems at the C7 position: in the case of 5,7-dimethoxy groups on indoles and benzimidazoles the activation is directed to C4.[10,11] It is well established that targeted reactivity at other sites can immensely expand the synthetic applications of these heterocyclic systems. In order to extend this chemistry, the related benzothiazole system was considered. We now report the synthesis and reactivity of a range of 2-substituted-5,7-dimethoxybenzothiazoles **1** and 2-substituted-4,6-dimethoxybenzothiazoles **2**.

Benzothiazoles are most commonly synthesized *via* one of two major routes. A direct method involves the condensation of 2-aminothiophenols with electrophilic reagents. Substituted alkyl, aryl, and heteroaryl aldehydes react with 2-aminothiophenols in dimethyl sulfoxide to give the corresponding 2-substituted benzothiazoles. Similar reactions with carboxylic acids, esters, acyl chlorides and nitriles have been reported.[12,13] These methods however suffer from limitations such as difficulties encountered in the synthesis of readily oxidizable 2-aminothiophenols bearing substituent groups. Instead, an effective route is based on the potassium ferricyanide mediated radical cyclization in basic medium of thiobenzanilides (Jacobson synthesis). In this case, cyclization occurs on an unsubstituted position adjacent to the thioanilido nitrogen. This method is usually applied to the preparation of substituted benzothiazoles.[3,14] Other alternative methods for the preparation of 2-substituted benzothiazoles from 2-halothioanilides,[15] or oxidative coupling between thiophenols and aromatic nitriles in the presence of ceric ammonium nitrate[13] do not represent convenient general routes to functionalized 2-substituted benzothiazoles. Hence, the method of choice for the preparation of 4,6-dimethoxy- or 5,7-dimethoxy-benzothiazoles with various 2-substitutents was considered to be the Jacobson synthesis.

RESULTS AND DISCUSSION

Preparation of dimethoxybenzothiazoles

To follow the Jacobson synthetic procedure, in general 3,5-dimethoxyaniline and 2,4-dimethoxyaniline were first acylated by the respective acid chlorides to their corresponding 3,5-dimethoxyanilides **3** and 4,6-dimethoxyanilides **4** in dichloromethane or pyridine in good to high yields (Scheme 1). However, the formanilides **3a** and **4a** were prepared from the corresponding dimethoxyanilines by treatment with formic acid, and the acetamides **3b** and **4b** were obtained by reacting the corresponding dimethoxyanilines with acetic anhydride. Thionation of the anilides was accomplished by reaction either with Lawesson's reagent in refluxing toluene or phosphorus pentasulfide in refluxing pyridine to yield the thioamides **5**,**6**. These thioamides **5**,**6** were oxidatively cyclized to the corresponding 5,7-dimethoxybenzothiazoles **1** and 4,6-dimethoxybenzothiazoles **2** by reaction with potassium ferricyanide in aqueous sodium hydroxide solution. Usually, the acylation reactions were performed in dry dichloromethane containing anhydrous potassium carbonate giving high yields. In contrast, the nitrobenzamides **5f**,**g** and **6f**,**g** were obtained only in low yields using these conditions, presumably due to the presence of electron withdrawing substituents on the 2-phenyl ring. However, improved yields of nitrobenzanilides **5f**,**g** and **6f**,**g** were obtained when pyridine was used instead of dichloromethane. Thionation of the amide carbonyl groups with Lawesson's reagent was usually superior to use of phosphorus pentasulfide. Lawesson's reagent gave higher yields of the thioamides **5b**,**g** compared to those obtained using phosphorus pentasulfide and the products could be purified more readily by recrystallization. In the case of phosphorus pentasulfide, recrystallization was not always sufficient to give a pure product and short column chromatography was necessary. However, Lawesson's reagent did not give the thioamide **5g**, probably due to the deactivating effect of the nitro group, and the steric effect of the bulky Lawesson's reagent could also account for this. The thioanilides **5a** and **6a** were obtained only in trace amounts when the corresponding formanilides were reacted with phosphorus pentasulfide: use of Lawesson's reagent resulted in a small improvement to allow isolation of these products in low yields after column chromatography.



1-6	R
a	H
b	Me
c	Ph
d	4-$MeOC_6H_4$
e	4-ClC_6H_4
f	4-$NO_2C_6H_4$
g	2-$NO_2C_6H_4$

5a	9%
5b	76%
5c	81%
5d	77%
5e	66%
5f	69%
5g	41%

1a	19%
1b	55%
1c	74%
1d	95%
1e	91%
1f	96%
1g	20%

6a	6%
6b	53%
6c	77%
6d	62%
6e	60%
6f	79%
6g	46%

2a	25%
2b	27%
2c	78%
2d	71%
2e	87%
2f	86%
2g	25%

Scheme 1

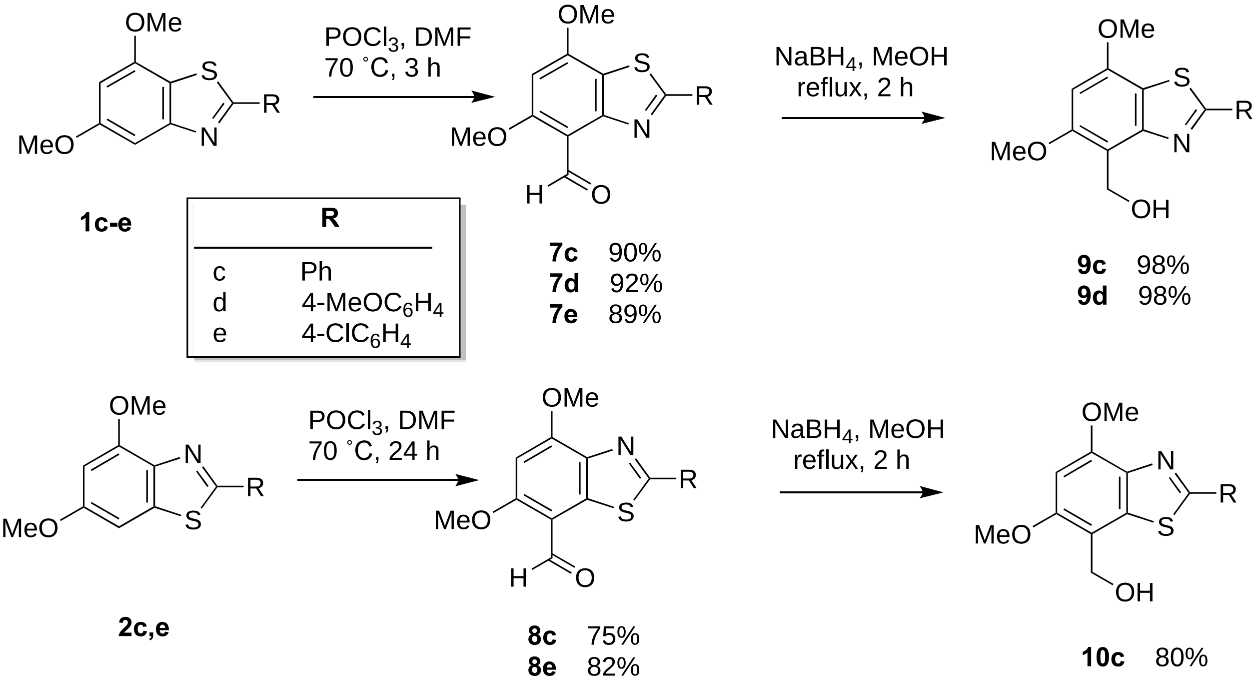
The 5,7-dimethoxybenzothiazoles **1c**,[16] **1d**,[17] and **1f**[18,19] and the 4,6-dimethoxybenzothiazoles **2b**,[20] **2c**,[21] **2d**,[14] and **2g**[18,19] have been reported previously. However, since the synthetic and spectroscopic details are frequently unavailable, our full experimental details are provided in Supplementary Material.

Selected reactions of dimethoxybenzothiazoles

Representative examples of the 2-arylbenzothiazoles were used as starting materials in these reactions to provide the most useful comparison with related dimethoxyindoles and dimethoxybenzimidazoles.

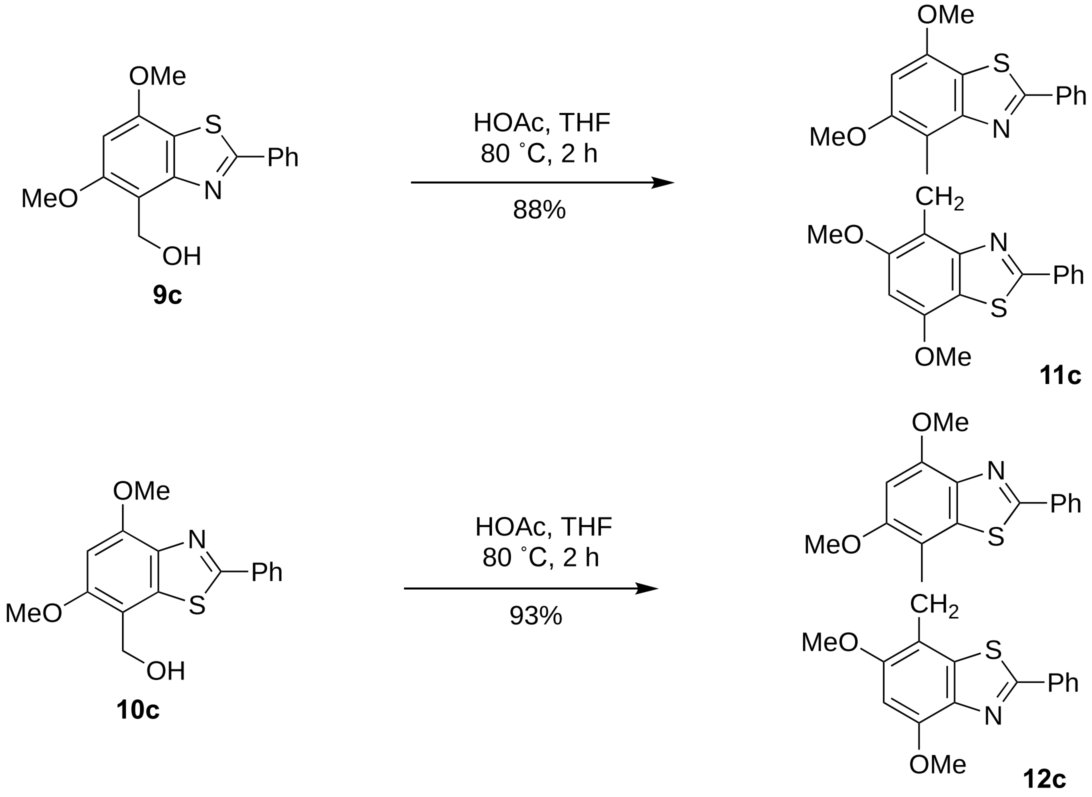
Formylation of activated benzothiazoles and reduction of benzothiazolecarbaldehydes

The Vilsmeier-Haack reaction normally occurs in high yields and there is often a significant difference in the conditions needed to achieve the formylation.[22] Therefore, this reaction is particularly useful for the determination of the reactivity of the nucleophilic sites (C7 and C4) of dimethoxy activated benzothiazoles. It is also important to compare this reactivity with the known reactivity of the dimethoxy activated indoles[23] and benzimidazoles.[9] The formylation reaction was carried out using a similar method as described earlier for the indoles and benzimidazoles. The Vilsmeier reagent failed to react with benzothiazoles **1c-e** at room temperature with overnight stirring. However, use of 1.5 equivalents of the formylating reagent and heating the reaction mixture at 70 ˚C for 2 h gave the benzothiazole-4-carbaldehydes **7c-e** in 89-92% yields (Scheme 2). Similarly, the benzothiazole-7-carbaldehydes **8c**,**e** were prepared from the benzothiazoles **2c**,**e** in 75 and 82% yields respectively. There appeared to be no difference in the reactivity of the benzothiazoles **1** and **2** based on the different methoxy substituent patterns. The formylation of benzothiazoles was found to be slower than that for the related dimethoxyindoles,[23] but faster than for the corresponding benzimidazoles.[9]



Scheme 2

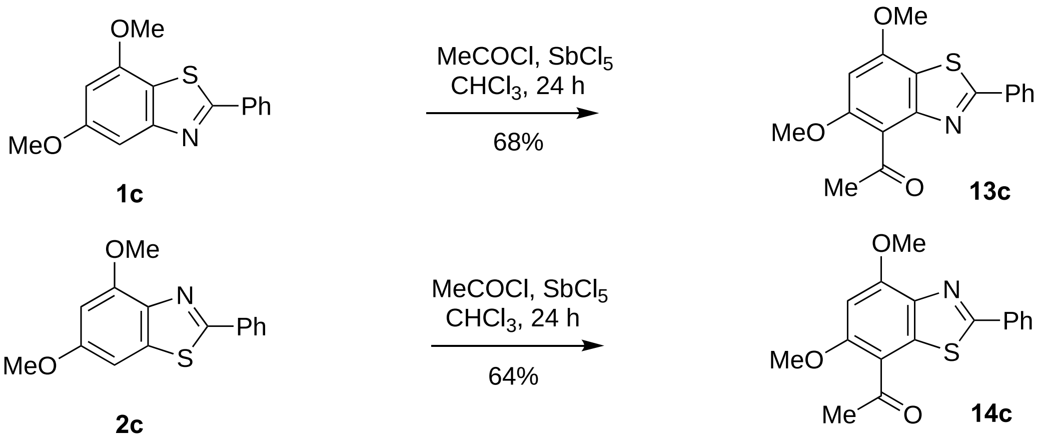
The ^{1}H and ^{13}C NMR spectra of the 5,7-dimethoxybenzothiazole-4-carbaldehydes **7c-e** and the 4,6-dimethoxybenzothiazole-7-carbaldehydes **8c**,**e** exhibited the characteristic aldehyde proton and carbonyl carbon resonances. The benzothiazolecarbaldehydes **7c**,**d** and **8c** were reduced in high yields to their corresponding alcohols **9c**,**d** and **10c** by heating under reflux with sodium borohydride in methanol (Scheme 2). The representative hydroxymethylbenzothiazoles **9c** and **10c** underwent facile acid catalyzed addition reactions in acetic acid at 80 ˚C to produce the di(benzothiazolyl)methane derivatives **11c** and **12c** respectively in 88 and 93% yields (Scheme 3). In their ^{1}H NMR spectra the methylene proton resonances were found at lower field positions compared with the starting alcohols. Molecular ion peaks at *m/z* 556 (M+1) for both the compounds provided further evidence for the formation of the di(benzothiazolyl)methane structures. This *ipso*-substitution behaviour matches that reported for related dimethoxyindoles[4] and dimethoxybenzimidazoles.[9] Once again the benzothiazole reactivity is shown to be greater than that of the corresponding benzimidazoles but less than that of the corresponding indoles.



Scheme 3

Acetylation of activated benzothiazoles

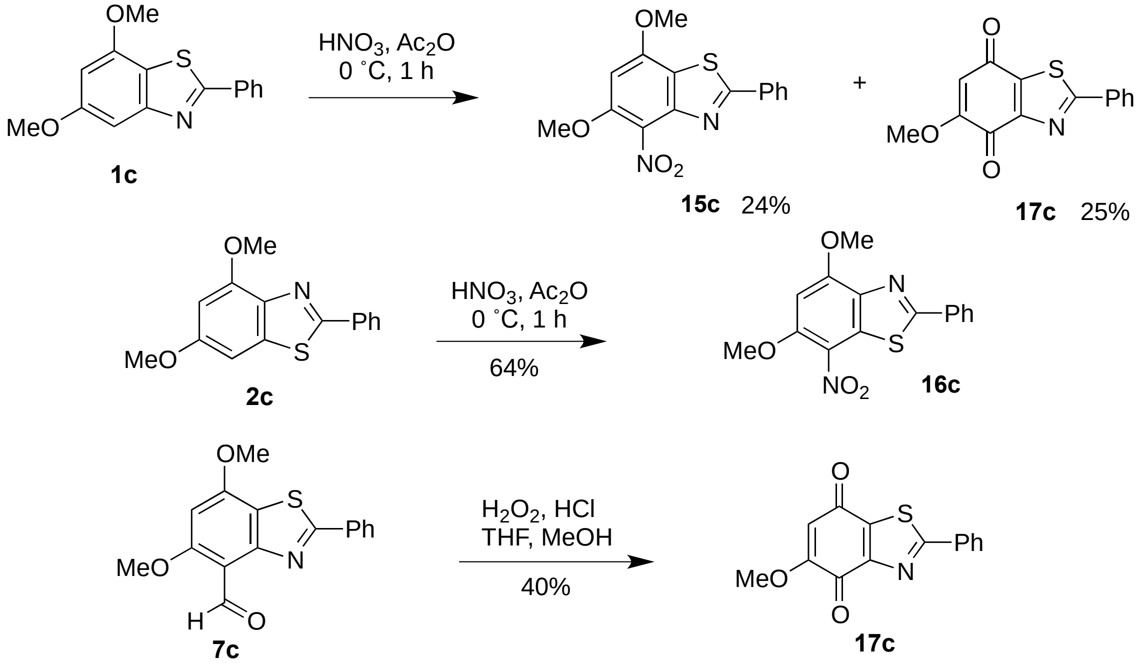
The modified Vilsmeier-Haack acetylation reaction of the benzothiazole **1c** using phosphoryl chloride and *N*,*N*-dimethylacetamide was found to be unsuccessful despite treatment with a large excess of the reagent and heating the reaction mixture at 60 ˚C for a week. Instead, the 4- and 7-acetyl compounds **13c** and **14c** were prepared in moderate yields by the Friedel-Crafts reaction with acetyl chloride using antimony pentachloride as the Lewis acid (Scheme 4). Under these similar reaction conditions, the Friedel-Crafts acylation reactivity of the benzothiazoles is again lower than that of the corresponding indoles, but similar to that of the activated benzimidazoles. Disappearance of the H4 and H7 protons in the ^{1}H NMR spectra and the appearance of peaks for the additional acetyl protons supported the structures.



Scheme 4

Nitration of activated benzothiazoles

Treatment of benzothiazoles **1c** and **2c** with nitric acid in a cold solution of acetic anhydride resulted in the respective formation of the 4-nitrobenzothiazole **15c** in 24% yield and the 7-nitrobenzothiazole **16c** in 64% yield, both as yellow crystals (Scheme 5). However, in addition to the 4-nitrobenzothiazole **15c** a product identified as the 4,7-dione **17c** was also isolated in 25% yield after column chromatography. The formation of the 4,7-dione **17c** during nitration thus explained the low yield of the 4-nitrobenzothiazole **15c**. It is considered that the 4,7-dione **17c** was produced by rearrangement of the nitro group of 4-nitrobenzothiazole **15c** to nitrite and subsequent demethylation and oxidation.[24] The 4,7-dione **17c** showed only one methoxy proton resonance in its ^{1}H NMR spectrum and a singlet resonance at 6.06 ppm corresponding to the H6 proton.

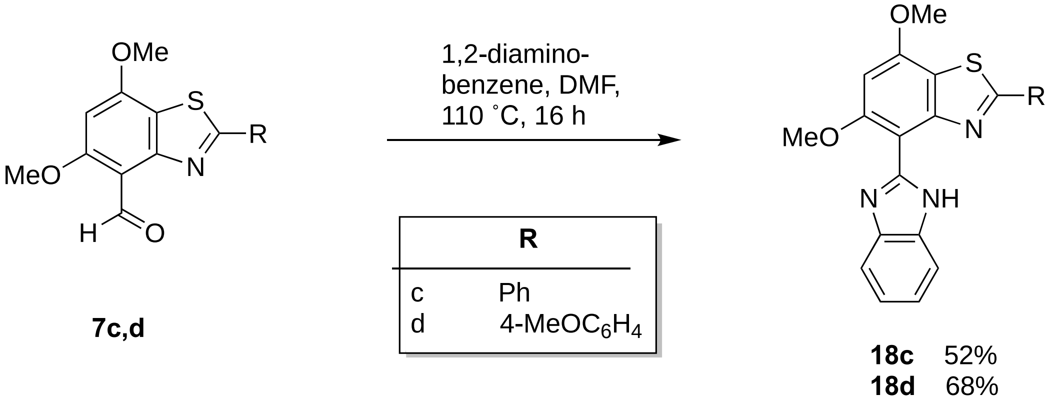


Scheme 5

The carbonyl functionality was indicated by resonances at 173 and 179 ppm in the ^{13}C NMR spectrum, and infrared stretching frequencies at 1697 cm^{-1} and 1639 cm^{-1}. The 4,7-dione **17c** could alternatively be prepared in 40% yield from the 4-formylbenzothiazole **7c** by the modified Dakin oxidation method using hydrogen peroxide in a solution of tetrahydrofuran/methanol under acidic conditions.[25] Heterocyclic quinones represent an important class of bioactive molecules and some benzothiazole-4,7-diones have been reported to have antimicrobial activities.[26,27]

Preparation of (benzothiazolyl)benzimidazoles

Overnight heating of the benzothiazole-4-carbaldehydes **7c**,**d** with one equivalent of 1,2-diaminobenzene in *N*,*N*-dimethylformamide gave the (benzothiazolyl)benzimidazoles **18c**,**d** in respective yields of 52 and 68% (Scheme 6). The (benzothiazolyl)benzimidazoles **18c**,**d** are presumably formed by the oxidative dehydrogenation of dihydrobenzimidazoles in *N*,*N*-dimethylformamide as described for the related indoles.[23] Only a few examples of (benzothiazolyl)benzimidazoles have been reported and these relate to 5-(2-benzothiazolyl)benzimidazoles.[28, 29] Therefore the new (benzothiazolyl)benzimidazoles **18c**,**d** offer a new heterocyclic structure with considerable potential for development in areas including medicinal chemistry and metal coordination chemistry.

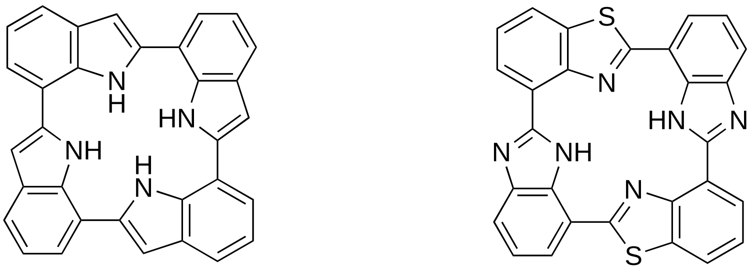


	R
c	Ph
d	4-MeOC_6H_4

Scheme 6

Functionalisation of benzothiazoles for potential dimerization to form macrocycles

Shinokubo and co-workers[30] and our group[31] have both synthesized examples of the tetraindolyl macrocyclic system **19**, using dimerization processes involving a suitable 2,7'-biindolyl (Figure 1). This is the first example of a generically larger group of structures incorporating a range of selected heterocyclic segments. The structure **19** was found to be rather strained and non-planar, presumably in order to avoid steric interactions between the four internal NH protons. Therefore it could be desirable to modify the heterocyclic segments to avoid this situation by the introduction of systems such as benzimidazoles and benzothiazoles. As a case study, we initiated experiments designed to build potential precursors for the synthesis of the macrocycle **20**, which incorporates two benzothiazoles and two benzimidazoles, and which would avoid the steric problems of macrocycle **19** (Figure 1). Completion of the synthesis of macrocycle **20** has so far not been achieved, but the work is unable to be continued by us, so we report our preliminary findings to exemplify further reactivity properties of the activated 4,6-dimethoxybenzothiazoles.

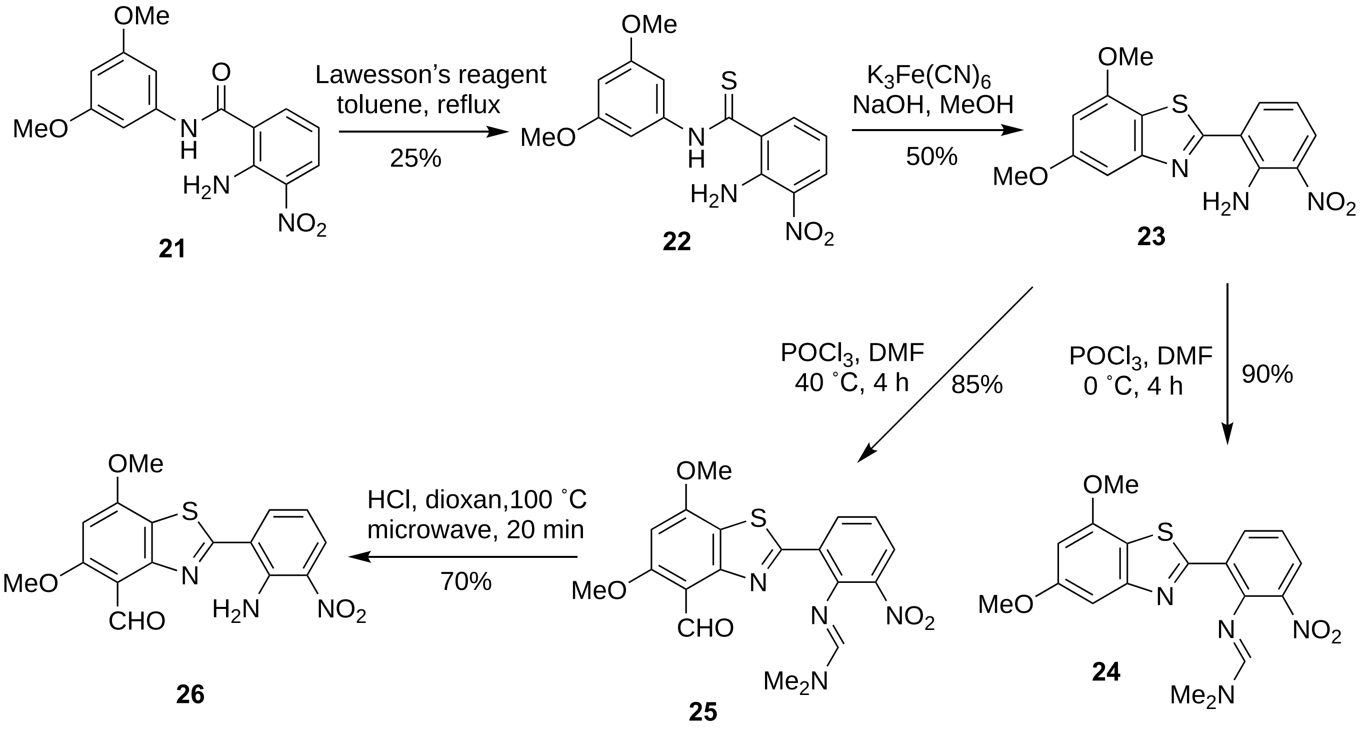


19 **20**

Figure 1. Structures of tetraindolyl **19** and tetrabenzothiazolyl **20**

Our approach to the synthesis of structure **20** was based on the application of imine formation as illustrated by the synthesis of compounds **18** (Scheme 6). Therefore, through the use of 4,6-dimethoxybenzothiazoles we aimed to place a formyl group at C7 and build a diaminophenyl moiety at C2. This strategy requires selective protection and deprotection.

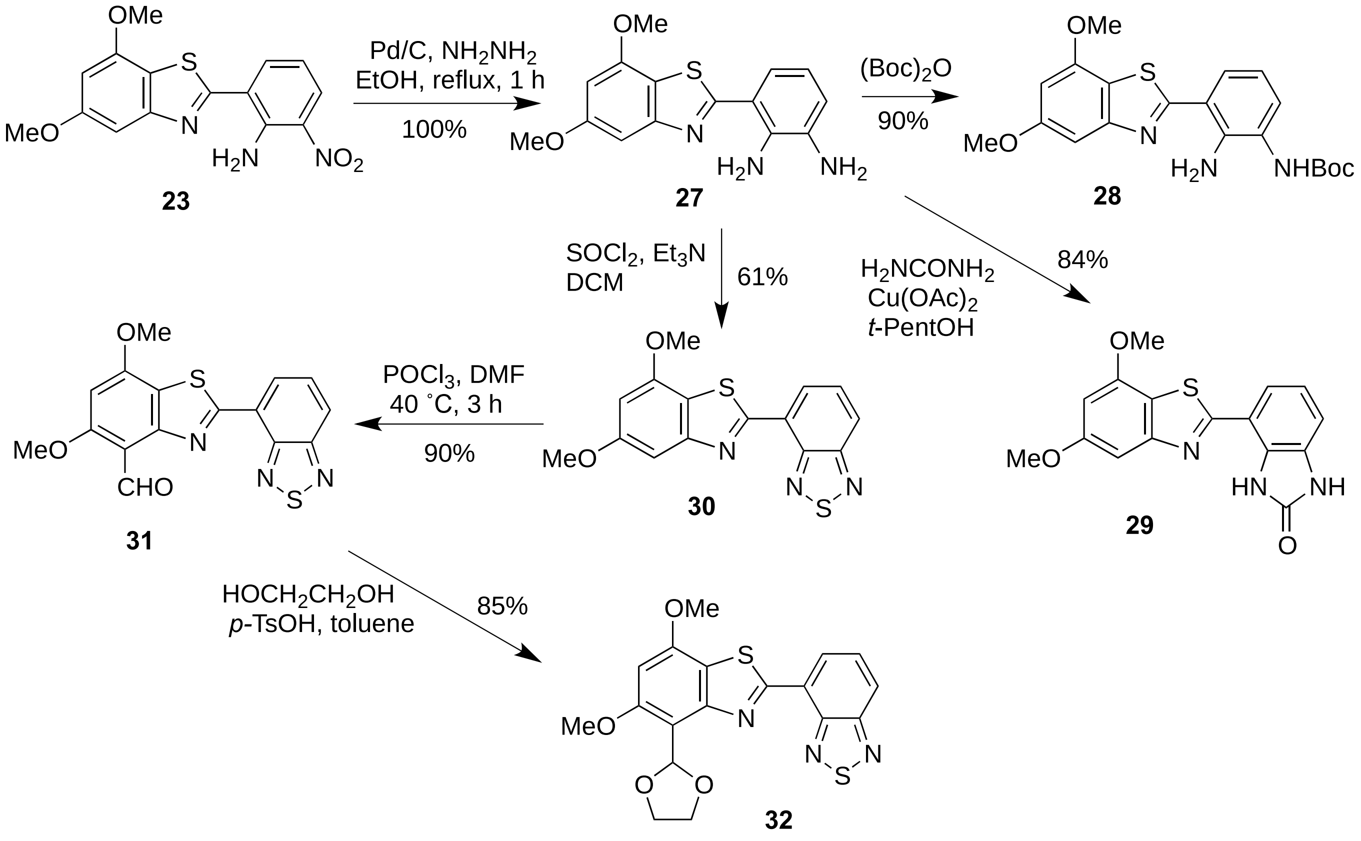
The previously unreported benzanilide **21** was prepared in 65% yield from 3,5-dimethoxyaniline and 2-amino-3-nitrobenzoic acid by treatment with thionyl chloride in dichloromethane. It was then converted into the corresponding thioamide **22** by reaction with Lawesson's reagent. The low yield of 25% could not be improved and is presumably the consequence of considerable steric hindrance. Subsequent potassium ferricyanide mediated oxidative cyclisation of thioamide **22** gave the benzothiazole **23** in 50% yield (Scheme 7).



Scheme 7

Vilsmeier formylation of benzothiazole **23** at 0 ˚C gave the amidine **24** in 90% yield, but use of an excess of reagent at 40 ˚C delivered the formyl amidine **25** in 85% yield. Acidic hydrolysis[32] of the amidine **25** under microwave irradiation gave the benzothiazole-4-carbaldehyde **26** in 70% yield (Scheme 7). Despite numerous attempts to reduce the nitro group selectively it was not possible to obtain a macrocylic dimer with the structure **20**, and complex polymeric mixtures were obtained in all cases.

The nitro group of benzothiazole **23** was reduced by Pd/C/hydrazine catalyzed hydrogenation to give the diaminobenzothiazole **27** in quantitative yield. In an attempt to protect the amino groups, the diamine **27** was reacted directly with di-(*t*-butyl)carbonate, but only the less-hindered amino group was able to be protected and the product was the benzothiazole **28** in 90% yield (Scheme 8). The structure was confirmed by an X-ray crystal structure (Figure 2).



Scheme 8

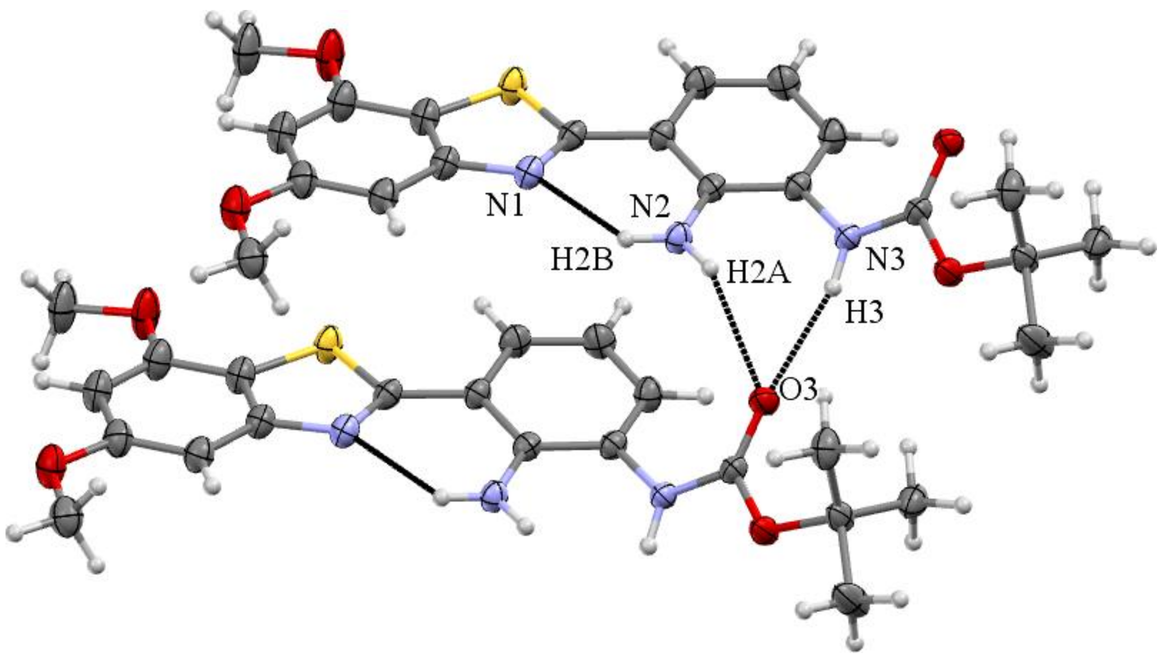


Figure 2. X-Ray crystal structure of compound **28**

However, both amino groups could be protected by the copper-catalyzed reaction of diamine **27** with urea in *t*-pentanol and the (benzothiazolyl)benzimidazolone **29** was obtained in 84% yield (Scheme 8). An X-ray crystal structure of this compound was also obtained (Figure 3).

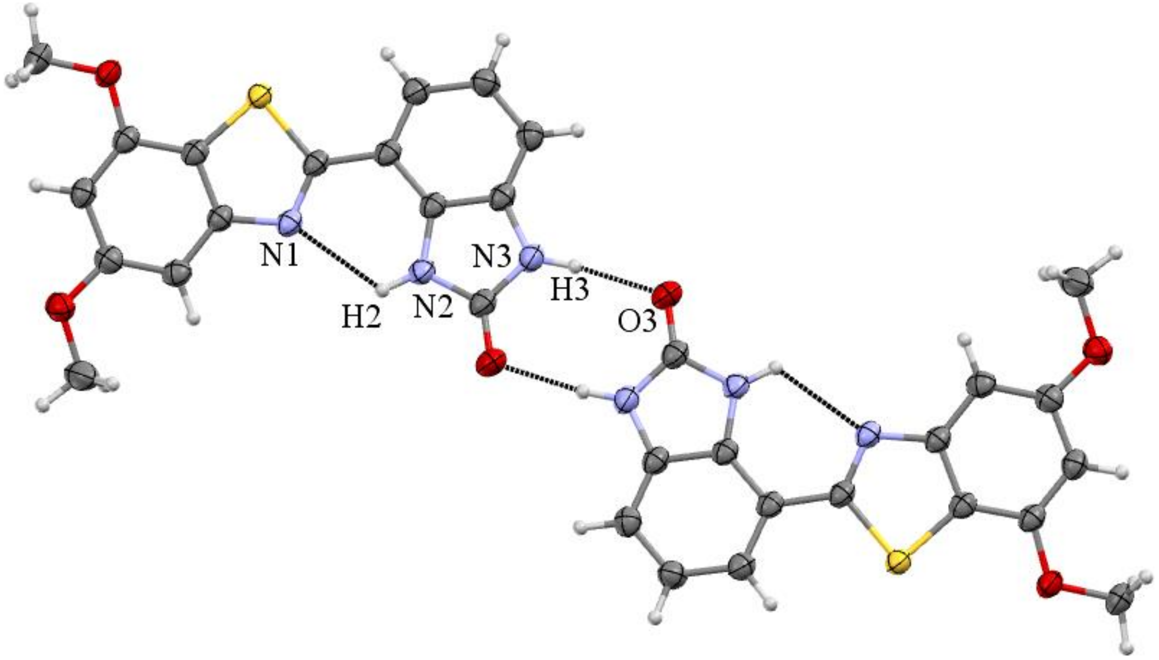


Figure 3. X-Ray crystal structure of compound **29**

It is interesting to note the different molecular association which uses the same hydrogen bonding bridges, namely N-H…N and N-H…O in the two compounds (Figures 2 and 3). In compound **28**, a bifurcated N-H…O bond (N3-H3…O3 and N2-H2A…O3) is formed between the translated molecules, whereas centre of symmetry related molecules form N3-H3…O3 dimeric association in compound **29**. However, in both the crystals, the intramolecular N-H…N bond (N2-H2B…N1 and N2-H2…N1 in Figures 2 and 3) is conserved and keeps the two rings in planarity. Tables 1 and 2 (Supplementary Information) provide selected hydrogen bonding parameters for compounds **28** and **29** respectively.

All attempts to carry out Vilsmeier formylation on the benzothiazole ring led to complex intractable polymeric mixtures. Furthermore, the possibility of effecting an iminium-promoted dimerization (in effect a modified Vilsmeier reaction)[33] by reaction with phosphoryl chloride or triflic anhydride met with similar results.

Benzothiadiazoles have been reported as protecting groups for 1,2-diamines.[34] Therefore the diamine **27** was converted to the benzothiadiazole **30** by reaction with thionyl chloride in dichloromethane in 61% yield. Vilsmeier formylation at the benzothiazole C4 was successful to give the aldehyde **31** in 90% yield.

Despite the fact that the benzothiadiazole **30** could be effectively deprotected to deliver the diamine **27** using sodium borohydride modified by nickel chloride,[35,36] use of these conditions failed in the case of the aldehyde **31**. Consequently, the need for a more powerful reducing agent, such as lithium aluminium hydride, would require protection of the formyl group. This was achieved by preparation of the dioxolane **32** in 85% yield by reaction of the aldehyde **31** with ethylene glycol and *p*-toluenesulfonic acid (Scheme 8). However, all attempts to reduce the benzothiadiazole **32**, using previously successful conditions for compound **30** and more powerful reagents, led to intractable mixtures.

While it is possible that further studies using this synthetic approach might eventually be successful, there are alternative strategies such as the organometallic one[30] used in the synthesis of the macrocyclic tetraindolyl **19** that would warrant serious investigation to achieve the attractive structure **20**.

CONCLUSIONS

A new range of benzothiazoles, which are activated by the incorporation of methoxy groups at the C5 and C7 positions, or at the C4 and C6 positions, have been synthesized using the oxidative cyclization of the related benzothioanilides. They undergo formylation, acetylation and nitration at C4 and C7 respectively. Di(benzothiazolyl)methanes and (benzothiazolyl)benzimidazoles can be prepared from the 4- and 7-carbaldehydes, and a range of 5,7-dimethoxybenzothiazoles functionalized in the 2-aryl ring have also been prepared as potential precursors for macrocyclic structures.

EXPERIMENTAL

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz), DNP400 (400 MHz) or DMX600 (600 MHz) spectrometer. Mass spectra were recorded on either a Bruker Daltonics Bio Apex II FTICR MS (HRMS-ESI) at School of Chemistry, University of New South Wales, or a Shimadzu LCMS QP 8000 (EI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet-visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. X-Ray crystallography was conducted with suitable single crystals and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Compound **28** - Deposition Number 2013303, Compound **29** - Deposition Number 2013304.

Dimethoxybenzothiazoles 1 and 2. Synthetic details for these compounds are contained in

Supplementary Material.

5,7-Dimethoxy-2-phenylbenzothiazole-4-carbaldehyde (7c). An ice-cooled solution of $POCl_3$ (1.06 mL, 10.98 mmol, 1.5 eq.) in anhydrous DMF (3 mL) was added dropwise to an ice cooled solution of benzothiazole **1c** (2.0 g, 7.32 mmol) in anhydrous DMF (9 mL) at 0 ˚C. The reaction mixture was allowed to come to room temperature and heated at 70 ˚C for 2 h. The reaction was quenched with ice water, basified with 20% NaOH solution and vigorously stirred for 2 h. The resulting precipitate was filtered, thoroughly washed with water, and recrystallized from $EtOH/H_2O$ to afford the 4-formylbenzothiazole **7c** as a light brown powder (1.97 g, 90%), mp 193-194 ˚C. ν_{max} (KBr): 2846, 1673, 1569, 1470, 1448, 1431, 1375, 1216, 1179, 1136, 952, 804, 701 cm^{-1}. λ_{max} (MeOH): 205 nm (ε 15,400 $cm^{-1}M^{-1}$), 229 (14,600), 266 (19,000), 313 (11,900), 353 (6,900). ^1H NMR (300 MHz, CDCl3): δ 4.03 (s, 3H, OMe), 4.07 (s, 3H, OMe), 6.51 (s, 1H, aryl H6), 7.48-7.50 (m, 3H, aryl H), 8.11-8.15 (m, 2H, aryl H), 10.96 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 56.6 (OMe), 91.8, 127.6, 128.9, 131.3 (aryl CH), 112.0, 116.7, 133.1, 156.7, 158.7, 162.6, 171.4 (aryl C), 188.8 (C=O). Mass Spectrum (+EI): *m/z* (%) 301 (M+2, 19), 300 (M+1, 100). Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.29; H, 4.52; N, 4.61.

5,7-Dimethoxy-2-(4'-methoxyphenyl)benzothiazole-4-carbaldehyde (7d). This compound was prepared as described for the compound **7c** from benzothiazole **1d** (3.0 g, 10 mmol) in anhydrous DMF (10 mL) and $POCl_3$ (1.43 mL, 15 mmol, 1.5 eq.) in anhydrous DMF (3 mL) followed by heating at 70 ˚C for 2 h. Base workup and recrystallization from EtOH afforded the title 4-formylbenzothiazole **7d** as a white solid (3.03 g, 92%), mp 231-232 ˚C. ν_{max} (KBr): 3448, 1676, 1577, 1477, 1366, 1340, 1257, 1234, 1214, 1134, 1032, 957, 825 cm^{-1}. λ_{max} (MeOH): 207 nm (ε 20,800$cm^{-1}M^{-1}$), 227 (21,100), 279 (23,600), 324 (20,400), 353 (15,600). ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H, OMe), 4.03 (s, 3H, OMe), 4.07 (s, 3H, OMe), 6.49 (s, 1H, aryl H6), 6.99 (d, *J* 8.3 Hz, 2H, aryl H), 8.08 (d, *J* 8.3 Hz, 2H, aryl H), 10.94 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 56.2, 56.7 (OMe), 91.7, 114.3, 129.3 (aryl CH), 112.1, 116.4, 126.1, 157.0, 158.7, 162.3, 162.5, 172.9 (aryl C), 188.9 (C=O). Mass Spectrum (+EI): *m/z* (%) 331 (M+2, 24), 330 (M+1, 100). Anal. Calcd for $C_{17}H_{15}NO_4S$ 0.4 H_2O: C, 60.99; H, 4.70; N, 4.18. Found: C, 60.93; H, 4.73; N, 4.10.

2-(4'-Chlorophenyl)-5,7-dimethoxybenzothiazole-4-carbaldehyde (7e). This compound was prepared as described for the compound **7c** from benzothiazole **1e** (3.05 g, 10 mmol) in anhydrous DMF (25 mL) and $POCl_3$ (1.43 mL, 15 mmol, 1.5 eq.) in anhydrous DMF (3 mL) followed by heating at 70 ˚C for 2 h. Base workup and recrystallization from EtOH afforded the title 4-formylbenzothiazole **7e** as an off white solid (2.97 g, 89%), mp 361-362 ˚C. ν_{max} (KBr): 3434, 1691, 1575, 1471, 1340, 1213, 1136, 1090, 953, 825 cm^{-1}. λ_{max} (MeOH): 203 nm (ε 15,900 $cm^{-1}M^{-1}$), 231 (13,400), 269 (19,400), 315 (12,500). ^1H NMR (300 MHz, $CDCl_3$): δ 4.04 (s, 3H, OMe), 4.09 (s, 3H, OMe), 6.53 (s, 1H, aryl H6), 7.46 (d, *J* 8.6 Hz, 2H, aryl H), 8.07 (d, *J* 8.6 Hz, 2H, aryl H), 10.92 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.2, 56.8

(OMe), 92.2, 128.8, 129.2 (aryl CH), 99.5, 112.3, 131.7, 137.5, 156.5, 158.8, 162.9, 170.2 (aryl C), 188.7 (C=O). Mass Spectrum (+ESI): *m/z* (%) 358 (M+Na, ^{37}Cl, 20), 356 (M+Na, ^{35}Cl, 100). HRMS (+ESI): $C_{16}H_{12}ClNO_3S$ [M+Na]$^+$ requires 356.0119, found 356.0110. Anal. Calcd for $C_{16}H_{12}ClNO_3S$ 0.1H_2O: C, 57.26; H, 3.66; N, 4.17. Found: C, 57.00; H, 3.70; N, 4.24.

4,6-Dimethoxy-2-phenylbenzothiazole-7-carbaldehyde (8c). This compound was prepared as described for the compound **7c** from benzothiazole **2c** (0.50 g, 1.84 mmol) in anhydrous DMF (3 mL) and $POCl_3$ (0.26 mL, 2.76 mmol, 1.5 eq.) in anhydrous DMF (2 mL) followed by heating at 70 ˚C for 2 h. Base workup and recrystallization from EtOH afforded the title 7-formylbenzothiazole **8c** as a light brown powder (0.41 g, 75%), mp 160-162 ˚C. ν_{max} (KBr): 1677, 1649, 1567, 1465, 1385, 1302, 1270, 1215, 1148, 1065, 1044, 765 cm^{-1}. λ_{max} (MeOH): 205 nm (ε 14,800 cm^{-1}M^{-1}), 298 (16,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H, OMe), 4.14 (s, 3H, OMe), 6.51 (s, 1H, aryl H5), 7.43-7.44 (m, 3H, aryl H), 8.09-8.12 (m, 2H, aryl H), 10.42 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 56.6 (OMe), 92.9, 127.3, 128.8, 130.5 (aryl CH), 112.3, 133.4, 136.0, 139.6, 159.2, 163.3, 168.3 (aryl C), 185.8 (C=O). Mass Spectrum (+EI): *m/z* (%) 301 (M+2, 18), 300 (M+1, 100). Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.10; H, 4.28; N, 4.79.

2-(4'-Chlorophenyl)-4,6-dimethoxybenzothiazole-7-carbaldehyde (8e). This compound was prepared as described for the compound **7c** from benzothiazole **2e** (3.05 g, 10 mmol) in anhydrous DMF (25 mL) and $POCl_3$ (1.43 mL, 15 mmol, 1.5 eq.) in anhydrous DMF (3 mL) followed by heating at 70 ˚C for 2 h. Base workup and recrystallization from EtOH afforded the title 7-formylbenzothiazole **8e** as a light yellow solid (2.7 g, 82%), mp 365-366 ˚C. ν_{max} (KBr): 3444, 1655, 1568, 1462, 1388, 1300, 1214, 1153, 1065, 1045, 975, 826 cm^{-1}. λ_{max} (MeOH): 202 nm (ε 35,500 cm^{-1}M^{-1}), 301 (43,200), 327 (29,700). ^{1}H NMR (300 MHz, acetone-d_6): δ 4.15 (s, 3H, OMe), 4.21 (s, 3H, OMe), 6.99 (s, 1H, aryl H5), 7.58 (d, *J* 8.6 Hz, 2H, aryl H), 8.15 (d, *J* 8.6 Hz, 2H, aryl H), 10.43 (s, 1H, CHO). Compound is too insoluble for ^{13}C NMR in acetone-d_6 or DMSO-d_6. Mass Spectrum (+EI): *m/z* (%) 337 (M+2, ^{37}Cl, 7), 336 (M+1, ^{37}Cl, 40), 335 (M+2, ^{35}Cl, 20), 334 (M+1, ^{35}Cl, 100). Anal. Calcd for $C_{16}H_{12}ClNO_3S$ 0.1H_2O: C, 57.26; H, 3.66; N, 4.17. Found: C, 57.23; H, 3.65; N, 4.20.

5,7-Dimethoxy-2-phenyl-4-hydroxymethylbenzothiazole (9c). A solution of 4-formylbenzothiazole **7c** (0.20 g, 0.67 mmol) in anhydrous MeOH (20 mL) was reacted with $NaBH_4$ (0.20 g) under reflux for 1.5 h to yield the 4-hydroxymethylbenzothiazole **9c** as a white solid (0.197 g, 98%), mp 134-135 ˚C. ν_{max} (KBr): 3457, 2938, 2840, 1585, 1477, 1326, 1207, 1120, 982, 764 cm^{-1}. λ_{max} (MeOH): 212 nm (ε 29,300 cm^{-1}M^{-1}), 244 (19,400), 299 (15,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.19 (s, 2H, CH_2), 6.53 (s, 1H, aryl H6), 7.46-7.48 (m, 3H, aryl H), 8.05-8.09 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.7 (OMe), 57.6 (CH_2), 93.0, 127.4, 128.9, 131.0 (aryl CH), 115.3, 116.0, 133.3, 153.5, 154.1, 156.6, 169.3 (aryl C). Mass Spectrum (+EI): *m/z* (%) 303 (M+2, 15), 302

(M+1, 100), 301 (M, 5), 300 (46), 284 (70). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.77; H, 5.00; N, 4.60.

5,7-Dimethoxy-2-(4'-methoxyphenyl)-4-hydroxymethylbenzothiazole (9d). A solution of 4-formylbenzothiazole **7d** (0.20 g, 0.61 mmol) in anhydrous MeOH (10 mL) was reacted with $NaBH_4$ (0.20 g) under reflux for 3 h to yield the 4-hydroxymethylbenzothiazole **9d** as a white solid (0.198 g, 98%), mp 178-179 ˚C. ν_{max} (KBr): 3377, 2940, 2837, 1589, 1484, 1486, 1332, 1315, 1257, 1216, 1175, 1125, 1034, 825 cm^{-1}. λ_{max} (MeOH): 216 nm (ε 47,400 $cm^{-1}M^{-1}$), 310 (37,500). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.96 (s, 2H, CH_2), 6.48 (s, 1H, aryl H6), 6.79 (d, *J* 9.0 Hz, 2H, aryl H), 7.91 (d, *J* 9.0 Hz, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.7, 57.4 (OMe), 56.9 (CH_2), 94.2, 113.9, 128.9 (aryl CH), 115.7, 118.0, 127.0, 151.9, 155.2, 157.4, 161.4, 166.6 (aryl C). Mass Spectrum (+EI): *m/z* (%) 332 (M+1, 5), 331 (M, 9), 330 (M-1, 44), 315 (20), 314 (100). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.32; H, 5.28; N, 4.10.

4,6-Dimethoxy-2-phenyl-7-hydroxymethylbenzothiazole (10c). A solution of 7-formylbenzothiazole **8c** (0.20 g, 0.67 mmol) in anhydrous MeOH (20 mL) was reacted with $NaBH_4$ (0.20 g) under reflux for 1.5 h to yield the 7-hydroxymethylbenzothiazole **10c** as a white solid (0.16 g, 80%), mp 134-135 ˚C. ν_{max} (KBr): 3455, 2938, 2841, 1585, 1477, 1327, 1207, 1120, 1003, 805 cm^{-1}. λ_{max} (MeOH): 212 nm (ε 32,300 $cm^{-1}M^{-1}$), 245 (23,100), 299 (18,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H, OMe), 4.06 (s, 3H, OMe), 4.86 (s, 2H, CH_2), 6.53 (s, 1H, aryl H5), 7.41-7.44 (m, 3H, aryl H), 8.04-8.07 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.2, 56.4 (OMe), 59.9 (CH_2), 94.0, 127.3, 128.7, 130.3 (aryl CH), 113.3, 133.6, 137.4, 138.8, 153.3, 155.5, 164.9 (aryl C). Mass Spectrum (+EI): *m/z* (%) 302 (M+1, 100), 301 (9), 300 (50), 285 (16), 284 (71). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.77; H, 5.02; N, 4.54.

Di(5,7-dimethoxy-2-phenylbenzothiazol-4-yl)methane (11c). To a solution of 4-hydroxymethylbenzothiazole **9c** (50 mg, 0.16 mmol) in THF (2 mL), HOAc (2 mL) was added and the mixture stirred at room temperature for 6 h and then the mixture was heated at 80 ˚C for 2 h. The solution was allowed to come to room temperature before ice water was added and the resulting precipitate was filtered, washed with water and dried to yield the di(benzothiazolyl)methane **11c** as a white solid (35 mg, 88%), mp 183-184 ˚C. ν_{max} (KBr): 2935, 1579, 1478, 1495, 1371, 1327, 1212, 1119, 948, 768, 693 cm^{-1}. λ_{max} (MeOH): 211 nm (ε 10,800 $cm^{-1}M^{-1}$), 239 (8,100), 262 (7,300), 294 (6,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 6H, OMe), 4.02 (s, 6H, OMe), 5.68 (s, 2H, CH_2), 6.56 (s, 2H, aryl H6), 7.46-7.48 (m, 6H, aryl H), 8.08-8.11 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.8 (OMe), 58.3 (CH_2), 92.8, 127.5, 128.8, 130.9 (aryl CH), 110.1, 116.0, 133.6, 154.8, 155.6, 158.7, 169.4 (aryl C). Mass Spectrum (+EI): *m/z* (%) 556 (M+1, 7), 555 (M, 18), 316 (35), 302 (25), 284 (100). Anal. Calcd for $C_{31}H_{26}N_2O_4S_2$ $1.5H_2O$: C, 64.01; H, 5.02; N, 4.82. Found: C, 63.81; H, 5.05; N, 4.81.

Di(4,6-dimethoxy-2-phenylbenzothiazol-7-yl)methane (12c). This compound was prepared as described for the benzothiazole **11c** from a solution of 7-hydroxymethylbenzothiazole **10c** (50 mg, 0.16 mmol) in HOAc (2 mL) at 80 ˚C for 2 h to yield the di(benzothiazolyl)methane **12c** as a white solid (40 mg, 93%), mp 112-114 ˚C. ν_{max} (KBr): 2932, 1729, 1580, 1459, 1435, 1372, 1305, 1249, 1133, 1046, 974, 763 cm^{-1}. λ_{max} (MeOH): 213 nm (ε 58,100 $cm^{-1}M^{-1}$), 269 (31,900), 315 (34,700). ^1H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 6H, OMe), 4.10 (s, 6H, OMe), 5.35 (s, 2H, CH_2), 6.61 (s, 2H, aryl H5), 7.44-7.45 (m, 6H, aryl H), 8.07-8.08 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.3, 56.7 (OMe), 60.4 (CH_2), 94.1, 127.3, 128.7, 130.4 (aryl CH), 108.5, 133.4, 138.9, 154.1, 156.5, 164.8, 171.0 (aryl C). Mass Spectrum (+EI): *m/z* (%) 556 (M+2, 13), 555 (M+1, 35), 344 (100), 316 (35), 302 (52). HRMS (+ESI): $C_{31}H_{26}N_2O_4S_2$ $[M+Na]^+$ requires 577.1226, found 577.1235. Anal. Calcd for $C_{31}H_{26}N_2O_4S_2$ 0.3$CHCl_3$: C, 63.66; H, 4.49; N, 4.74. Found: C, 63.74; H, 4.64; N, 4.78.

1-(5,7-Dimethoxy-2-phenylbenzothiazol-4-yl)ethanone (13c). Acetyl chloride (0.29 g, 3.68 mmol) was added to an ice cooled solution of benzothiazole **1c** (0.50 g, 1.84 mmol) in anhydrous $CHCl_3$ (25 mL) followed by $SbCl_5$ (1.10 g, 2.76 mmol). The mixture was stirred under argon for 24 h and the resulting crude precipitate was filtered and chromatographed ($CHCl_3$/MeOH, 95:5) to afford the 4-acetylbenzothiazole **13c** as a brown solid (0.39 g, 68%), mp 180-182 ˚C. ν_{max} (KBr): 1602, 1460, 1401, 1368, 1256, 1222, 1000, 948, 761 cm^{-1}. λ_{max} (MeOH): 210 nm (ε 5,300 $cm^{-1}M^{-1}$), 238 (5,800), 262 (8,800), 295 (5,700). ^1H NMR (300 MHz, acetone-d_6): δ 2.75 (s, 3H, COMe), 4.24 (s, 3H, OMe), 4.29 (s, 3H, OMe), 7.26 (s, 1H, aryl H6), 7.74-7.79 (m, 3H, aryl H), 8.25-8.28 (m, 2H, aryl H). ^{13}C NMR (75 MHz, acetone-d_6): δ 29.1 (CO$\underline{\text{Me}}$), 57.1, 57.2 (OMe), 95.6, 128.6, 129.9, 134.8 (aryl CH), 103.4, 114.4, 129.7, 145.1, 155.1, 163.8, 172.6 (aryl C), 205.2 (C=O). Mass Spectrum (+EI): *m/z* (%) 315 (M+2, 20), 314 (M+1, 100). HRMS (+ESI): $C_{17}H_{16}NO_3S$ $[M+H]^+$ requires 314.0845, found 313.0850.

1-(4,6-Dimethoxy-2-phenylbenzothiazol-7-yl)ethanone (14c). This compound was prepared from an ice cooled solution of benzothiazole **2c** (0.50 g, 1.84 mmol) in anhydrous $CHCl_3$ (25 mL), acetyl chloride (0.29 g, 3.68 mmol) and $SbCl_5$ (1.10 g, 2.76 mmol) under argon for 24 h to afford the 7-acetylbenzothiazole **14c** as a brown solid (0.37 g, 64%), mp 150-152 ˚C. ν_{max} (KBr): 1599, 1527, 1468, 1414, 1302, 1218, 1158, 1038, 730 cm^{-1}. λ_{max} (MeOH): 212 nm (ε 6,600 $cm^{-1}M^{-1}$), 268 (4,500), 296 (4,800), 315 (4,700). ^1H NMR (300 MHz, acetone-d_6): δ 2.77 (s, 3H, COMe), 4.30 (s, 3H, OMe), 4.33 (s, 3H, OMe), 7.39 (s, 1H, aryl H5), 7.75-7.78 (m, 3H, aryl H), 8.22-8.25 (m, 2H, aryl H). ^{13}C NMR (75 MHz, acetone-d_6): δ 32.4 (CO$\underline{\text{Me}}$), 56.2, 56.3 (OMe), 96.4, 127.0, 129.7, 131.0 (aryl CH), 133.5, 137.3, 138.9, 153.9, 159.2, 162.9, 167.1 (aryl C), 194.4 (C=O). Mass Spectrum (+EI): *m/z* (%) 315 (M+2, 19), 314 (M+1, 100), 272 (34). HRMS (+ESI): $C_{17}H_{16}NO_3S$ $[M+H]^+$ requires 314.0845 found 314.0824.

5,7-Dimethoxy-4-nitro-2-phenylbenzothiazole (15c) and 5-Methoxy-2-phenylbenzothiazole-4,7-dione (17c). A previously cooled solution of HNO_3 (0.37 mL, 0.56 mmol) in Ac_2O (2 mL) was added dropwise over 10 min to an ice cooled solution of benzothiazole **1c** (0.10 g, 0.378 mmol) in Ac_2O (30 mL). The mixture was stirred at 0 ˚C for 1 h before ice water was added and the mixture stirred for a further 1 h. The mixture was made neutral by 2 M sodium hydroxide solution and the resulting precipitate was filtered, washed with water and dried. The crude solid was column chromatographed ($CHCl_3$) to afford the following two products.

(i) 5,7-Dimethoxy-4-nitro-2-phenylbenzothiazole (15c) was isolated as the first band, recrystallized from EtOH/H_2O and dried to afford a yellow solid (28 mg, 24%), mp 237-238 ˚C. ν_{max} (KBr): 1604, 1572, 1525, 1468, 1383, 1322, 1216, 1164, 1113, 950 cm^{-1}. λ_{max} (MeOH): 209 nm (ε 19,500 $cm^{-1}M^{-1}$), 256 (12,200), 294 (10,600). ^1H NMR (300 MHz, $CDCl_3$): δ 4.02 (s, 3H, OMe), 4.06 (s, 3H, OMe), 6.53 (s, 1H, aryl H6), 7.47-7.51 (m, 3H, aryl H), 8.07-8.10 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.3, 57.4 (OMe), 92.3, 127.8, 129.0, 131.6 (aryl CH), 117.0, 129.4, 132.8, 147.8, 152.5, 155.6, 172.3 (aryl C). Mass Spectrum (+EI): *m/z* (%) 318 (M+2, 17), 317 (M+1, 100). Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86. Found: C, 57.10; H, 3.91; N, 8.75.

(ii) 5-Methoxy-2-phenylbenzothiazole-4,7-dione (17c) was isolated as the second band, recrystallized from MeOH/H_2O and dried to afford a light orange solid (25 mg, 25%), mp 226-227 ˚C. ν_{max} (KBr): 1697, 1639, 1599, 1460, 1328, 1256, 1107 cm^{-1}. λ_{max} (MeOH): 205 nm (ε 13,700 $cm^{-1}M^{-1}$), 273 (26,200). ^1H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H, OMe), 6.06 (s, 1H, aryl H6), 7.49-7.54 (m, 3H, aryl H), 8.06-8.09 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.9 (OMe), 108.0, 127.5, 129.2, 132.1 (aryl CH), 131.9, 140.3, 151.6, 160.1, 173.7 (aryl C), 173.8, 179.3 (C=O). Mass Spectrum (+EI): *m/z* (%) 273 (M+2, 18), 272 (M+1, 100). Anal. Calcd for $C_{14}H_9NO_3S$ $0.3CH_3OH$: C, 61.14; H, 3.66; N, 4.99. Found: C, 61.41; H, 3.75; N, 4.91.

This compound **17c** was also prepared by treatment of 7-formylbenzothiazole **7c** (0.25 g, 0.836 mmol) in THF/MeOH (50 mL) with concentrated HCl (2 drops) and 30% H_2O_2 solution (5 mL) to afford the benzothiazole-4,7-dione **17c** as a light orange solid (90 mg, 40%).

4,6-Dimethoxy-7-nitro-2-phenylbenzothiazole (16c). This compound was prepared as described for the 7-nitrobenzothiazole **15c** from an ice cooled solution of benzothiazole **2c** (0.10 g, 0.378 mmol) in Ac_2O (30 mL), and a previously cooled solution of HNO_3 (0.37 mL, 0.56 mmol) in Ac_2O (2 mL) at 0 ˚C for 1 h to afford the 7-nitrobenzothiazole **16c** as a yellow solid (74 mg, 64%), mp 239 ˚C. ν_{max} (KBr): 1592, 1563, 1494, 1474, 1348, 1276, 1218, 1123, 1040, 814, 761 cm^{-1}. λ_{max} (MeOH): 210 nm (ε 15,600 $cm^{-1}M^{-1}$), 306 (16,400). ^1H NMR (300 MHz, $CDCl_3$): δ 4.13 (s, 3H, OMe), 4.21 (s, 3H, OMe), 6.64 (s, 1H, aryl H5), 7.47-7.49 (m, 3H, aryl H), 8.09-8.11 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.0, 57.3 (OMe), 94.4, 127.3, 129.0, 131.0 (aryl CH), 107.7, 127.6, 132.8, 140.3, 156.9, 158.6, 172.1 (aryl C). Mass Spectrum (+EI): *m/z* (%) 318 (M+2, 19), 317 (M+1, 100). Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86. Found: C, 56.74; H, 3.89; N, 8.70.

2-(5,7-Dimethoxy-2-phenylbenzothiazol-4-yl)benzimidazole (18c). This compound was prepared from a solution of benzothiazole-4-carbaldehyde **7c** (1.0 g, 3.34 mmol) in anhydrous DMF (10 mL) and 1,2-diaminobenzene (0.39 g, 3.68 mmol) at 110 ˚C overnight to yield the (benzothiazolyl)benzimidazole **18c** as a brown powder (0.82 g, 52%), mp 245-246 ˚C. ν_{max} (KBr): 3458, 1585, 1450, 1416, 1331, 1278, 1217, 1142, 1118, 1099, 950, 743 cm^{-1}. λ_{max} (MeOH): 207 nm (ε 31,900 $cm^{-1}M^{-1}$), 254 (22,100), 294 (21,700), 322 (17,300). ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H, OMe), 4.13 (s, 3H, OMe), 6.63 (s, 1H, aryl H6), 7.26-7.29 (m, 2H, aryl H), 7.52-7.54 (m, 3H, aryl H), 7.76-7.79 (m, 2H, aryl H), 8.03-8.06 (m, 2H, aryl H), 11.97 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 57.0, 57.3 (OMe), 94.5, 115.2, 122.3, 127.7, 129.6, 132.0 (aryl CH), 106.1, 115.5, 132.8, 138.3, 147.1, 154.1, 155.6, 159.4, 169.4 (aryl C). Mass Spectrum (+EI): *m/z* (%) 389 (M+2, 30), 388 (M+1, 100). Anal. Calcd for $C_{22}H_{17}N_3O_2S$: C, 68.20; H, 4.42; N, 10.85. Found: C, 68.30; H, 4.43; N, 10.82.

2-(5,7-Dimethoxy-2-(4'-methoxyphenyl)benzothiazol-4-yl)benzimidazole (18d). This compound was prepared from a solution of 4-formylbenzothiazole **7d** (1.0 g, 3.34 mmol) in anhydrous DMF (10 mL) and 1,2-diaminobenzene (0.39 g, 3.68 mmol) at 110 ˚C overnight to yield the (benzothiazolyl)benzimidazole **18d** as a light brown powder (0.88 g, 68%), mp 124-126 ˚C. ν_{max} (KBr): 3441, 1581, 1464, 1324, 1257, 1221, 1175, 1139, 1115, 1029, 952, 744 cm^{-1}. λ_{max} (MeOH): 208 nm (ε 18,400 $cm^{-1}M^{-1}$), 289 (15,600), 300 (15,800), 337 (14,100). ^1H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H, OMe), 4.02 (s, 3H, OMe), 4.13 (s, 3H, OMe), 6.70 (s, 1H, aryl H6), 7.09 (d, *J* 8.7 Hz, 2H, aryl H), 7.47-7.50 (m, 2H, aryl H), 8.04 (d, *J* 8.7 Hz, 2H, aryl H), 8.22-8.25 (m, 2H, aryl H), 11.56 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.9, 57.3, 57.6 (OMe), 94.1, 114.9, 115.1, 123.8, 129.9 (aryl CH), 104.8, 115.6, 125.2, 135.4, 146.1, 153.6, 156.8, 160.0, 162.6, 170.4 (aryl C). Mass Spectrum (+EI): *m/z* (%) 419 (M+2, 30), 418 (M+1, 100). HRMS (+ESI): $C_{23}H_{19}N_3O_3S$ $[M+H]^+$ requires 418.1220, found 418.1204. Anal. Calcd for $C_{23}H_{19}N_3O_3S$ $0.1H_2O$: C, 65.89; H, 4.62; N, 10.02. Found: C, 65.73; H, 4.62; N, 9.95.

2-Amino-*N*-(3,5-dimethoxyphenyl)-3-nitrobenzamide (21). 2-Amino-3-nitrobenzoic acid (200 mg, 1.10 mmol) was suspended in THF (10.0 mL) and thionyl chloride (119 μL, 1.65 mmol) and DMF (2 drops) were added. The resulting mixture was stirred at room temperature until the carboxylic acid had been consumed (monitoring by TLC). The mixture was added dropwise to 3,5-dimethoxyaniline (252 mg, 1.10 mmol) solution in CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 2 h and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from MeOH to yield the title compound (223 mg, 65%), mp 175 ˚C. ν_{max} (KBr): 3446, 3269, 3090, 2922, 2840, 2342, 2110, 1737, 1607, 1543, 1451, 1419, 1348, 1253, 1153, 1059, 934, 819, 737, 675 cm^{-1}. λ_{max} (MeOH): 260 nm (ε 20,300 $cm^{-1}M^{-1}$), 204 (35,800). ^1H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 6H, OMe), 6.40 (t, *J* 2.3 Hz, 1H, aryl H), 6.78 (dd, *J* 8.9, 7.5 Hz, 1H, aryl H), 7.00 (d, *J* 2.3 Hz, 2H, aryl H), 7.97 (m, 3H, NH_2, aryl H), 8.23 (dd, *J* 8.6, 1.5 Hz, 1H), 10.36 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6 (OMe), 96.6, 99.3 (aryl CH), 114.6 (aryl C), 121.5, 129.8, 132.6 (aryl CH), 136.9, 140.8, 145.5, 160.9 (aryl C), 166.8 (C=O). HRMS (+ESI): $C_{15}H_{15}N_3NaO_5$ $[M+Na]^+$ requires 340.0904, found 340.0903.

2-Amino-*N*-(3,5-dimethoxyphenyl)-3-nitrobenzothioamide (22). To a solution of amide **21** (100 mg, 0.32 mmol) in toluene (15.0 mL) was added Lawesson's reagent (77 mg, 0.19 mmol) and the solution was heated at reflux overnight. The solvent was evaporated under reduced pressure and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were washed with water, brine and dried over Na_2SO_4. The product was purified by column chromatography to give the thioamide **22** as a yellow solid (26 mg, 25%), mp 179 °C. ν_{max} (KBr): 3442, 3328, 3266, 2998, 2943, 2839, 2343, 2102, 1901, 1607, 1549, 1511, 1448, 1380, 1302, 1259, 1200, 1147, 1055, 922, 870, 816, 740 cm^{-1}. λ_{max} (THF): 372 nm (ε 8,600 $cm^{-1}M^{-1}$), 289 (9,100), 232 (26,100), 207 (20, 200). ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 6H, OMe), 6.38 (d, *J* 2.0 Hz, 2H, aryl H), 6.54 (t, *J* 2.0 Hz, 1H, aryl H), 6.89 (t, *J* 8.1 Hz, 1H, aryl H), 8.19 (s, 2H, NH_2), 8.35 (dd, *J* 8.3, 1.2 Hz, 1H, aryl H), 8.89 (dd, *J* 7.9, 0.8 Hz, 1H, aryl H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 55.7 (OMe), 99.2, 99.8 (aryl C), 101.7, 115.7, 128.1, 132.7 (aryl CH), 133.5, 139.6, 142.7 (aryl C), 161.2 (aryl CH). HRMS (+ESI): $C_{15}H_{16}N_3O_4S$ $[M+H]^+$ requires 334.0856, found 334.0852.

2-(5,7-Dimethoxybenzothiazol-2-yl)-6-nitroaniline (23). The thioamide **22** (100 mg, 0.301 mmol) was suspended in absolute EtOH (1 mL) and 30% NaOH solution (224 μL, 2.40 mmol) was added dropwise with stirring. The resulting mixture was stirred for 5 min and diluted with water (736 μL) to make 10% NaOH solution and stirred again for 5 min. This solution was slowly added to a previously heated (80 °C) solution of $K_3Fe(CN)_6$ (395 mg, 1.20 mmol) in water (5 mL) and the mixture was stirred for 30 min. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered, washed with water, and purified by flash column chromatography to give the benzothiazole **23** as an orange-red solid (50 mg, 50%). mp 213 °C. ν_{max} (KBr): 3437, 3209, 2988, 2941, 2836, 2343, 2093, 1910, 1605, 1572, 1511, 1475, 1432, 1328, 1255, 1152, 1122, 1094, 961, 812, 730, 711 cm^{-1}. λ_{max} (MeOH): 296 nm (ε 8,500 $cm^{-1}M^{-1}$), 227 (20,500), 206 (27,500). ^1H NMR (600 MHz, $CDCl_3$) δ 3.92 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.53 (d, *J* 2.0 Hz, 1H, benzothiazole H6), 6.72 (t, *J* 8.0 Hz, 1H, aryl H), 7.13 (d, *J* 2.0 Hz, 1H, benzothiazole H4), 8.01 (dd, *J* 7.6, 1.3 Hz, 1H, aryl H), 8.30 (dd, *J* 8.5, 1.3 Hz, 1H, aryl H), 9.27 (br s, 2H, NH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.0, 56.2 (OMe), 97.5, 97.6 (aryl CH), 114.5 (aryl C), 114.7 (aryl CH), 119.5 (aryl C), 129.4 (aryl CH), 133.5 (aryl C), 137.0 (aryl CH), 144.7, 154.3, 154.9, 160.8, 168.6 (aryl C). HRMS (+ESI): $C_{15}H_{14}N_3O_4S$ $[M+H]^+$ requires 332.0700, found 332.0703.

***N*'-(2-(5,7-Dimethoxybenzothiazol-2-yl)-6-nitrophenyl)-*N*,*N*-dimethylformimide (24).** To an ice-cold solution of $POCl_3$ (140 μL, 1.57 mmol) in dry DMF (2.0 mL) was added a cold solution of benzothiazole **23** (200 mg, 0.60 mmol) in dry DMF (5.0 mL). The mixture was stirred at room temperature for 4 h, then quenched with ice-water and the crude solid was filtered, washed with water, and dried to yield the title compound **24** (208 mg, 90%). mp 237 °C. ν_{max} (KBr): 3384, 2920, 2341, 2108, 1920, 1630, 1565, 1510, 1460, 1329, 1278, 1210, 1099, 977, 836, 798, 729 cm^{-1}. λ_{max} (MeOH): 327 nm (ε 29,700 cm^{-1}M^{-1}), 301 (43,200), 202 (35,500). ^{1}H NMR (300 MHz, acetone-*d$_6$*): δ 3.19 (s, 3H, Me), 3.33 (s, 3H, Me), 3.91 (s, 3H, OMe). 4.00 (s, 3H, OMe), 6.59 (d, *J* 2.0 Hz, 1H, benzothiazole H6), 7.16 (d, *J* 2.0 Hz, 1H, benzothiazole H4), 7.25 (t, *J* 8.0 Hz, 1H, aryl H), 7.54 (s, 1H, C=N), 7.89 (dd, *J* 8.0, 1.6 Hz, 1H, aryl H), 8.76 (dd, *J* 8.0, 1.6 Hz, 1H, aryl H). ^{13}C NMR (75 MHz, acetone-*d$_6$*): δ 36.1 (Me), 55.7, 56.3 (OMe), 98.5, 99.6 (aryl CH), 114.5 (aryl C), 125.2, 128.4 (aryl CH), 130.5 (aryl C), 134.3 (aryl CH), 142.7, 143.5 (aryl C), 154.3 (aryl CH), 157.0, 157.2, 158.8, 166.5 (aryl C, C=N). HRMS (+ESI): $C_{18}H_{18}N_4NaO_4S$ [M+Na]$^+$ requires 409.0941, found 409.0941.

***N'*-(2-(4-Formyl-5,7-dimethoxybenzothiazol-2-yl)-6-nitrophenyl)-*N*,*N*-dimethylformimide (25).** The title compound was synthesised following the same route as that for compound **24** using benzothiazole **23** (200 mg, 0.60 mmol) and $POCl_3$ (200 µL, 2.24 mmol) in DMF (10.0 mL) at 40 ˚C and was obtained as a white solid (211 mg, 85%). mp 267 ˚C. ν_{max} (KBr): 3384, 2920, 2341, 2108, 1920, 1630, 1565, 1510, 1460, 1329, 1278, 1210, 1099, 977, 836, 798, 729 cm^{-1}. λ_{max} (MeOH): 353 nm (ε 6,900 cm^{-1}M^{-1}), 313 (11,900), 266 (19,000), 229 (14,600), 205 (15,400). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.12 (s, 3H, Me), 3.37 (s, 3H, Me), 4.04 (s, 3H, OMe), 4.09 (s, 3H, OMe), 6.51 (s, 1H, benzothiazole H6), 7.18 (t, *J* 8.0 Hz, 1H, aryl H), 7.33 (s, 1H, CH=N), 7.89 (dd, *J* 8.0, 1.5 Hz, 1H, aryl H), 8.88 (dd, *J* 8.0, 1.5 Hz, 1H, aryl H), 10.98 (s, 1H, CHO). ^{13}C NMR (150 MHz, $CDCl_3$): δ 35.2, 40.7 (Me), 56.3, 56.9 (OMe), 77.4 (aryl C), 91.8 (aryl CH), 111.9, 119.4 (aryl C), 127.3 (aryl CH), 129.3 (aryl C), 133.7 (aryl CH), 143.9, 145.0 (aryl C), 154.7 (aryl CH), 154.9, 159.3, 163.0, 166.6, 189.2 (aryl C, C=N, C=O). HRMS (+ESI): $C_{19}H_{19}N_4O_5S$ [M+H]$^+$ requires 415.1071, found 415.1070.

2-(2-Amino-3-nitrophenyl)-5,7-dimethoxybenzothiazole-4-carbaldehyde (26). The reaction was carried out using a microwave tube (10.0 mL) equipped with a magnetic stirring bar in the presence of air. A solution of benzothiazole **25** in 4M 1,4-dioxane HCl solution was added. The resulting mixture was reacted by microwave irradiation at 100 ˚C for 20 min. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by column chromatography to give the title compound **26** (31.6 mg, 70% yield). mp 201 ˚C. ν_{max} (KBr): 3205, 3126, 2967, 2836, 2320, 2110, 16701, 1597, 1500, 1449, 1341, 1248, 1210, 1110, 980, 822, 785. λ_{max} (MeOH): 353 nm (ε 15,600 cm^{-1}M^{-1-}), 324 nm (20,400), 279 (23,600), 227 (21,100), 207 (20,800). ^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 4.08 (s, 3H, OMe), 4.16 (s, 3H, OMe), 6.85 (t, *J* 8.0 Hz, 1H, aryl H), 6.99 (s, 1H, benzothiazole H6), 8.26 (d, *J* 8.0 Hz, 1H, aryl H), 8.31 (d, *J* 8.0 Hz, 1H, aryl H), 9.49 (br s, 2H, NH_2), 10.60 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 55.4, 55.9 (OMe), 97.3 (aryl CH), 108.2, 112.3 (aryl C), 120.1 (aryl CH), 124.1 (aryl C), 125.9, 134.1 (aryl CH), 137.6, 140.2, 160.8, 163.0, 164.4, 166.5 (aryl C), 189.7 (CHO). HRMS (+ESI): $C_{16}H_{14}N_3O_5S_2$ [M+H]$^+$ requires 360.0648, found 360.0646.

3-(5,7-Dimethoxybenzothiazol-2-yl)benzene-1,2-diamine (27). To a refluxing solution of benzothiazole

23 (100 mg, 0.32 mmol) in absolute EtOH (10 mL), 10% Pd/C (15 mg 0.014 mmol) was added followed by hydrazine hydrate (20 µL, 4.12 mmol) over a period of about 15 min. The mixture was refluxed under N_2 during 1 h. After cooling to room temperature, Pd/C was filtered off and the solvent was removed under reduced pressure. CH_2Cl_2 (20 mL) was added and the organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield the unpurified title compound **27** (86 mg, 95%). ^1H NMR (300 MHz, DMSO-*d*$_6$): δ 3.87 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.87 (br s, 2H, NH_2), 6.50 (t, *J* 7.6 Hz, 1H, aryl H), 6.65 (m, 2H, aryl H, benzothiazole H6), 6.84 (br s, 2H, NH_2), 7.00 (dd, *J* 8.2, 1.1 Hz, 1H, aryl H), 7.21 (d, *J* 1.9 Hz, 1H, benzothiazole H4). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 55.9, 56.4 (OMe), 97.0, 97.4 (aryl CH), 113.5 (aryl C), 115.7 (aryl CH), 120.3 (aryl C), 129.4 (aryl CH), 131.5 (aryl C), 137.0 (aryl CH), 144.7, 155.3, 157.9, 160.8, 166.6 (aryl C). HRMS (+ESI): $C_{15}H_{15}N_3NaO_2S_1$ $[M+Na]^+$ requires 324.0777, found 324.0776.

***tert*-Butyl (2-amino-3-(5,7-dimethoxybenzothiazol-2-yl)phenyl)carbamate (28).** To a solution of diaminobenzothiazole **27** (100 mg, 0.33 mmol) in a mixture of *t*-BuOH (5.00 mL) and THF (5.00 mL) was added di-*t*-butyl carbonate (151 µL, 0.66 mmol) and NaOH (27 mg, 0.66 mmol). The mixture was stirred for 1 h at room temperature overnight. The solvent was evaporated and the resulting solid was purified by column chromatography to yield the title compound **28** (119 mg, 90%). mp 198 ˚C. ν_{max} (KBr):: 3444, 1655, 1568, 1462, 1389, 1300, 1215, 1153, 1066, 1045, 975, 826 cm^{-1}. λ_{max} (MeOH): 353 nm (ε 16,900 $cm^{-1}M^{-1}$), 324 (20,400), 279 (21,100), 227 (21,100), 207 (20,800). ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 9H, *t*-butyl), 3.89 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.22 (br s, 1H, NH), 6.46 (d, *J* 2.0 Hz, 1H, benzothiazole H6), 6.76 (t, *J* 8.0 Hz, 1H, aryl H), 7.08 (d, *J* 2.0 Hz, 1H, benzothiazole H4), 7.39 (d, *J* 7.2 Hz, 1H, aryl H), 7.57 (dd, *J* 8.0, 1.1 Hz, 1H, aryl H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5 (*t*-butyl), 55.9, 56.1 (OMe), 77.4, 81.0 (aryl C), 96.9, 97.4 (aryl CH), 114.7 (aryl C), 117.6 (aryl CH), 125.3, 127.5 (aryl CH), 127.9, 154.3, 155.3, 160.4, 170.2 (aryl C, C=O). HRMS (+ESI): $C_{20}H_{24}N_3O_4S$ $[M+H]^+$ requires 402.1482, found 402.1480.

4-(5,7-Dimethoxybenzothiazol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (29). In a Schlenk tube (25 mL) equipped with a magnetic stirrer bar, $Cu(OAc)_2$ (7 mg, 0.3 mmol), diaminobenzothiazole **27** (100 mg, 0.33 mmol), urea (60 mg, 1.0 mmol) and *t*-pentanol (2 mL) were added successively. The Schlenk tube was closed and the resulting mixture was stirred at 140 ˚C for 8 h under argon atmosphere. After cooling to room temperature, the reaction mixture was directly filtered through a pad of Celite eluting with EtOH and concentrated to afford the crude product, which was purified by column chromatography as a white solid (91 mg, 84%). mp 297-300 ˚C. ν_{max} (KBr): 3381, 3134, 2939, 2342, 2115, 1902, 1708, 1599, 1451, 1410, 1356, 1309, 1219, 1129, 1055, 934, 818, 750. ^1H NMR (400 MHz, DMSO-*d*$_6$): δ 3.88 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.69 (d, *J* 2.1 Hz, 1H, benzothiazole H6), 7.11 (m, 2H, aryl H), 7.44 (d, *J* 2.1 Hz, 1H, benzothiazole H4), 7.47 (t, *J* 4.5 Hz, 1H, aryl H), 10.60 (br s, 1H, NH), 11.02 (br s, 1H, NH). ^{13}C NMR

(100 MHz, DMSO-d_6): δ 55.7, 56.2 (OMe), 97.2, 98.4, 110.9 (aryl CH), 113.8, 113.9 (aryl C), 119.4, 121.2 (aryl CH), 127.3, 130.7, 153.8, 155.02, 155.3, 160.2 (aryl C), 165.9 (C=O). HRMS (+ESI): $C_{16}H_{13}N_3NaO_3S$ $[M+Na]^+$ requires 350.0570, found 350.0565.

4-(5,7-Dimethoxybenzothiazol-2-yl)benzo[*c*][1,2,5]thiadiazole (30). A solution of diaminobenzothiazole **27** (100 mg, 0.33 mmol) in CH_2Cl_2 (10.00 mL) was added $SOCl_2$ (36 µL, 0.50 mmol) and excess Et_3N (50 µL). The solution was heated at 60 ˚C for 1 h. After cooling to room temperature, the solution was washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was evaporated and the resulting solid was purified by column chromatography to yield the title compound **30** (68 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OMe), 4.01 (s, 3H, OMe), 6.57 (d, *J* 1.8 Hz, 1H, benzothiazole H6), 7.35 (d, *J* 1.8 Hz, 1H, benzothiazole H4), 7.81 (dd, *J* 8.8, 7.2 Hz, 1H, aryl H), 8.17 (dd, *J* 8.2, 0.5 Hz, 1H, aryl H), 8.91 (d, *J* 7.2 Hz, 1H, aryl H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 56.2 (OMe), 97.2, 97.8 (aryl CH), 111.6 (aryl C), 115.7, 121.8, 127.7 (aryl CH), 129.7, 153.7, 155.3, 156.9, 157.2, 157.8, 166.6 (aryl C). HRMS (+ESI): $C_{15}H_{11}N_3NaO_2S_2$ $[M+Na]^+$ requires 352.0185, found 352.0179.

2-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-5,7-dimethoxybenzothiazole-4-carbaldehyde (31).

To an ice-cold solution of $POCl_3$ (140 µL, 1.57 mmol) in dry DMF (2.0 mL) was added a cold solution of benzothiazole **30** (200 mg, 0.61 mmol) in dry 1,2-dichloroethane (5.0 mL). The mixture was stirred at 40 ˚C for 3 h, then quenched with ice-water and basified with 10% aqueous NaOH. The resulting mixture was stirred for 30 min and the precipitated solid was filtered, washed with water, and dried to yield the title compound (196 mg, 90%). mp >250 ˚C (dec). ν_{max} (KBr): 3457, 2995, 2932, 2837, 1605, 1554, 1435, 1420, 1388, 1209, 1144, 1098, 994, 821 cm^{-1}. λ_{max} (THF): 332 nm (ε 36,100 cm^{-1}M^{-1}), 240 (97,500), 226 (103,000), 202 (127,800). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, OMe), 3.94 (s, 3H, OMe), 6.78 (s, 1H, benzothiazole H6), 7.71 (dd, *J* 8.1, 7.0 Hz, 1H, aryl H), 7.99 (dd, *J* 8.1, 0.5 Hz, 1H, aryl H), 8.26 (d, *J* 7.0 Hz, 1H, aryl H). 10.06 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.8 (OMe), 97.6 (aryl CH), 109.0, 112.9 (aryl C), 121.7, 127.7 (aryl CH), 129.7 (aryl C), 130.7 (aryl CH), 153.3, 155.8, 160.1, 163.0, 164.4, 166.6 (aryl C), 183.8 (C=O). HRMS (+ESI): $C_{16}H_{12}N_3O_3S_2$ $[M+H]^+$ requires 358.0315, found 358.0316.

4-(4-(1,3-Dioxolan-2-yl)-5,7-dimethoxybenzo[*d*]thiazol-2-yl)benzo[*c*][1,2,5]thiadiazole (32). A suspension of benzothiazole-7-carbaldehyde **31** (50 mg, 0.14 mmol) in toluene (10.00 mL) was added ethylene glycol (40 µL, 0.7 mmol) and *p*-toluenesulfonic acid (3 mg, 0.016 mmol). The mixture was heated to reflux until the starting material was consumed completely (monitored by TLC). The solvent was evaporated and washed with water to yield the title compound **32** (46 mg, 85%). mp 247 ˚C. ν_{max} (KBr): 3549, 3314, 3110, 2343, 2118, 1934, 1661, 1592, 1512, 1419, 1366, 1255, 1223, 1162, 1110, 997, 923, 846, 781, 677 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (m, 1H, OCH), 3.96 (s, 3H, OMe), 4.02 (s, 3H, OMe), 4.15 (m, 1H, OCH), 4.24 (m, 2H, OCH), 4.34 (m, 1H, OCH), 6.59 (s, 1H, benzothiazole H6), 7.85 (t, *J* 8.3 Hz, 1H, aryl H), 8.21 (d, *J* 8.4 Hz, 1H, aryl H), 9.12 (d, *J* 6.8 Hz, 1H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7, 55.9 (OMe), 65.1 (OCH), 96.3 (aryl CH), 100.0 (OCH), 108.7, 118.0 (aryl C), 120.8, 127.2 (aryl CH), 128.7 (aryl C), 131.9 (aryl CH), 153.0, 153.9, 155.9, 155.9, 158.2, 165.9 (aryl C). HRMS (+ESI): $C_{18}H_{16}N_3O_4S_2$ $[M+H]^+$ requires 402.0577, found 402.0571.

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