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SYNTHESIS OF DIMETHOXY ACTIVATED BENZIMIDAZOLES AND BISBENZIMIDAZOLES

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Abstract – A range of 2-substituted-4,6-dimethoxy activated benzimidazoles and 2,2'-bisbenzimidazoles have been synthesized from 2-aminoanilide derivatives under acidic conditions. The starting materials were prepared either by acylation from 3,5-dimethoxyaniline followed by nitration, or by acylation from 3,5-dimethoxy-2-nitroaniline. The 2-nitroanilides were then reduced by palladium catalyzed reaction with hydrazine and subsequent acid catalyzed cyclization giving the corresponding 4,6-dimethoxybenzimidazoles and 4,6-dimethoxy-2,2'-bisbenzimidazoles. In addition, 2-phenyl-4,5,6-trimethoxybenzimidazole has been synthesized using a similar procedure.

INTRODUCTION

Strategically positioned methoxy substituents on indoles at C4 and C6 have led to some very interesting and characteristic reactions which do not occur in the case of simple indoles.[1-4] This substitution pattern not only activates C7 in particular, but also enhances the general reactivity of the indoles, so that new reactions can be observed. In addition, given suitable substitution patterns, reaction can occur at C7 alone, C2 and C7, C2 and N1, and C7 and N1.[3-8] These reactions make the synthesis of new classes of natural and unnatural indoles possible.[9] Subsequently, this type of chemistry has also been investigated for the related benzofuran system by our group.[10-13]

The related 4,6-dimethoxybenzimidazoles would also be expected to be similarly active at C7, but the C2 position is not nucleophilic enough for electrophilic aromatic substitution. However, replacement of a C3 aryl group in indoles with a nitrogen atom in benzimidazoles would provide different steric features and basicity to the molecule, and therefore influence its chemistry, making it different from the indoles. Thus, as part of a programme aimed at expanding the chemical reactivity of dimethoxy activated

heterocyclic systems we describe the preparation of new activated 2-substituted benzimidazoles and 2,2'-bisbenzimidazoles. Although the benzimidazole scaffold features mainly in herbicides, fungicides and anthelmintics, it also possesses other significant biological activities.[14]

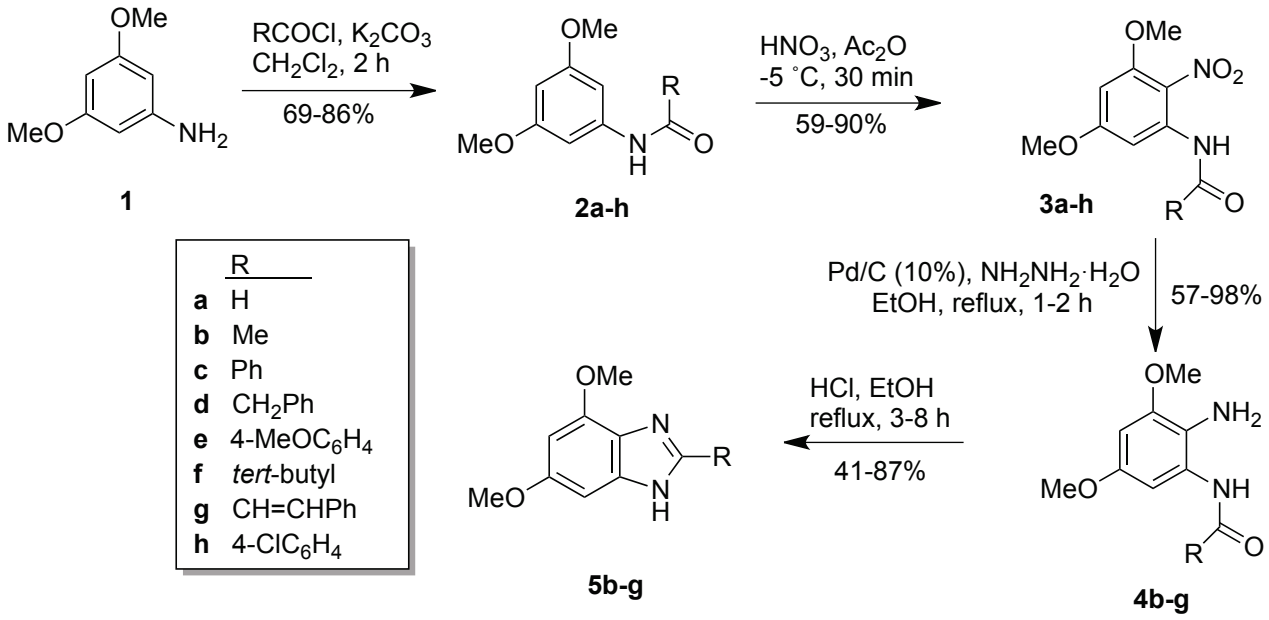
RESULTS AND DISCUSSION

Synthesis of 4,6-dimethoxybenzimidazoles

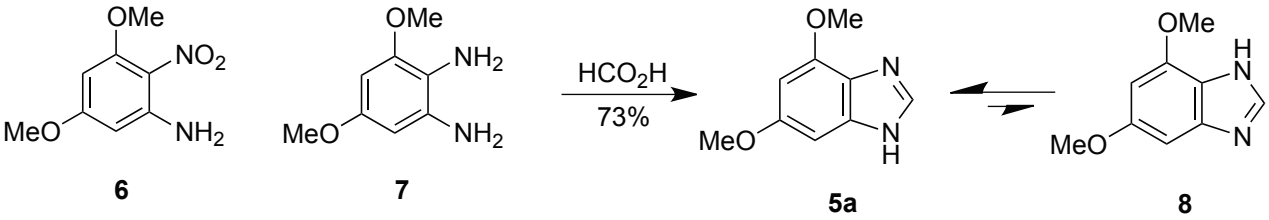
Various methods have been described for the synthesis of benzimidazoles.[14,15] Traditionally, benzimidazoles have most commonly been prepared from the reaction of 1,2-diaminobenzenes with carboxylic acids or acid derivatives such as nitriles, imidates, orthoesters, anhydrides or lactones under harsh dehydrating reaction conditions utilizing strong acids (e.g., polyphosphoric acid).[16-18] On the other hand, synthesis of benzimidazoles via condensation of 1,2-diaminobenzenes with aldehydes requires an oxidation step from the dihydro intermediate.[19]

Synthesis of 2-substituted-4,6-dimethoxybenzimidazoles was carried out efficiently by cyclization of 2-aminoanilide derivatives under acidic conditions (Scheme 1). In this procedure usually 3,5-dimethoxyaniline **1** was first acylated with respective acid chlorides to give the amides **2c-h** in moderate to high yields. Acetic anhydride is a more effective reagent for the formation of amide **2b**. The formamide **2a** was formed by the reaction of 3,5-dimethoxyaniline **1** with formic acid and showed restricted rotation of the amide bond in its ^{1}H NMR spectrum.[20] The amides **2** were then nitrated using nitric acid in acetic anhydride to produce the 2-nitroanilides **3a-h** in usually high yields of 59-90%. It is essential that the nitration step should be carried out carefully at 0-5 ˚C with slow addition of the nitrating agent to avoid dinitration.

The 2-nitroanilides **3b-g** were reduced to the corresponding 2-aminoanilides **4b-g** with palladium catalyzed hydrazine reduction. The aminoanilides could be isolated and characterized, but usually subsequent cyclization reactions were carried out directly by acid catalysis to give the corresponding 2-substituted-4,6-dimethoxybenzimidazoles **5b-g** in high yields of 41-87%.



Scheme 1



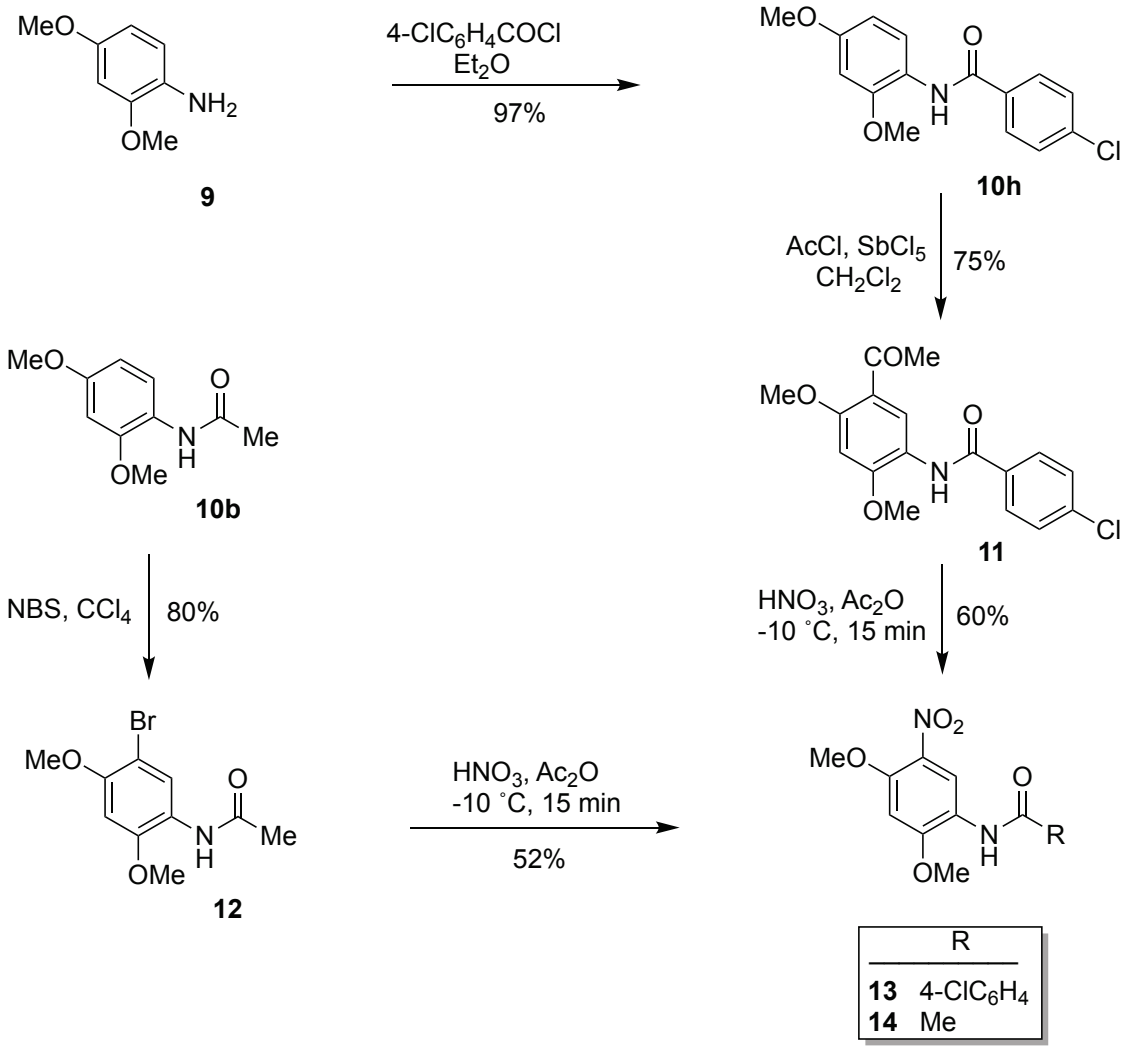
Scheme 2

The benzimidazole **5a** was prepared *via* a slightly different route. Nitration of the formanilide **2a** at C2 yielded **3a** and removal of the formyl group by Claisen's base gave the 2-nitroaniline **6** (Scheme 2). Alternatively, use of a large excess of acetic anhydride in the nitration step and a longer stirring time during aqueous workup resulted in the hydrolysis of 2-nitroformanilide **3a** yielding the 2-nitroaniline **6** in 67% yield. This was then converted to the 1,2-diaminobenzene **7** by palladium-catalyzed hydrazine reduction. The highly electron rich 3,5-dimethoxy-1,2-diaminobenzene **7** was unstable and required storage under an inert atmosphere and refrigeration to prevent decomposition. Therefore, it was used immediately in reaction with formic acid to give a 9:1 mixture of 4,6-dimethoxybenzimidazole **5a** and its tautomer 5,7-dimethoxybenzimidazole **8** in 73% yield (Scheme 2). The two tautomeric structures were indicated[15] by the ^{1}H NMR spectrum in $CDCl_3$. When the spectrum was carried out in DMSO-d_6, it was found that the 4,6-tautomer **5a** was still dominant over the 5,7-tautomer **8**. The existence of tautomerism is also apparent in 2-*tert*-butylbenzimidazole **5f**. The H5 and H7 protons of the benzimidazoles appeared in the ^{1}H NMR spectra as *meta* coupled doublets which were characteristic for their identification.

The palladium catalyzed hydrazine reduction and subsequent cyclization of 2-nitrobenzamide **3h** gave a low yield of the phenylbenzimidazole **5c** instead of the chlorophenylbenzimidazole **5h**. Such dechlorination of aromatic halides under reductive conditions is well documented in the literature.[21-24]

The nitrobenzamides **3c** and **3d** were also prepared by reacting 2-nitroaniline **6** with benzoyl chloride and phenylacetyl chloride respectively. In addition, reaction of 2-nitrobenzamide **3c** with tin(II) chloride dihydrate and hydrochloric acid yielded the 2-phenylbenzimidazole **5c** in a single step. However, this sequence was not considered further due to the low yield (18%) and the need for chromatography to isolate the product. Furthermore, the 1,2-diaminobenzene **7** failed to undergo the Phillips reaction[25] with carboxylic acids such as phenyl acetic acid, chloracetic acid, and mandelic acid, but did react with benzaldehyde under acidic conditions to give the 2-phenylbenzimidazole **5c** in modest yield (32%).

Attempted synthesis of 4,6-dimethoxy benzimidazoles from 2,4-dimethoxyaniline

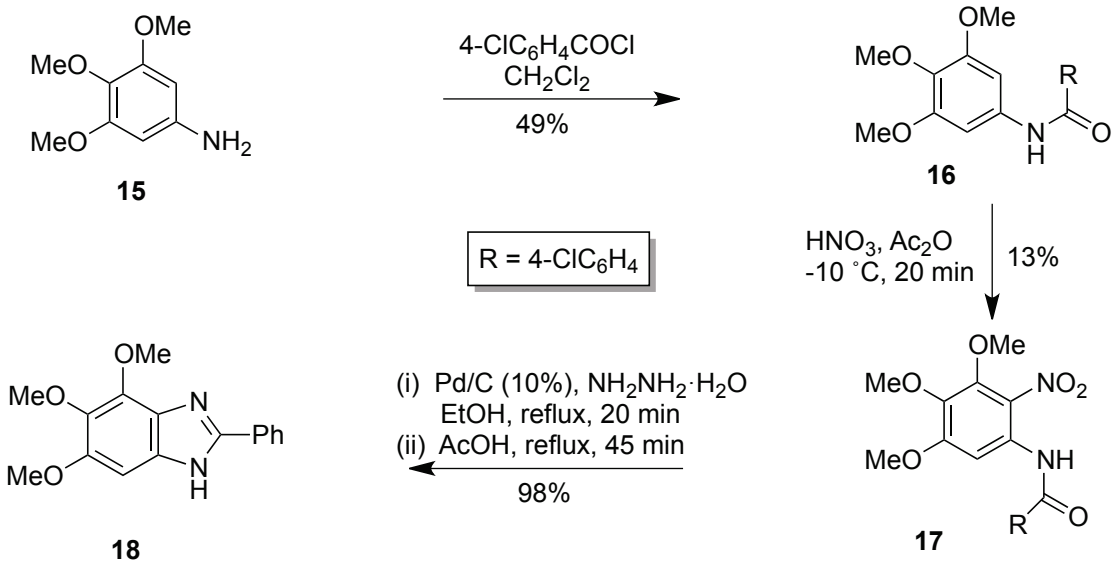


Scheme 3

2,4-Dimethoxyaniline **9** was considered as a potential alternative starting material for the preparation of 4,6-dimethoxybenzimidazoles **5** by a similar acylation, nitration and cyclization procedure (Scheme 3). The challenge was to achieve selective nitration at C6, which after reduction would undergo cyclization to the 4,6-dimethoxybenzimidazoles **5**. Therefore, the anilide was substituted at C5 by acetyl and bromine functionalities in the hope that nitration would then occur at C6. A modified Friedel-Crafts acylation of amide **10h** using acetyl chloride and antimony pentachloride gave the 5-acetylbenzamide **11**, whereas the 5-bromoanilide **12** was prepared by reaction of amide **10b** with *N*-bromosuccinimide in carbon tetrachloride. However, nitration of 5-acetylbenzamide **11** and 5-bromoanilide **12** was accompanied by *ipso*-susbtitution and formation of 5-nitroanilides **13** and **14** respectively in moderate yield.

Synthesis of 4,5,6-trimethoxy-2-phenylbenzimidazole

Acylation of 3,4,5-trimethoxyaniline **15** with 4-chlorobenzoyl chloride gave only a modest yield (49%) of the desired benzamide **16** and subsequent nitration gave a very low yield (13%) of the 2-nitrophenylbenzamide **17** (Scheme 4). Use of nitric acid absorbed on silica did not improve the yield. However, palladium catalyzed reduction of the 2-nitrophenylbenzamide **17** and subsequent cyclization gave 4,5,6-trimethoxy-2-phenylbenzimidazole **18** in quantitative yield. Once again, dechlorination occurred during the reduction process.



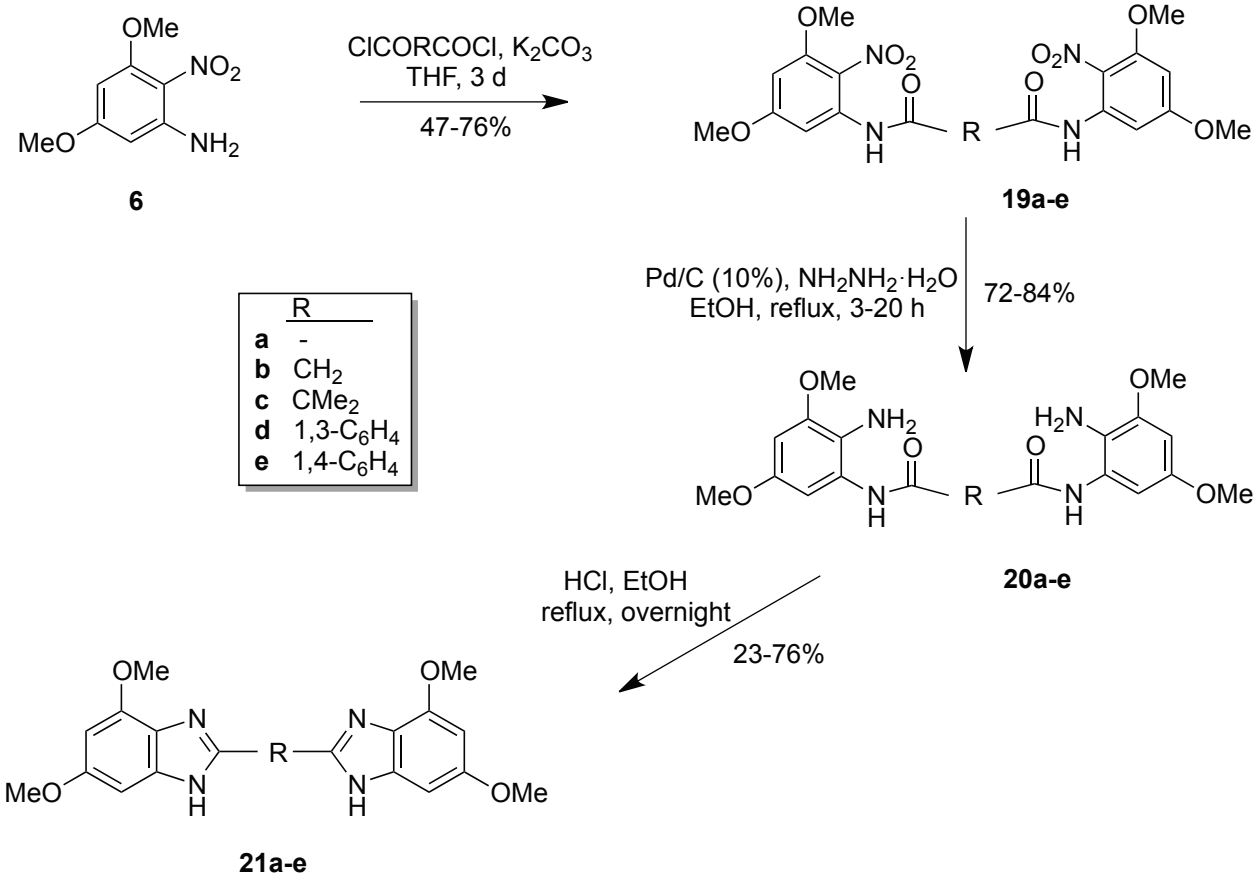
Scheme 4

Synthesis of 4,4’,6,6’-tetramethoxy-2,2'-bisbenzimidazoles

The acid chloride method was extended to include diacid chlorides with a strategy to synthesize 4,4’,6,6’-tetramethoxy-2,2'-bisbenzimidazoles directly attached at the C2 positions or incorporating alkyl or aryl spacer groups. Thus oxalyl chloride, malonyl chloride, dimethylmalonyl chloride, isophthaloyl chloride and terephthaloyl chloride were reacted with the 2-nitroaniline **6** to prepare the bis-2-nitroamides

19a-e (Scheme 5). The sequence of preparation starting from 3,5-dimethoxyaniline **1** could not be followed because the low solubility of the amides in the nitration media resulted in multiple nitration products. The bis-2-nitroamides **19a-e** were then converted to bis-2-aminoanilides **20a-e** with palladium-catalyzed hydrazine reduction in good yields (72-84%), and these products were then cyclized by acid catalysis to give the corresponding 2,2'-bisbenzimidazoles **21a-e** in moderate yields of 23-76%.

The 4,6-dimethoxy-2,2'-bisbenzimidazoles **21d** and **21e** showed tautomerism to the corresponding 5,7-dimethoxybenzimidazoles in a ratio (1:0.34) according to the ^{1}H NMR spectrum taken in DMSO-d_6. Interestingly, DNA specific binding properties are well described for some bisbenzimidazoles (e.g., Hoechst 33258)[26,27] related to the synthesized compounds **21**. In addition, these methoxy activated head-to-head 2,2'-bisbenzimidazoles **21** having a spacer group are interesting for further chemical reactivity towards electrophiles and the formation of metal complexes.



Scheme 5

CONCLUSIONS

A new range of benzimidazoles and 2,2'-bisbenzimidazoles, which are activated by the incorporation of methoxy groups at the C4 and C6 positions, have been synthesised using a critical selection of established strategies. The reactivity of these activated benzimidazoles will be described in a following article.

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, Univeristy of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 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 Univeristy 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.

Synthesis of 3,5-dimethoxyanilides

***N*-(3,5-Dimethoxyphenyl)-4'-methoxybenzamide (2e).** Anisoyl chloride (18.0 g, 130.7 mmol) was added dropwise to an ice cooled solution of 3,5-dimethoxyaniline **1** (10.0 g, 65.35 mmol) in dry CH_2Cl_2 (150 mL) containing anhydrous potassium carbonate (5 g). The reaction mixture was stirred in an ice bath for 2 h. Water was then added to the reaction mixture and the organic phase was separated and washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated off and the benzamide **2e** crystallized out from EtOH/H_2O as colourless needles (12.87 g, 69%), mp 110-112 ˚C. ν_{max} (KBr): 3313, 1686, 1642, 1600, 1536, 1508, 1456, 1429, 1314, 1289, 1258, 1201, 1177, 1106, 1065, 1028, 846, 763 cm^{-1}. λ_{max} (MeOH): 206 nm (ε 47,200 cm^{-1}M^{-1}), 274 (20,800). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (6H, s, OMe), 3.84 (3H, s, OMe), 6.25 (1H, t, *J* 1.9 Hz, aryl H4), 6.89 (2H, d, *J* 1.9 Hz, aryl H2,6), 6.91-6.94 (2H, m, aryl H), 7.79-7.83 (2H, m, aryl H), 7.79 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.3 (OMe), 96.8, 98.3, 113.9, 128.8 (aryl CH), 113.9, 127.0, 139.9 162.4, 165.2 (aryl C), 161.0 (C=O). Mass Spectrum (+EI): *m/z* (%) 289 (M+2, 20), 288 (M+1, 100). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.9; H, 6.0; N, 4.9. Found: C, 66.7; H, 6.0; N, 4.8.

***N*-(3',5'-Dimethoxyphenyl)pivalamide (2f).** Pivaloyl chloride (25 mL, 0.20 mol) was added dropwise, over 10 min, to a stirred solution of 3,5-dimethoxyaniline **1** (30.0 g, 0.196 mol) and triethylamine (28 mL, 0.20 mol) in dry CH_2Cl_2 (260 mL) with cooling in an iced water bath. The resulting mixture was stirred overnight at room temperature and then washed sequentially with water, dilute HCl, brine, then dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give a white solid. Recrystallization from Et_2O gave the trimethylacetanilide **2f** as large translucent crystals (39.88 g, 86%), mp 117 ˚C. R_f (1% MeOH/CH_2Cl_2) 0.31. ν_{max} (KBr): 3316, 1655, 1616, 1555, 1479, 1451, 1419, 1208, 1156, 1059, 942, 842, 827, 687 cm^{-1}. λ_{max} (THF): 230 nm (ε 10,000 cm^{-1}M^{-1}), 250 (13,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (9 H, s, $C(Me)_3$), 3.71 (6 H, s, OMe), 6.19 (1 H, t, *J* 2.3 Hz, aryl H4), 6.78 (2 H, d, *J* 2.3 Hz, aryl H2,H6), 7.44 (1 H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.4 ($C(\underline{Me})_3$), 39.6 ($\underline{C}(Me)_3$), 55.2 (OMe), 96.8, 98.0 (Aryl CH), 139.9, 160.9 (aryl C), 176.7 (C=O). Mass spectrum: (+EI): *m/z* (%) 238 (M+1, 9),

237 (M, 67), 153 (58), 125 (12), 124 (33), 57 (100). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9. Found: C, 65.9; H, 8.3; N, 6.0.

***N*-(3,5-Dimethoxyphenyl)cinnamide (2g).** Cinnamoyl chloride (10.87 g, 65.28 mmol) in dry CH_2Cl_2 (20 mL) at 0 ˚C was added dropwise with stirring to 3,5-dimethoxyaniline **1** (5 g, 32.64 mmol) in dry CH_2Cl_2 (80 mL) over half an hour. The mixture was then stirred for 4 h at room temperature during which time a white precipitation formed. The reaction mixture was poured into 1M HCl and extracted with Et_2O. The organic layer was washed with water, brine, then dried over anhydrous Na_2SO_4, filtered and evaporated to produce a pale yellow solid. This was recrystallized from *i*PrOH to form the cinnamide **2g** as colorless needles (7.10 g, 77%), mp 145-146 ˚C. ν_{max} (KBr): 3350, 1660, 1626, 1549, 1345, 1222, 1206, 1160, 1069, 1053, 976, 838, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (6H, s, OMe), 6.26 (1H, t, *J* 2.6 Hz, aryl H4), 6.51 (1H, d, *J* 15.4 Hz, CH=), 6.86 (2H, d, *J* 2.6 Hz, aryl H2, H6), 7.37-7.39 (3H, m, aryl H), 7.51-7.55 (2H, m, aryl H), 7.74 (1H, d, *J* 15.4 Hz, =CH), 7.78 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3 (OMe), 96.9, 98.2 (aryl CH), 127.9, 128.8, 129.9 (aryl CH), 120.7, 142.5 (CH=CH), 134.9, 139.7, 164.1 (aryl C), 161.0 (C=O). Mass Spectrum (+EI): *m/z* (%) 284 (M+1, 5), 283 (M, 18), 282 (10), 206 (22), 153 (80), 131 (100), 103 (95), 77 (55), 69 (18). Anal. Calcd for $C_{17}H_{17}NO_3$: C,72.1; H, 6.1; N, 4.9. Found: C, 71.9; H, 5.9; N, 4.9.

***N*-(3',5'-Dimethoxyphenyl)-4-chlorobenzamide (2h).** A solution of *p*-chlorobenzoyl chloride (18.3 mL, 0.144 mol) in anhydrous CH_2Cl_2 (25 mL) was added dropwise over 45 min to a stirred solution of 3,5-dimethoxyaniline **1** (20 g, 0.13 mol) in anhydrous CH_2Cl_2 (100 mL) with cooling in an iced water bath. The mixture was then stirred and allowed to warm to room temperature before it was washed sequentially with water, dilute HCl, saturated Na_2CO_3 solution, brine, then dried over anhydrous $MgSO_4$, and the solvent evaporated in vacuo to give an off-white solid. Recrystallization from $CHCl_3$/light petroleum gave the *p*-chlorobenzamide **2h** as colorless prisms (28.45 g, 75%), mp 130-131 ˚C. R_f (CH_2Cl_2) 0.53. ν_{max} (KBr): 3315, 1648, 1616, 1604, 1531, 1455, 1421, 1347, 1291, 1208, 1156, 1090, 1067, 1055, 1014, 929, 895, 848, 829, 804, 675 cm^{-1}. λ_{max} (THF): 238 nm (ε 16,400 $cm^{-1}M^{-1}$), 269 (11,400), 289 (10,100). ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (6H, s, OMe), 6.27 (1H, t, *J* 2.3 Hz, aryl H4), 6.87 (2H, d, *J* 2.3 Hz, aryl H2, H6), 7.76 (2H, d, *J* 8.7 Hz, *p*-chlorophenyl CH), 7.40 (2H, d, *J* 8.7 Hz, *p*-chlorophenyl CH), 7.93 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8 (OMe), 97.6, 99.1 (aryl CH), 129.4, 128.9 (*p*-chlorophenyl CH), 133.7, 138.6, 139.9, 161.6 (aryl C), 165.2 (C=O). Mass spectrum: (+EI): *m/z* (%) 294 (M+1, ^{37}Cl, 1), 293 (M, ^{37}Cl, 9), 292 (M+1, ^{35}Cl, 3), 291 (M, ^{35}Cl, 27), 141 (36), 139 (100). Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.8; H, 4.8; N, 4.8. Found: C, 62.0; H, 4.8; N, 4.8.

Synthesis of 3,5-dimethoxynitroanilides

***N*-(3,5-Dimethoxy-2-nitrophenyl)formamide (3a).** To an ice/salt cooled solution (-10 ˚C) of formanilide **2a**[28-30] (1 g, 5.51 mmol) in Ac_2O (10 mL) was added previously cooled HNO_3 (0.7 mL) in Ac_2O (2 mL) dropwise with continuous stirring over half an hour at such a rate that the temperature stayed between 0 to -5 ˚C. The solution was stirred for another half an hour before ice water was added and the mixture stirred overnight. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O (1:1) to yield the 2-nitroformanilide **3a** as yellow crystals (1.12 g, 90%), mp 120-122 ˚C. ν_{max} (KBr): 3335, 1715, 1700, 1600, 1550, 1320, 1270, 1240, 1180, 1160, 1120, 1080, 1070, 930, 830, 760, 720, 660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 6.32 (1H, d, *J* 2.3 Hz, aryl H4), 7.74 (1H, d, *J* 2.3 Hz, aryl H6), 8.46 (1H, s, CHO), 9.15 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.6 (OMe), 96.1, 98.1 (aryl CH), 134.0, 155.5, 161.2, 163.5 (aryl C), 159.2 (C=O). Mass Spectrum (+EI): *m/z* (%) 226 (M, 11), 180 (100). Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.8; H, 4.4; N, 12.4. Found: C, 48.0; H, 4.6; N, 12.3.

***N*-(3,5-Dimethoxy-2-nitrophenyl)acetamide (3b).** *Method A:* The 2-nitroacetamide **3b** was prepared as described for the compound **3a** from a partially dissolved ice/salt cooled solution (-10 ˚C) of acetanilide **2b**[31] (5 g, 25.61 mmol) in Ac_2O (65 mL) and a previously cooled solution of HNO_3 (2.4 mL) in Ac_2O (10 mL) under stirring for half an hour to yield a yellow solid which was recrystallized from EtOH/H_2O (1:1) to yield the 2-nitroacetanilide **3b** as yellow needles (4.27 g, 70%).

Method B: 3,5-Dimethoxyaniline **1** (5 g, 32.64 mmol) was stirred in Ac_2O (100 mL) in an ice-salt bath to -10 ˚C for 1 h. Previously cooled HNO_3 (6.5 mL) in Ac_2O (20 mL) was added dropwise to this cooled solution under continuous stirring for half an hour at such a rate that the temperature stayed between 0 to -5 ˚C. The mixture was stirred for another half an hour before ice water was added and stirred further overnight. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O (1:1) to yield the 2-nitroacetanilide **3b** as yellow needles (5.10 g, 65%), mp 141-142 ˚C. ν_{max} (KBr): 3380, 1700, 1610, 1595, 1550, 1500, 1420, 1380. 1310, 1295, 1240, 1210, 1120, 835, 775, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (3H, s, Me), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 6.27 (1H, d, *J* 2.6 Hz, aryl H4), 7.69 (1H, d, *J* 2.6 Hz, aryl H6), 9.15 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3 (Me), 55.8, 56.6 (OMe), 95.6, 97.7 (aryl CH), 129.3, 135.2, 155.4, 163.4 (aryl C), 168.7 (C=O). Mass Spectrum (+EI): *m/z* (%) 240 (M, 5), 194 (100), 168 (20), 151 (35). Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.0; N, 11.7. Found: C, 50.0; H, 4.9; N, 11.4.

***N*-(3',5'-Dimethoxy-2'-nitrophenyl)benzamide (3c).** *Method A:* To an ice/salt cooled solution (-10 ˚C) of benzamide **2c**[32] (9 g, 35.0 mmol) in Ac_2O (125 mL) was added previously cooled HNO_3 (5.5 mL) in Ac_2O (10 mL) dropwise with continuous stirring over half an hour at such a rate that the temperature stayed between 0 to -5 ˚C. The mixture was stirred for another half an hour before ice water was added

and then stirred further overnight. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O (1:1) to yield the 2-nitrophenylbenzamide **3c** as minute brown crystals (7.93 g, 75%), mp 128-130 ˚C. R_f (CH_2Cl_2) 0.64. ν_{max} (KBr): 3317, 1681, 1666, 1608, 1542, 1502, 1456, 1422, 1323, 1271, 1210, 1170, 1141, 1076, 937, 826, 796, 686 cm^{-1}. λ_{max} (THF): 240 nm (ε 12,500 $cm^{-1}M^{-1}$), 261 (15,800), 335 (5,260). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 6.32 (1H, d, *J* 2.6 Hz, aryl H4), 7.48-7.61 (3H, m, aryl H), 7.90-7.93 (2H, m, aryl H), 7.99 (1H, d, *J* 2.6 Hz, aryl H6) 10.32 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.6 (OMe), 95.8, 97.3, 127.2, 128.9, 132.5 (aryl CH), 125.1, 133.8, 136.0, 155.8, 163.8 (aryl C), 165.6 (C=O). Mass Spectrum (+EI): *m/z* (%) 303 (M+1, 25), 271 (21), 257 (42), 256 (25), 255 (100), 105 (32). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.6; H, 4.7; N, 9.3. Found: C, 59.6; H, 4.7; N, 9.4.

Method B: To a solution of 2-nitroaniline **9** (0.50 g, 2.5 mmol) in dry CH_2Cl_2 (10 mL) triethylamine (2 eq., 0.70 mL) was added. A mixture of benzoyl chloride (2 eq., 0.53 mL) in CH_2Cl_2 (5 mL) was added dropwise to the mixture while stirring at room temperature. The mixture was stirred for 6 h at room temperature before it turned darker in colour and a precipitate formed. The mixture was then filtered and the organic layer was washed with brine, 2M NaOH, brine again and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the solid was recrystallized from EtOH/H_2O (1:1) to yield the 2-nitrobenzamide **3c** as pale yellow needles (0.64 g, 85%).

***N*-[(3',5'-Dimethoxy-2'-nitrophenyl)phenyl]acetamide (3d).** To a solution of 2-nitroaniline **9** (1.0 g, 5.10 mmol) in dry CH_2Cl_2 (20 mL), triethylamine (1.5 eq., 1.1 mL) was added. A mixture of phenylacetyl chloride (2 eq., 1 mL) in CH_2Cl_2 (5 mL) was added dropwise to the 2-nitroaniline solution while stirring at room temperature. The mixture was stirred for 6 h at room temperature, then filtered and the organic layer was washed with brine, 2M NaOH, brine again and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the solid was recrystallized from EtOH/H_2O (1:1) to yield the nitroacetamide **3d** as pale yellow needles (0.95 g, 59%), mp 124-126 ˚C. ν_{max} (KBr): 3300, 1665, 1590, 1530, 1510, 1340, 1220, 1200, 1160, 1120, 1040, 950, 935, 830, 720, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (2H, s, CH_2), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 6.25 (1H, d, *J* 2.6 Hz, aryl H4), 7.33 (5H, m, aryl H), 7.72 (1H, d, *J* 2.6 Hz, aryl H6), 9.19 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.5 (CH_2), 55.9, 56.6 (OMe), 95.8, 97.4, 127.9, 129.3, 129.5 (aryl CH), 125.2, 133.3, 135.2, 155.4, 163.4 (aryl C), 170.0 (C=O). Mass Spectrum (+EI): *m/z* (%) 317 (M+1, 1), 316 (M, 1), 270 (72), 91 (100), 65 (22). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.8; H, 5.1; N, 8.9. Found: C, 60.4; H, 5.4; N, 8.8.

***N*-(3',5'-Dimethoxy-2'-nitrophenyl)-4-methoxybenzamide (3e).** Previously cooled HNO_3 (0.50 mL) in Ac_2O (10 mL) was added dropwise over half an hour to an ice/salt cooled (-10 ˚C) solution of benzamide **2e** (1.0 g, 3.48 mmol) in Ac_2O (25 mL) with continuous stirring at such a rate that the temperature stayed between 0 to -5 ˚C. The solution was stirred for another half an hour before ice water was added and the

mixture stirred overnight. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O (1:1) to yield the 2-nitrobenzamide **3e** as yellow crystals (0.97 g, 83%), mp 180-182 ˚C. ν_{max} (KBr): 3379, 1688, 1613, 1557, 1491, 1454, 1311, 1285, 1262, 1180, 1123, 1030, 838 cm^{-1}. λ_{max} (MeOH): 205 nm (ε 35,800 $cm^{-1}M^{-1}$), 263 (20,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 3.91 (3H, s, OMe), 6.28 (1H, d, *J* 2.6 Hz, aryl H4), 6.96-6.99 (2H, m, aryl H), 7.85-7.88 (2H, m, aryl H), 7.97 (1H, d, *J* 2.6 Hz, aryl H6), 10.26 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.9, 56.6 (OMe), 95.6, 97.1, 114.1, 129.1 (aryl CH), 125.0, 126.0, 136.3, 155.8, 163.0, 163.8 (aryl C), 165.1 (C=O). Mass Spectrum (+EI): *m/z* (%) 333 (M+1, 21), 288 (M-NO_2, 20), 199 (100), 153 (23). Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.8; H, 4.9; N, 8.4. Found: C, 57.8; H, 5.0; N, 8.4.

3,5-Dimethoxy-α,α,α-trimethyl-2-nitroacetanilide (3f). A solution of trimethylacetanilide **2f** (5.0 g, 21.1 mmol) in Ac_2O (150 mL) was stirred with cooling in a salt-ice slurry. The internal temperature was monitored and kept below –10 ˚C during the addition of HNO_3 (3.5 mL), which was added dropwise intermittently over 20 min, and stirring was continued for a further 1.5 h. The mixture was diluted with water and heated to initiate hydrolysis of the intermediate complex and the resulting mixture was cooled in an iced water bath. The resulting precipitate was filtered, dried, and purified via gravity column chromatography (CH_2Cl_2), then recrystallized from CH_2Cl_2/*n*-hexane, to give the 2-nitroacetanilide **3f** as a bright yellow powder (4.16 g, 70%), mp 98-100 ˚C. R_f (CH_2Cl_2) 0.38. ν_{max} (KBr): 3385, 1689, 1609, 1563, 1500, 1450, 1285, 1234, 1207, 1174, 1120, 951, 806 cm^{-1}. λ_{max} (THF): 242 nm (ε 12,100 $cm^{-1}M^{-1}$), 279 (3,770), 330 (4,770). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (9H, s, $C(Me)_3$), 3.88 (3H, s, OMe), 3.87 (3H, s, OMe), 6.26 (1H, s, H4), 7.82 (1H, s, H6), 9.70 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.8 ($C(\underline{Me})_3$), 40.9 ($\underline{C}(Me)_3$), 57.1, 56.4 (OMe), 97.5, 96.1 (aryl CH), 136.5, 125.4, 164.2, 156.1 (aryl C), 178.2 (C=O). Mass spectrum: *m/z* (%) 282 (M, 2), 236 (100), 151 (27). Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.3; H, 6.4; N, 9.9. Found: C, 55.5; H, 6.6; N, 10.1.

***N*-(3,5-Dimethoxy-2-nitrophenyl)cinnamide (3g).** To an ice/salt cooled solution (-10 ˚C) of cinnamide **2g** (6.75 g, 23.85 mmol) in Ac_2O (100 mL) was added previously cooled HNO_3 (3 mL) in Ac_2O (10 mL) dropwise with continuous stirring over half an hour at such a rate that the temperature stayed between 0 to -5 ˚C. The solution was stirred for another half an hour before ice water was added and the mixture stirred overnight. The resulting precipitate was filtered, washed with water and recrystallized from *i*PrOH to yield the 2-nitrophenylcinnamide **3g** as yellow crystals (6.28 g, 80%), mp 146-148 ˚C. ν_{max} (KBr): 3362, 1681, 1602, 1533, 1333, 1295, 1238, 1210, 1158, 1124, 1104, 981, 765, 711 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 6.29 (1H, d, *J* 2.6 Hz, aryl H4), 6.52 (1H, d, *J* 15.8 Hz, =CH), 7.38-7.41 (3H, m, aryl H), 7.54-7.57 (2H, m, aryl H), 7.73 (1H, d, *J* 15.8 Hz, CH=), 7.91 (1H, d, *J* 2.6 Hz, aryl H6), 9.51 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.6 (OMe), 95.8, 97.4 (aryl CH), 120.6, 143.6 (CH=CH), 128.1, 128.9, 130.3 (aryl CH), 125.1, 134.1, 135.7, 155.6, 163.6 (aryl C),

164.3 (C=O). Mass Spectrum (+EI): *m/z* (%) 329 (M+1, 6), 328 (M, 5), 283 (28), 282 (100), 181 (25), 180 (90), 168 (38), 167 (45), 166 (25), 151 (55), 150 (63), 149 (62), 131 (50), 103 (100), 77 (50). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.2; H, 4.9; N, 8.5. Found: C, 61.9; H, 5.0; N, 8.7.

4-Chloro-*N*-(3',5'-dimethoxy-2'-nitrophenyl)benzamide (3h). A suspension of benzamide **2h** (25.0 g, 85.7 mmol) in Ac_2O (600 mL) was stirred with cooling via a salt-ice slurry. HNO_3 (16 mL) was added dropwise over 2 h, intermittently, at such a rate that the internal temperature remained below –10 ˚C. The resulting suspension was stirred further for 1 h before it was poured into iced water and allowed to warm. The mixture was then carefully heated to 90 ˚C and then allowed to stir at room temperature overnight. The resulting precipitate was filtered, dried, and recrystallised from EtOH to give the 2-nitrobenzamide **3h** as fine apricot needles (22.1 g, 77%), mp 178-179 ˚C. R_f (CH_2Cl_2) 0.56. ν_{max} (KBr): 3353, 1660, 1592, 1537, 1487, 1468, 1434, 1330, 1301, 1269, 1231, 1214, 1175, 1138, 1081, 1015, 967, 907, 831, 766 cm^{-1}. λ_{max} (THF): 247 nm (ε 17,500 $cm^{-1}M^{-1}$), 261 (18,600), 334 (5,610). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (3H, s, OMe), 3.92 (3H, s, OMe), 6.32 (1H, d, *J* 2.6 Hz, H4), 7.48 (2H, d, *J* 8.6 Hz, 4-ClC_6H_4), 7.85 (2H, d, *J* 8.6 Hz, 4-ClC_6H_4), 7.94 (1H, d, *J* 2.6 Hz, H6), 10.32 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 57.1 (OMe), 96.4, 97.9 (aryl CH, C4, C6), 129.1, 129.7 (phenyl CH), 125.5, 132.7, 136.3, 139.4, 156.4, 164.3, 164.9 (C=O and aryl C). Mass spectrum (+EI): *m/z* (%) 336 (M, 1), 290 (48), 141 (38), 139 (100), 111 (45). Anal. Calcd for $C_{15}H_{13}ClN_2O_5$: C, 53.5; H, 3.9; N, 8.3. Found: 53.4; H, 3.8; N, 8.2.

Synthesis of 3,5-dimethoxyaminoanilides

***N*-(2-Amino-3,5-dimethoxyphenyl)acetamide (4b).** To a refluxing solution of 2-nitroacetamide **3b** (1.0 g, 4.1 mmol) in absolute EtOH (50 mL), 10% Pd/C (0.10 g) was added under argon followed by hydrazine monohydrate (2 mL) dropwise over 15 min, and reflux continued for another 2 h. The solution was filtered and solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to yield the 2-aminoacetamide **4b** as a brown solid (0.77 g, 90%), mp 86-88 ˚C. ν_{max} (KBr): 3459, 3424, 3321, 3226, 1652, 1601, 1544, 1459, 1371, 1276, 1205, 1150, 1051, 800 cm^{-1}. λ_{max} (MeOH): 211 nm (ε 52,400 $cm^{-1}M^{-1}$), 299 (7,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (3H, s, Me), 3.67 (3H, s, OMe), 3.77 (3H, s, OMe), 3.83 (2H, s, NH_2), 6.28 (1H, d, *J* 1.9 Hz, aryl H4), 6.57 (1H, d, *J* 1.9 Hz, aryl H6), 8.02 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (Me), 55.5, 55.7 (OMe), 96.7, 100.2 (aryl CH), 122.6, 126.2, 150.1, 153.2 (aryl C), 168.9 (C=O). Mass spectrum (+EI): *m/z* (%) 211 (M+1, 20), 193 (100). HRMS (+ESI): $C_{10}H_{14}N_2O_3$ $[M+H]^+$ requires 211.1077, found 211.1028.

***N*-(2'-Amino-3',5'-dimethoxyphenyl)benzamide (4c).** A mixture of 2-nitrophenylbenzamide **3c** (25.30 g, 83.7 mmol) and 10% Pd/C (0.50 g) in absolute EtOH (300 mL) was heated at reflux during the dropwise addition of hydrazine monohydrate (26 mL) over 20 min. Heating at reflux was continued for

40 min before the hot mixture was filtered and the filtrate was allowed to cool slowly. The resulting precipitate was filtered, dissolved in CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give the 2-aminobenzamide **4c** as an off-white powder (17.85 g, 78%), mp 173-174 ˚C. R_f (CH_2Cl_2) 0.23. ν_{max} (KBr): 3459, 3353, 3252, 1636, 1597, 1578, 1531, 1498, 1487, 1471, 1430, 1284, 1202, 1174, 1149, 1053, 902, 828, 798, 714, 692 cm^{-1}. λ_{max} (THF): 239 nm (ε 15,300 $cm^{-1}M^{-1}$), 312 (5,270). ^1H NMR (300 MHz, $CDCl_3$): δ 3.43 (2H, bs, NH_2), 3.73 (3H, s, OMe), 3.81 (3H, s, OMe), 6.31 (1H, d, *J* 2.6 Hz, H4), 6.94 (1H, d, *J* 2.6 Hz, H6), 7.43 (H, d, *J* 7.1 Hz, aryl H), 7.51 (1H, t, *J* 7.1 Hz, aryl H), 7.88 (2H, d, *J* 7.1 Hz, aryl H), 8.48 (1H, bs, NHCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6, 55.7 (OMe), 96.5, 99.1, (aryl CH C4, C6), 127.2, 128.6, 131.7 (phenyl CH), 121.3, 127.7, 134.4, 150.8, 153.9 (aryl C), 165.5 (C=O). Mass spectrum: (+EI): *m/z* (%) 273 (M+1, 7), 272 (M, 49), 167 (100), 105 (70), 77 (60). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 66.2; H, 6.1; N, 10.5.

***N*-(2'-Amino-3',5'-dimethoxyphenyl)-4-methoxybenzamide (4e).** To a refluxing solution of 2-nitroacetamide **3e** (1.40 g, 4.2 mmol) in absolute EtOH (25 mL), 10% Pd/C (0.14 g) was added under argon followed by hydrazine monohydrate (2 mL) dropwise over 15 min, and reflux continued for another 2 h. The solution was filtered and solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to yield the 2-aminobenzamide **4e** as a white solid (1.24 g, 98%), mp 154-156 ˚C. ν_{max} (KBr): 3406, 3287, 1639, 1606, 1532, 1510, 1495, 1464, 1296, 1254, 1202, 1187, 1157, 1058, 1029, 852 cm^{-1}. λ_{max} (MeOH): 207 nm (ε 47,400 $cm^{-1}M^{-1}$), 255 (20,600), 305 (3,200). ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (3H, s, OMe), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 3.39 (2H, s, NH_2), 6.29 (1H, d, *J* 1.9 Hz, aryl H4), 6.89 (1H, d, *J* 1.9 Hz, aryl H6), 6.91 (2H, d, *J* 8.7 Hz, aryl H), 7.83 (2H, d, *J* 8.7 Hz, aryl H), 8.39 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.5, 55.6 (OMe), 96.3, 99.2, 113.8, 129.0 (aryl CH), 121.2, 126.6, 128.0, 150.8, 153.9, 162.4 (aryl C), 165.0 (C=O). Mass spectrum (+EI): *m/z* (%) 303 (M+1, 30), 286 (17), 285 (100). HRMS (+ESI): $C_{16}H_{18}N_2O_4$ $[M+Na]^+$ requires 325.1158, found 325.1150. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.4; H, 6.2; N, 9.2.

***N*-(2-Amino-3,5-dimethoxyphenyl)cinnamide (4g).** To a solution of 2-nitrocinnamide **3g** (1.0 g, 3.08 mmol) in dry EtOH (25 mL), Pd/C (0.05 g, 10%) was added followed by hydrazine monohydrate (3 mL) dropwise over 15 min with stirring under argon at room temperature. The mixture was further stirred under argon at room temperature for 4 h, and filtered through Celite. The filtrate was concentrated under reduced pressure to give a yellow residue, which was dissolved in CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The resulting solvent was evaporated and the residue dried to yield the 2-aminocinnamide **4g** as a yellow solid (0.52 g, 57%), mp 168-170 ˚C. ν_{max} (KBr): 3375, 3000, 2938, 1661, 1610, 1530, 1498, 1450, 1336, 1220, 1202, 1167, 1151, 1053, 982, 835, 766 cm^{-1}. λ_{max} (MeOH): 208 nm (ε 40,500 $cm^{-1}M^{-1}$), 282 (27,800). ^1H NMR (300 MHz, $CDCl_3$): δ 3.32 (2H, s, NH_2), 3.74 (3H, s, OMe), 3.81 (3H, s,

OMe), 6.30 (1H, s, aryl H4), 6.56 (1H, d, *J* 16.2 Hz, =CH), 6.92 (1H, s, aryl H6), 7.34-7.36 (3H, m, aryl H), 7.48-7.50 (2H, m, aryl H), 7.73 (1H, d, *J* 16.2 Hz, CH=), 8.10 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6, 55.7 (OMe), 96.5, 99.2 (aryl CH), 120.5, 142.1 (CH=CH), 127.9, 128.7, 129.8 (aryl CH), 125.8, 127.8, 134.6, 150.7, 154.0 (aryl C), 164.0 (C=O). Mass spectrum (+EI): *m/z* (%) 300 (M+2, 20), 299 (M+1, 100). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.4; H, 6.1; N, 9.4. Found: C, 68.3; H, 6.3; N, 9.3.

3,5-Dimethoxy-2-nitroaniline (6). *Method A:* The 2-nitroformanilide **3a** (1 g, 4.4 mmol) was dissolved in Claisen's base (18 mL) and the mixture was refluxed for 15 min during which time a red solution formed. Water (18 mL) was then added and the mixture was refluxed further for 15 min. After cooling in an ice bath an orange solid was formed which was then filtered and recrystallized from EtOH/H_2O (1:1) to give the 2-nitroaniline **6** as orange plates (0.72 g, 82%).

Method B: To an ice/salt cooled solution (-10 ˚C) of formanilide **2a** (3 g, 16.56 mmol) in Ac_2O (80 mL) previously cooled HNO_3 (1.4 mL) in Ac_2O (20 mL) was added dropwise with continuous stirring over half an hour at such a rate that the temperature stayed between 0 to -5 ˚C. The mixture was stirred for another half an hour. Ice water was added and after stirring the mixture for another 48 h, it was extracted with CH_2Cl_2, and the extract thoroughly washed with water several times and Na_2CO_3 solution and then with brine. The organic solvent was evaporated and the residue recrystallized from EtOH/H_2O (1:1) to afford the 2-nitroaniline **6** as orange crystals (2.21 g, 11.16 mmol, 67%), mp 106-107 ˚C. ν_{max} (KBr): 3485, 3374, 1621, 1581, 1503, 1443, 1340, 1266, 1241, 1207, 1171, 1143, 1122, 1038, 994, 934, 806, 631 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (3H, s, OMe), 3.84 (3H, s, OMe), 5.53 (2H, br s, NH_2), 5.78 (1H, d, *J* 2.6 Hz, aryl H4), 5.84 (1H, d, *J* 2.6 Hz, aryl H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 56.3 (OMe), 90.1, 91.9 (aryl CH), 121.7, 146.6, 157.3, 163.7 (aryl C). Mass spectrum (+EI): *m/z* (%) 200 (M+2, 13), 199 (M+1, 100), 183 (55), 153 (26). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.8; H, 5.1; N, 14.0.

1,2-Diamino-3,5-dimethoxybenzene (7). 3,5-Dimethoxy-2-nitroaniline **6** (0.50 g, 2.5 mmol) was dissolved in dry EtOH (11 mL) and 30% Pd/C (50 mg) was added. Hydrazine monohydrate (0.61 mL) was then added dropwise with stirring under nitrogen. The mixture was then refluxed for 2.5 h under nitrogen, and the reaction mixture was allowed to cool to room temperature, filtered and reduced under vacuum to yield an off white solid that was recrystallized from EtOH to yield the 1,2-diaminobenzene **7** as colorless needles (0.31 g, 73%), mp 60-61 ˚C. The compound decomposed in air and was stored at 4 ˚C under nitrogen. ν_{max} (KBr): 3355, 3175, 1607, 1505, 1197, 1170, 1146, 1069, 994, 934, 812, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (3H, s, OMe), 3.78 (3H, s, OMe), 4.57 (4H, s, NH_2), 5.96 (1H, d, *J* 2.6 Hz, aryl H4), 6.00 (1H, d, *J* 2.6 Hz, aryl H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.7 (OMe), 92.5, 94.2 (aryl CH), 136.9, 140.1, 148.1, 152.5 (aryl C). Mass spectrum (+EI): *m/z* (%) 169 (M+1, 10), 168 (M,

100), 153 (50), 125 (78), 110 (48). Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.2; N, 16.6. Found: C, 57.3; H, 7.1; N, 16.9.

Synthesis of 4,6-dimethoxybenzimidazoles

4,6-Dimethoxybenzimidazole (5a) and 5,7-dimethoxybenzimidazole (8). To a refluxing solution of 2-nitroaniline **6** (2.56 g, 12.9 mmol) in absolute EtOH (50 mL), 10% Pd/C (0.25 g) was added followed by the addition of hydrazine monohydrate (3.80 mL) over a period of 15 min. The mixture was refluxed under a nitrogen atmosphere for 1 h, then allowed to cool to room temperature and filtered. The solvent was evaporated *in vacuo* and the remaining residue dissolved in CH_2Cl_2, the organic layer was washed with brine, dried over anhydrous $MgSO_4$ and solvent removed under reduced pressure to afford 1,2-diamine **7** as an oil. The oil was dissolved in HCO_2H (1.0 mL) and heated at 105 ˚C for 2 h. After cooling, the mixture was made basic with 2M NaOH and the resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O (1:1) to afford a tautomeric mixture of benzimidazole **5a** as off white crystals (2.10 g, 91%), mp 204-206 ˚C. R_f (5% MeOH/CH_2Cl_2) 0.21. ν_{max} (KBr): 1610, 1530, 1335, 1280, 1220, 1200, 1140, 1040, 1000, 960, 840, 810, 780 cm^{-1}. λ_{max} (MeOH): 280 (ε 3,650 $cm^{-1}M^{-1}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.7, 55.8 (OMe), 87.2, 94.3, 139.6 (aryl CH), 128.1, 135.3, 151.4, 157.0 (aryl C). Mass spectrum (+EI): *m/z* (%) 179 (M+1, 11), 178 (M, 100), 177 (28), 163 (43), 149 (28), 135 (70), 120 (40), 77 (21). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.7; H, 5.7; N, 15.7. Found: 60.9; H, 5.8; N, 15.5.

4,6-Dimethoxybenzimidazole (5a)

^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (3H, s, OMe), 3.96 (3H, s, OMe), 6.39 (1H, d, *J* 1.9 Hz, aryl H5), 6.71 (1H, d, *J* 1.9 Hz, aryl H7), 7.89 (1H, s, aryl H2), NH not observed.

5,7-Dimethoxybenzimidazole (8)

^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s, OMe), 4.03 (3H, s, OMe), 6.53 (1H, d, *J* 1.9 Hz, aryl H6), 6.99 (1H, d, *J* 1.9 Hz, aryl H4), 8.11 (1H, s, aryl H2), NH not observed.

4,6-Dimethoxy-2-methylbenzimidazole (5b). A mixture of 3,5-dimethoxy-2-nitroacetanilide **3b** (2.0 g, 8.33 mmol) and 10% Pd/C (0.20 g) in absolute EtOH (100 mL) was heated at reflux during the dropwise addition of hydrazine monohydrate (4.0 mL) over a period of 10 min. Heating at reflux was continued for 1 h before the mixture was allowed to cool to room temperature and then filtered. The solvent was evaporated *in vacuo* and the remaining residue dissolved in CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$ and the solvent evaporated *in vacuo* to give 2-aminoacetanilide **4b** as an oil. The oil was refluxed in glacial HOAc (2 mL) for 100 min, allowed to cool, and basified to high pH with 2M NaOH. The resulting precipitate was filtered, washed with water, and recrystallized from EtOH/H_2O (1:1) to give the 2-methylbenzimidazole **5b** (1.15 g, 72%) as a white powder, mp 200-202 ˚C. R_f (5% MeOH/CH_2Cl_2) 0.12. ν_{max} (KBr): 1610, 1540, 1500, 1340, 1250, 1220, 1200, 1150, 1130, 1050, 1020,

980, 940, 850, 820, 780 cm^{-1}. λ_{max} (MeOH): 282 nm (ε 4,400 $cm^{-1}M^{-1}$), 248 (6,900), 213 (19,100). ^1H NMR (300 MHz, $CDCl_3$): δ 2.58 (3H, d, *J* 2.0 Hz, Me), 3.78 (3H, s, OMe), 3.87 (3H, s, OMe), 6.33 (1H, d, *J* 2.1 Hz, aryl H), 6.61 (1H, s, aryl H), 7.50-6.80 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6 (Me), 55.4, 55.7 (OMe), 88.9, 93.8 (aryl CH), 124.5, 138.8, 148.9, 149.4, 156.9 (aryl C). Mass spectrum (+EI): *m/z* (%) 193 (M+1, 12), 192 (M, 100), 191 (30), 177 (48), 163 (20), 149 (72), 134 (39). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6. Found: C, 62.7; H, 6.3; N, 14.6.

4,6-Dimethoxy-2-phenylbenzimidazole (5c). A mixture of *N*-(3',5'-dimethoxy-2'-nitrophenyl)benzamide **3c** (3.50 g, 11.6 mmol) and 10% Pd/C (0.25 g) in absolute EtOH (100 mL) was heated at reflux during the dropwise addition of hydrazine monohydrate (5.6 mL) over 15 min. Reflux was continued for a further 2 h before the hot mixture was filtered and the solvent evaporated *in vacuo* to give a white solid. The solid was dissolved in CH_2Cl_2, the solution washed with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give *N*-(2'-amino-3',5'-dimethoxyphenyl)benzamide **4c** as an off-white powder; R_f (CH_2Cl_2) 0.20. The product was dissolved in EtOH and a few drops of 5 M HCl were added to acidify the mixture. The solution was then refluxed for a further 2 h, cooled to room temperature and the mixture was made highly basic using 2M NaOH. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O to give the 2-phenylbenzimidazole **5c** as white clusters (2.16 g, 73%), R_f (CH_2Cl_2) 0.25, mp 190-191 ˚C. ν_{max} (KBr): 3196, 1628, 1603, 1508, 1467, 1455, 1361, 1223, 1202, 1154, 1047, 964, 814, 690 cm^{-1}. λ_{max} (THF): 241 nm (ε 12,800 $cm^{-1}M^{-1}$), 255 (14,800), 309 (18,300). ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (3H, s, OMe), 3.78 (3H, s, OMe), 6.32 (1H, d, *J* 2.0 Hz, aryl H), 6.57 (1H, d, *J* 2.0 Hz, aryl H), 7.31 (3H, m, phenyl), 7.62 (1H, bs, NH), 8.09 (2H, m, phenyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 55.8 (OMe), 88.7, 94.7 (aryl CH), 126.6, 128.9, 129.7, (phenyl CH), 125.8, 129.8, 138.8, 149.8, 150.4, 157.7 (aryl C). Mass spectrum (+EI): *m/z* (%) 255 (M+1, 12), 254 (M, 100), 211 (31), 196 (29), 104 (29), 77 (29). HRMS (+ESI): $C_{15}H_{14}N_2O_2$ [M+H]+ requires 255.1128, found 255.1127. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.9; H, 5.6; N, 11.0. Found: C, 70.7; H, 5.7; N, 11.0.

2-Benzyl-4,6-dimethoxybenzimidazole (5d). To a refluxing solution of (2-nitrophenyl)phenylacetamide **3d** (1.0 g, 3.2 mmol) in absolute EtOH (40 mL), 10% Pd/C (0.10 g) was added followed by hydrazine monohydrate (2.0 mL) dropwise over a period of 15 min. Reflux was continued for further 2 h before the hot mixture was filtered and the solvent evaporated *in vacuo* to give a white solid. The solid was dissolved in CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give (2-aminophenyl)phenylacetamide **4d**. Without purification, this product was dissolved in EtOH and a few drops of 5M HCl were added to acidify the mixture. The solution was then refluxed for a further 2 h, cooled to room temperature and the mixture was made highly basic using 2M NaOH. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O to give the 2-benzyl-4,6-dimethoxybenzimidazole **5d** as white crystals (0.53 g, 62%), mp 190-192 ˚C. ν_{max} (KBr):

1630, 1610, 1540, 1310, 1250, 1220, 1200, 1150, 1020, 820, 790 cm^{-1}. λ_{max} (MeOH): 283 nm (ε 6,700 $cm^{-1}M^{-1}$), 252 (9,000), 212 (20,800). ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (3H, s, OMe), 3.78 (3H, s, OMe), 3.73 (2H, s, CH_2), 6.25 (1H, d, *J* 2.6 Hz, aryl H5), 6.73 (1H, d, *J* 2.6 Hz, aryl H7), 7.33 (5H, m, aryl H), NH not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.16 (CH_2), 55.73 (OMe), 87.03, 93.08, 126.69, 128.95 (aryl CH), 136.26, 138.31, 145.28, 146.08, 150.93, 156.68 (aryl C). Mass spectrum (+EI): *m/z* (%) 270 (M+2, 2), 269 (M+1, 15), 268 (M, 100), 267 (79), 91 (87), 77 (24), 69 (50), 55 (30), 43 (37). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.5; H, 6.2; N, 10.2.

4,6-Dimethoxy-2-(4'-methoxyphenyl)benzimidazole (5e). To a solution of 2-aminobenzamide **4e** (1.24 g, 4.10 mmol) in absolute EtOH (50 mL) was added a few drops of 5M HCl to make the mixture slightly acidic. The solution was then refluxed under argon for 8 h, cooled to room temperature and then made basic using 2M NaOH solution. The resulting precipitate was filtered, washed with water and recrystallized from EtOH/H_2O (1:1) to yield the (4'-methoxyphenyl)benzimidazole **5e** as an off white solid (0.92 g, 80%), mp 202-204 ˚C. ν_{max} (KBr): 3380, 1643, 1612, 1579, 1504, 1469, 1361, 1302, 1268, 1224, 1202, 1190, 1151, 1024, 837, 825 cm^{-1}. λ_{max} (MeOH): 208 nm (ε 30,200 $cm^{-1}M^{-1}$), 256 (15,700), 307 (18,200). ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (3H, s, OMe), 3.78 (3H, s, OMe), 3.85 (3H, s, OMe), 6.32 (1H, d, *J* 1.9 Hz, aryl H5), 6.58 (1H, d, *J* 1.9 Hz, aryl H7), 6.86 (2H, d, *J* 8.7 Hz, aryl H), 7.98 (2H, d, *J* 8.7 Hz, aryl H), 10.28 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 55.4, 55.6 (OMe), 89.0, 94.3, 114.1, 127.9 (aryl CH), 122.5, 125.2, 139.3, 149.3, 150.3, 157.3, 160.7 (aryl C). Mass spectrum (+EI): *m/z* (%) 286 (M+2, 21), 285 (M+1, 100). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.5; H, 5.7; N, 9.7. Found: C, 67.6; H, 5.7; N, 9.9.

2-*tert*-Butyl-4,6-dimethoxybenzimidazole (5f*)* and 2-*tert*-butyl-5,7-dimethoxybenzimidazole. A mixture of 3,5-dimethoxy-α,α,α-trimethyl-2-nitroacetanilide **3f** (9.54 g, 33.79 mmol) and 10% Pd/C (0.70 g) in absolute EtOH (150 mL) was heated at reflux during the dropwise addition of hydrazine monohydrate (10 mL) over 15 min. Heating at reflux was continued for 40 min before the hot mixture was filtered and the solvent evaporated *in vacuo* to give a yellow solid. The solid was dissolved in CH_2Cl_2, washed twice with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give 2-aminotrimethylacetanilide **4f** as a yellow powder; R_f (1% MeOH/CH_2Cl_2) 0.07. Without purification, this product was refluxed in glacial HOAc (30 mL) for 2 h, the solution allowed to cool, and then diluted with water. The mixture was basified to high pH with 5M NaOH and stirred overnight at room temperature. The resulting precipitate was filtered, washed with water, dried, and recrystallised from CH_2Cl_2/light petroleum to give a 1.6:1.0 tautomeric mixture of the *tert*-butyl-4,6-dimethoxybenzimidazole **5f** and 2-*tert*-butyl-5,7-dimethoxybenzimidazole an off-white powder (6.88 g, 87%), mp 236-240 ˚C. R_f (7.5% MeOH/ CH_2Cl_2) 0.43. ν_{max} (KBr): 3164, 3101, 1627, 1609, 1537, 1498, 1455, 1403, 1361, 1286, 1252, 1219, 1202, 1146, 1048, 998, 937, 814 cm^{-1}. λ_{max}

(THF): 234 nm (ε 6,220 $cm^{-1}M^{-1}$), 249 (7,860), 274 (3,680), 292 (1,980). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0 (C(Me)$_3$), 33.8 (C(Me)$_3$), 55.9, 56.2 (OMe), 86.6, 93.6, 93.9, 95.1, (aryl CH), 118.6, 128.3, 135.4, 144.9, 146.1, 151.7, 157.1, 157.6, 160.1, 162.0 (aryl C). Mass spectrum (+EI): *m/z* (%) 235 (7%), 234 (M, 100), 219 (89), 204 (39). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.6; H, 7.7; N, 12.0. Found: C, 66.7; H, 7.9; N, 11.8.

2-*tert*-Butyl-4,6-dimethoxybenzimidazole (5f)

^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s, C(Me)$_3$), 3.82 (3H, s, OMe), 3.92 (3H, s, OMe), 6.36 (1H, d, *J* 2.1 Hz, H5), 6.86 (1H, d, *J* 2.1 Hz, H7), 8.90 (1H, bs, NH).

2-*tert*-Butyl-5,7-dimethoxybenzimidazole

^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s, C(Me)$_3$), 3.82 (3H, s, OMe), 3.96 (3H, s, OMe), 6.33 (1H, d, *J* 2.1 Hz, H6), 6.48 (1H, d, *J* 2.1 Hz, H4), 8.90 (1H, bs, NH).

4,6-Dimethoxy-2-styrylbenzimidazole (5g). To a solution of 2-nitrocinnamide **3g** (1.0 g, 3.08 mmol) in dry EtOH (25 mL), 10% Pd/C (50 mg) was added followed by hydrazine monohydrate (3.0 mL) dropwise over 15 min with stirring under argon at room temperature. The mixture was further stirred under argon at room temperature for 4 h, and filtered through Celite. The filtrate was concentrated under reduced pressure to give a yellow residue of 2-aminocinnamide **4g**, which was dissolved in CH_2Cl_2, washed with brine and dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure and the residue dissolved in glacial HOAc (2 mL). The solution was heated at 65 ˚C for 3 h under argon before being allowed to come to room temperature and made basic using 2M NaOH solution. The resulting precipitate was collected, washed with water and recrystallized from *i*PrOH to give the 2-styrylbenzimidazole **5g** as a tan powder (0.35 g, 1.25 mmol, 41%), mp 218-219 ˚C. ν_{max} (KBr): 3370, 2992, 1624, 1605, 1451, 1424, 1311, 1223, 1203, 1150, 1042, 961, 815, 749 cm^{-1}. λ_{max} (MeOH): 208 nm (ε 28,600 $cm^{-1}M^{-1}$), 266 (13,400), 337 (23,300). ^1H NMR (300 MHz, $CDCl_3$): δ 3.79 (3H, s, OMe), 3.89 (3H, s, OMe), 6.33 (1H, d, *J* 1.9 Hz, aryl H5), 6.65 (1H, d, *J* 1.9 Hz, aryl H7), 7.08 (1H, d, *J* 16.2 Hz, =CH), 7.26-7.32 (3H, m, aryl H), 7.42-7.45 (2H, m, aryl H), 7.60 (1H, d, *J* 16.2 Hz, CH=), 8.96 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 55.7 (OMe), 88.5, 94.9, 126.9, 128.7, 128.8 (aryl CH), 115.6, 135.0 (CH=CH), 127.3, 135.6, 138.3, 149.0, 149.2, 158.0 (aryl C). Mass spectrum (+EI): *m/z* (%) 283 (M+2, 9), 282 (M+1, 19), 281 (M, 100). HRMS (+ESI): $C_{17}H_{16}N_2O_2$ $[M+H]^+$ requires 281.1285, found 281.1288. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.8; H, 5.8; N, 10.0. Found: C, 72.8; H, 5.9; N, 10.0.

Attempted synthesis of 4,6-dimethoxybenzimidazoles from 2,4-dimethoxyaniline

4-Chloro-*N*-(2',4'-dimethoxyphenyl)benzamide (10h). A solution of 4-chlorobenzoyl chloride (5.1 mL, 40 mmol) in anhydrous Et_2O (20 mL) was added dropwise over 30 min to a stirred solution of 2,4-dimethoxyaniline **9** (5.49 g, 35.8 mmol) in anhydrous Et_2O (50 mL), under nitrogen, at such a rate that slow boiling occurred. The mixture was then stirred for 1 h and allowed to cool to room

temperature before it was washed sequentially with water, dilute HCl, several times with a saturated Na_2CO_3 solution, several times with brine, then dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give an off-white solid. Purification via suction column chromatography (CH_2Cl_2), then recrystallization from *i*PrOH/light petroleum, gave the 4-chlorobenzamide **10h** as fine colorless needles (10.10 g, 97%), mp 123-124 ˚C. R_f (5% MeOH/CH_2Cl_2) 0.81. ν_{max} (KBr): 3436, 2989, 1661, 1613, 1542, 1501, 1483, 1461, 1415, 1285, 1258, 1209, 1155, 1039, 918, 838, 744 cm^{-1}. λ_{max} (MeOH): 211 nm (ε 25,500 $cm^{-1}M^{-1}$), 224 (14,000) , 286 (5,900). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (3H, s, OMe), 3.89 (3H, s, OMe), 6.51-6.54 (2H, m, aryl H3, H5), 7.45 (2H, d, *J* 8.3 Hz, aryl H), 7.81 (2H, d, *J* 8.3 Hz, aryl H), 8.26 (1H, br s, NH), 8.36 (1H, d, *J* 9.4 Hz, aryl H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.7 (OMe), 98.5, 103.8, 120.8, 128.3, 128.8 (aryl CH), 121.0, 133.6, 137.6, 149.5, 156.6 (aryl C), 163.8 (C=O). Mass spectrum (+EI): *m/z* (%) 295 (M+2, ^{37}Cl, 5), 294 (M+1, ^{37}Cl, 35), 293 (M+2, ^{35}Cl, 18), 292 (M+1, ^{35}Cl, 100). Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.8; H, 4.8; N, 4.8. Found: C, 62.0; H, 4.9; N, 4.8.

***N*-(5'-Acetyl-2',4'-dimethoxyphenyl)-4-chlorobenzamide (11).** A solution of *N*-(2',4'-dimethoxyphenyl)-4-chlorobenzamide **10h** (1.39 g, 4.76 mmol) and MeCOCl (0.6 mL, 8.4 mmol) in anhydrous CH_2Cl_2 (30 mL) was stirred at room temperature under nitrogen. $SbCl_5$ (1.2 mL, 9.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise over 7 min and stirring was continued at room temperature for 2 d. Water was added and stirring continued for 2 h before the mixture was acidified to low pH with 5M HCl. The organic layer was then washed sequentially with water, brine, dried over anhydrous $MgSO_4$, and then the solvent was evaporated *in vacuo* and the remaining solid purified via gravity column chromatography (2% MeOH/CH_2Cl_2) to give the 5'-acetylchlorobenzamide **11** as fine pale pink needles (1.19 g, 75%), mp 175-177 ˚C. R_f (5% MeOH/CH_2Cl_2) 0.63. ν_{max} (KBr): 3445, 1667, 1608, 1530, 1498, 1471, 1416, 1354, 1278, 1228, 1206, 1161, 1104, 1026, 901, 810, 751 cm^{-1}. λ_{max} (THF): 238 nm (ε 23,800 $cm^{-1}M^{-1}$), 261 (17,900), 302 (11,900). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (3H, s, COMe), 3.90 (3H, s, OMe), 3.96 (3H, s, OMe), 6.47 (1H, s, aryl H3), 7.42 (2H, d, *J* 8.3 Hz, phenyl), 7.78 (2H, d, *J* 8.3 Hz, phenyl), 8.10 (1H, bs, NH), 8.74 (1H, s, H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.9 (Me), 56.4, 56.6 (OMe), 95.4, 123.6 (aryl CH C3,6), 128.9, 129.4 (phenyl CH), 120.9, 121.0, 133.8, 138.3 (aryl C), 153.3, 157.6 (aryl C2, C4), 164.3 (NHC=O), 197.7 (C=O). Mass spectrum (+EI): *m/z* (%) 336 (M+1, M, ^{37}Cl, 1), 335 (M, ^{37}Cl, 9), 334 (M, ^{35}Cl, 4), 333 (M, ^{35}Cl, 27), 141 (38), 139 (100), 113 (20), 111 (49). Anal. Calcd for $C_{17}H_{16}ClNO_4$: C, 61.2; H, 4.8; N, 4.2. Found: C, 61.0; H, 4.9; N, 4.3.

5-Bromo-2,4-dimethoxyacetanilide (12). *N*-Bromosuccinimide (3.01 g, 16.9 mmol) was added to a stirred and refluxing solution of 2,4-dimethoxyacetanilide **10b**[32] (3 g, 15.4 mmol) in CCl_4 (50 mL). Heating was continued at reflux for 7 h before the resulting mixture was allowed to cool, filtered, and the solvent evaporated *in vacuo* to give a dark syrup. Purification via gravity column chromatography (5% MeOH/CH_2Cl_2), followed by recrystallization from CH_2Cl_2/light petroleum, gave the 5-bromoacetanilide

12 as colorless needles (3.37 g, 80%), mp 154-156 ˚C. R_f (5% MeOH/CH_2Cl_2) 0.51. ν_{max} (KBr): 3229, 1655, 1597, 1537, 1508, 1470, 1437, 1373, 1324, 1285, 1203, 1173, 1056, 1025, 891, 851, 820, 701, 657 cm^{-1}. λ_{max} (THF): 235 nm (ε 10,100 $cm^{-1}M^{-1}$), 252 (14,400), 299 (5,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (3H, s, MeCO), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 6.39 (1H, s, H3), 7.57 (1H, bs, NH), 8.39 (1H, s, H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4 (Me), 56.4, 55.8 (OMe), 96.0, 124.1 (aryl CH), 101.2, 121.5, 148.2, 152.0 (aryl C), 167.9 (C=O). Mass spectrum (+EI): *m/z* (%) 275 (M, ^{81}Br, 32), 273 (M, ^{79}Br, 30), 233 (42), 231 (42), 218 (66), 216 (65), 69 (52), 43 (100). Anal. Calcd for $C_{10}H_{12}BrNO_3$: C, 43.8; H, 4.4; N, 5.1. Found: C, 44.1; H, 4.2; N, 5.1.

4-Chloro-*N*-(2',4'-dimethoxy-5'-nitrophenyl)benzamide (13). A suspension of *N*-(5'-acetyl-2',4'-dimethoxyphenyl)-4-chlorobenzamide **11** (0.50 g, 1.50 mmol) in Ac_2O (50 mL) was stirred with cooling in a salt-ice slurry. HNO_3 (0.4 mL) was added dropwise over 10 min and stirring continued for 15 min further with cooling. The stirred mixture was then diluted with water and allowed to warm to room temperature before it was extracted with CH_2Cl_2. The organic extract was washed several times with an aqueous saturated Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give the 5'-nitrophenylbenzamide **13** as a bright yellow powder (0.30 g, 60%), mp 235-238 ˚C. R_f (5% MeOH/CH_2Cl_2) 0.74. ν_{max} (KBr): 3436, 1668, 1600, 1536, 1480, 1433, 1343, 1285, 1213, 1094, 1021, 911, 845, 747 cm^{-1}. λ_{max} (THF): 240 nm (ε 20,000 $cm^{-1}M^{-1}$), 272 (14,500), 292 (12,900), 350 (4,230). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (3H, s, OMe), 4.04 (3H, s, OMe), 6.57 (1H, s, H3'), 7.47 (2H, d, *J* 8.3 Hz, phenyl), 7.81 (2H, d, *J* 8.3 Hz, phenyl), 8.22 (1H, bs, NH), 9.14 (1H, s, H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.5, 56.9 (OMe), 96.0, 118.0 (aryl CH, C3, C6), 128.3, 129.0 (phenyl CH), 120.4, 132.1, 132.8, 138.3, 151.3, 153.0 (aryl C), 163.9 (C=O). Mass spectrum (+EI): *m/z* (%) 339 (M+1, ^{37}Cl, 1), 338 (M, ^{37}Cl, 9), 337 (M+1, ^{35}Cl, 3), 336 (M, ^{35}Cl, 26), 141 (39), 139 (100), 113 (18), 111 (51). Anal. Calcd for $C_{15}H_{13}ClN_2O_5$: C, 53.5; H, 3.9; N, 8.3. Found: C, 53.7; H, 4.0; N, 8.3.

2,4-Dimethoxy-5-nitroacetanilide (14). A solution of 5-bromo-2,4-dimethoxyacetanilide **12** (0.50 g, 1.82 mmol) in Ac_2O (24 mL) was stirred with cooling in an iced water bath. HNO_3 (0.6 mL) was added dropwise over 15 min and stirring continued for 15 min before the mixture was poured into chilled water and allowed to warm to room temperature. The mixture was extracted with EtOAc and the organic extract was washed with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give an orange solid that was purified via pressure column chromatography (2% MeOH/CH_2Cl_2) to give the 5-nitroacetanilide **17** as a yellow powder (0.23 g, 52%), mp 174-175 ˚C. R_f (2% MeOH/CH_2Cl_2) 0.42. ν_{max} (KBr): 3435, 3371, 1694, 1678, 1627, 1596, 1537, 1495s, 1397, 1337, 1273, 1245, 1218, 1080, 1020, 909, 825, 761 cm^{-1}. λ_{max} (THF): 232 nm (ε 16,300 $cm^{-1}M^{-1}$), 250 (20,100), 354 (4,230). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (3H, s, MeCO), 3.94 (3H, s, OMe), 3.98 (3H, s, OMe), 6.51 (1H, s, H3), 7.53 (1H, bs, NH), 8.96 (1H, s, H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7 (Me), 56.5, 57.0 (OMe), 96.0, 117.9 (aryl

CH, C3, C6), 101.4, 120.6, 151.2, 152.9 (aryl C), 168.1 (C=O). Mass spectrum (+EI): *m/z* (%) 241 (M+1, 10), 240 (M, 75), 199 (13), 198 (100), 183 (18), 181 (4), 125 (10), 109 (20). Anal. Calcd for $C_{10}H_{12}N_2O_5.0.2H_2O$: C, 49.3; H, 5.1; N, 11.5. Found: C, 49.3; H, 5.1; N, 11.6.

Synthesis of 4,5,6-trimethoxybenzimidazoles

4-Chloro-*N*-(3',4',5'-trimethoxyphenyl)benzamide (16). A solution of 4-chlorobenzoyl chloride (7.7 mL, mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise over 30 min to a stirred solution of 3,4,5-trimethoxyaniline **15** (10.0 g, 54.6 mmol) in anhydrous CH_2Cl_2 (120 mL) with cooling in an iced water bath, under nitrogen. After further stirring for 1 h, the solidified mixture was dissolved in $CH_2Cl_2$and washed sequentially with water, dilute HCl, saturated $NaHCO_3$ solution, brine, then dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give a solid. Purification via suction column chromatography (CH_2Cl_2), then recrystallization from *i*PrOH, gave the trimethoxybenzamide **16** as colorless rectangular prisms (8.581 g, 49%), mp 193-197 ˚C. R_f (2% MeOH/CH_2Cl_2) 0.48. ν_{max} (KBr): 3387, 1677, 1609, 1536, 1508, 1450, 1412, 1310, 1229, 1134, 1104, 996, 831, 753 cm^{-1}. λ_{max} (THF): 239 nm (ε 17,600 $cm^{-1}M^{-1}$), 260 (8,900), 294 (10,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (3H, s, OMe), 3.85 (6H, s, OMe), 6.94 (2H, s, H2, H6), 7.45 (2H, d, *J* 8.2 Hz, phenyl), 7.81 (2H, d, *J* 8.2 Hz, phenyl), 7.84 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.3, 60.9, (OMe), 98.1 (aryl CH), 128.3, 128.9 (phenyl CH), 133.1, 133.8, 135.0, 138.1, 153.3 (aryl C), 164.7 (C=O). Mass spectrum (+EI): *m/z* (%) 323 (M, ^{37}Cl, 5), 321 (M, ^{35}Cl, 13), 141 (40), 139 (100), 113 (16), 111 (48). Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.7; H, 5.0; N, 4.4. Found: C, 59.9; H, 5.0; N, 4.5.

4-Chloro-*N*-(3',4',5'-trimethoxy-2'-nitrophenyl)benzamide (17). A suspension of *N*-(3',4',5'-trimethoxyphenyl)-4-chlorobenzamide **16** (1 g, 3.11 mmol) in Ac_2O was stirred with cooling in a salt-ice slurry. HNO_3 (0.6 mL) was added dropwise over 3 min and stirring continued for 20 min further with cooling. The mixture was then treated with an aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give a solid that was purified via gravity column chromatography (1% MeOH/CH_2Cl_2) to give the 2'-nitrophenyl-4-chlorobenzamide **17** as a bright yellow powder (0.150 g, 13%), mp 142-143 ˚C. R_f (2% MeOH/CH_2Cl_2) 0.74. ν_{max} (KBr): 3391, 1690, 1591, 1550, 1507, 1407, 1329, 1123, 1029, 830, 747 cm^{-1}. λ_{max} (THF): 239 nm (ε 17,000 $cm^{-1}M^{-1}$), 266 (16,000), 292 (7,500), 354 (2,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (3H, s, OMe), 4.00 (3H, s, OMe), 4.05 (3H, s, OMe), 7.50 (2H, d, *J* 9.2 Hz, 4-ClC_6H_4), 7.84 (2H, d, *J* 9.2 Hz, 4-ClC_6H_4), 8.10 (1H, s, H6), 9.95 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.9, 61.6, 62.9 (OMe) 100.7 (C6'), 129.0, 129.8 (phenyl CH), 129.9, 130.1, 132.6, 139.5, 139.6, 149.4, 157.8 (aryl C), 165.0 (C=O). Mass spectrum (+EI): *m/z* (%) 368 (M, ^{37}Cl, 3%), 366 (M, ^{35}Cl, 7), 320 (27), 141 (42). Anal. Calcd for $C_{16}H_{15}ClN_2O_6$: C, 52.4; H, 4.1; N, 7.6. Found: C, 52.6; H, 4.3; N, 7.4.

4,5,6-Trimethoxy-2-phenylbenzimidazole (18).

A mixture of *N*-(3',4',5'-trimethoxy-2'-nitrophenyl)-*p*-chlorobenzamide **17** (100 mg, 0.273 mmol) and 10% Pd/C (10 mg) in absolute EtOH (11 mL) was heated at reflux during the dropwise addition of a solution of hydrazine monohydrate (0.2 mL) in absolute EtOH (4 mL), over 5 min. Heating at reflux was continued for 20 min before the hot mixture was filtered and the solvent evaporated *in vacuo* to give an off-white solid. The solid was dissolved in CH_2Cl_2, washed twice with brine, dried over anhydrous magnesium sulfate, and the solvent evaporated *in vacuo* to give an off-white powder; R_f (2% MeOH/ CH_2Cl_2) 0.23. The product was refluxed in glacial HOAc (2 mL) for 45 min, allowed to cool, and then diluted with water. The resulting mixture was basified to high pH with 5M NaOH solution and extracted with EtOAc. The organic extract was washed twice with brine, dried over anhydrous $MgSO_4$, and the solvent evaporated *in vacuo* to give the 4,5,6-trimethoxy-2-phenylbenzimidazole **18** as a yellow tinted glass (85 mg, 98%), mp 65-67 ˚C (softens), approx. 82 ˚C (melts). R_f (2% MeOH/ CH_2Cl_2) 0.14. ν_{max} (KBr): 3410, 3304, 1630, 1591, 1499, 1463, 1424, 1402, 1368, 1291, 1266, 1200, 1144, 1118, 1048, 1000, 775, 695 cm^{-1}. λ_{max} (THF): 239 nm (ε 12,200 $cm^{-1}M^{-1}$), 254 (8,320), 319 (21,400). ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 4.17, (3H, s, OMe), 6.74 (1H, s, H7), 7.37 (3H, m, phenyl), 8.03 (2H, m, phenyl), NH not observed. ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.7, 61.6, 61.9, (OMe), 92.9 (C7), 126.7, 130.1, 129.4 (phenyl CH), 130.3, 136.0, 138.2, 141.9, 150.7, 151.9 (aryl C). Mass spectrum (+EI): *m/z* (%) 285 (M+1, 16%), 284 (M, 95), 283 (M-1, 16), 269 (100), 226 (37), 211 (48), 173 (46), 172 (28), 155 (49), 104 (59), 91 (84). Anal. Calcd for $C_{16}H_{16}N_2O_3.0.33H_2O$: C, 66.2; H, 5.8; N, 9.7. Found: C, 66.2; H, 5.7; N, 9.5.

Synthesis of 4,6-dimethoxy-2,2'-bisbenzimidazoles

***N,N'*-Bis(3,5-dimethoxy-2-nitrophenyl)oxalamide (19a).** To a solution of 2-nitroaniline **6** (0.50 g, 2.5 mmol) in anhydrous CH_2Cl_2 (10 mL) and triethylamine (0.35 mL) a mixture of oxalyl chloride (0.11 mL, 0.5 eq) in anhydrous CH_2Cl_2 (5 mL) was added dropwise with continuous stirring. The mixture was allowed to stir for 1 h and the yellow precipitated solid was filtered and washed with water, then $CH_2Cl_2$to afford the dinitrophenyl oxalamide **19a** as yellow crystals (0.31 g, 56%), mp 298-300 ˚C. ν_{max} (KBr): 3300, 1710, 1610, 1550, 1330, 1290, 1240, 1210, 1170, 1120, 1080, 940, 820 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.87 (6H, s, OMe), 3.91 (6H, s, OMe), 6.73 (2H, d, *J* 2.6 Hz, aryl H5), 6.94 (2H, d, *J* 2.6 Hz, aryl H7), 11.01 (2H, br s, NH). Sample too insoluble for ^{13}C NMR. Mass spectrum (+EI): *m/z* (%) 450 (M, 1), 404 (84), 209 (60), 194 (98), 181 (46), 168 (75), 151 (100), 136 (36), 123 (80), 120 (43), 93 (31), 77 (36), 69 (44), 65 (25). Anal. Calcd for $C_{18}H_{18}N_4O_{10}$: C, 48.0; H, 4.0; N, 12.5. Found: C, 47.9; H, 4.3; N, 12.3.

***N,N'*-Bis(3,5-dimethoxy-2-nitrophenyl)malonamide (19b).** 3,5-Dimethoxy-2-nitroaniline **6** (4.0 g, 20.2 mmol) and K_2CO_3 (3.46 g, 25 mmol) were stirred in THF (50 mL) under nitrogen. Malonyl dichloride

(1.0 mL, 10.2 mmol) was added slowly to the mixture which was stirred for a further 14 h. Hot water (250 mL) and EtOAc (500 mL) were added to the reaction mixture. The organic layer was separated, dried and evaporated under reduced pressure to dryness. The solid residue was recrystallized from EtOAc to give the dinitrophenyl malonamide **19b** as yellow crystals (3.60 g, 76%), mp 215 ˚C. ν_{max} (KBr): 3402, 3176, 1703, 1614, 1596, 1494, 1242, 1206, 1115, 1005, 860, 715 cm^{-1}. λ_{max} (MeOH): 209 nm (ε 65,700 $cm^{-1}M^{-1}$), 240 (25,000), 346 (8,400). ^{1}H NMR (300 MHz, acetone-*d*$_6$): δ 3.71 (2H, s, CH_2), 3.88 (6H, s, OMe), 3.92 (6H, s, OMe), 6.59 (2H, d, *J* 2.6 Hz, aryl H4), 7.33 (2H, d, *J* 2.6 Hz, aryl H6), 9.69 (2H, br s, NH). ^{13}C NMR (75 MHz, acetone-*d*$_6$): δ 43.9 (CH_2), 55.4, 56.2 (OMe), 95.7, 100.8 (aryl CH), 128.2, 132.6, 153.8, 162.2 (aryl C), 165.9 (C=O). Mass spectrum (+EI): *m/z* (%) 464 (M, 20), 243 (22), 242 (80), 241 (31), 199 (95), 155 (100). Anal. Calcd for $C_{19}H_{20}N_4O_{10}$: C, 49.1; H, 4.3; N, 12.1. Found: C, 49.3; H, 4.6; N, 11.9.

***N,N'*-Bis(3,5-dimethoxy-2-nitrophenyl)dimethyl malonamide (19c).** 3,5-Dimethoxy-2-nitroaniline **6** (3 g, 15.15 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) were stirred in THF (80 mL) under nitrogen. Dimethylmalonyl chloride (1.0 mL, 7.61 mmol) in THF (10 mL) was added slowly to the mixture over 10 min and the mixture stirred for a further 48 h. The mixture was diluted with water (200 mL) and extracted with EtOAc (2x300 mL). The combined organic layers were dried and evaporated to dryness under reduced pressure. The solid residue was recrystallized from EtOAc to give the dinitrophenyl-dimethylmalonamide **19c** as yellow crystals 92.4 g, 64%), mp 189 ˚C. ν_{max} (KBr): 3591, 3080, 1695, 1599, 1301, 1151, 1100, 964, 847, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (6H, s, CMe), 3.85 (6H, s, OMe), 3.87 (6H, s, OMe), 6.28 (2H, d, *J* 2.6 Hz, aryl H5), 7.62 (2H, d, *J* 2.6 Hz, aryl H5), 10.04 (2H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4 (Me), 32.3 (CMe), 56.0, 56.6 (OMe), 96.4, 98.1 (aryl CH), 125.8, 134.5, 155.2, 163.4 (aryl C), 171.6 (C=O). Mass spectrum (+EI): *m/z* (%) 493 (M+1, 1), 446 (24), 221 (57), 220 (100), 205 (22). Anal. Calcd for $C_{21}H_{24}N_4O_{10}$: C, 51.2; H, 4.9; N, 11.4. Found: C, 51.1; H, 4.8; N, 11.3.

***N,N'*-Bis(3,5-dimethoxy-2-nitrophenyl)isophthalamide (19d).** To a solution of 2-nitroaniline **6** (5.0 g, 25.25 mmol) in dry THF (100 mL) containing anhydrous K_2CO_3 (5 g) isophthaloyl chloride (5.2 g, 25.25 mmol) was added portionwise to this solution. The mixture was stirred under argon for 3 d, followed by addition of water. The resulting precipitate was filtered, washed with water and recrystallized from EtOH to afford the dinitrophenyl isophthalamide **19d** as a yellow powder (3.11 g, 47%), mp 227-228 ˚C. ν_{max} (KBr): 3328, 3164, 1661, 1627, 1558, 1456, 1420, 1326, 1203, 1158, 1061, 973, 831, 745, 676 cm^{-1}. λ_{max} (MeOH): 208 nm (ε 87,200 $cm^{-1}M^{-1}$), 225 (53,000), 316 (26,800). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (6H, s, OMe), 3.93 (6H, s, OMe), 6.35 (2H, d, *J* 2.6 Hz, aryl H4), 7.64-7.69 (1H, m, aryl H), 7.94 (2H, d, *J* 2.6 Hz, aryl H6), 8.06-8.09 (2H, m, aryl H), 8.51 (1H, s, aryl H), 10.42 (2H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 56.6 (OMe), 96.1, 97.6, 126.6, 129.6, 130.6 (aryl CH), 125.2, 134.9, 135.7, 155.9, 163.8

(aryl C), 164.4 (C=O). Mass spectrum (+EI): *m/z* (%) 528 (M+2, 30), 527 (M+1, 100), 497 (22), 482 (20), 481 (54). Anal. Calcd for $C_{24}H_{22}N_4O_{10}$: C, 54.8; H, 4.2; N, 10.6. Found: C, 54.8; H, 4.3 ; N, 10.5.

***N,N*-Bis(3,5-dimethoxy-2-nitrophenyl)terephthalamide (19e).** To a solution of 2-nitroaniline **6** (5.0 g, 25.25 mmol) in dry THF (120 mL) containing anhydrous K_2CO_3 (5 g) terephthaloyl chloride (3.07 g, 15.15 mmol) was added portionwise. The mixture was stirred under argon for 5 d, followed by addition of water. The resulting precipitate was filtered, washed with water and recrystallized from EtOH to afford the dinitrophenyl terephthalamide **19e** as a yellow solid (3.39 g, 51%), mp 287 ˚C. ν_{max} (KBr): 3362, 2945, 1722, 1695,1605, 1556, 1493, 1454, 1419, 1280, 1206, 1119, 1069, 939, 838, 719 cm^{-1}. λ_{max} (MeOH): 205 nm (ε 64,600 $cm^{-1}M^{-1}$). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 3.31 (6H, s, OMe), 3.87 (6H, s, OMe), 6.72 (4H, s, aryl H), 7.89-8.01 (4H, m, aryl H4, H6), 10.54 (2H, br s, NH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 56.4, 57.3 (OMe), 97.6, 103.8, 128.3 (aryl CH), 130.8, 133.2, 136.8, 153.9, 161.9 (aryl C), 165.3 (C=O). Mass spectrum (-EI): *m/z* (%) 526 (M, 22), 525 (M-1, 100). Anal. Calcd for $C_{24}H_{22}N_4O_{10}$: C, 54.8; H, 4.2; N, 10.6. Found: C, 54.7; H, 4.3; N, 10.4.

***N,N*-Bis(2-amino-3,5-dimethoxyphenyl)malonamide (20b).** To a refluxing solution of dinitrophenyl-malonamide **19b** (2.50 g, 5.38 mmol) in absolute EtOH and THF (100 mL, 3:2), 10% Pd/C (0.50 g) was added under argon followed by hydrazine monohydrate (5.2 mL) dropwise over 15 min and reflux was continued for another 20 h. The solution was filtered and solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with brine, and dried over anhydrous $MgSO_4$. The organic solvent was removed under reduced pressure to yield the crude diaminomalonamide **20b** as a light yellow solid (1.80 g, 84%), mp 238-240 ˚C. ν_{max} (KBr): 3112, 3000, 2985, 2831, 1634, 1603, 1496, 1450, 1357, 1311, 1223, 1192, 1043, 1027, 993, 931 cm^{-1}. λ_{max} (MeOH): 210 nm (ε 63,900 $cm^{-1}M^{-1}$), 252 (15,900), 284 (12,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (6H, s, OMe), 3.76 (6H, s, OMe), 4.69 (2H, s, CH_2), 6.26 (2H, d, *J* 1.8 Hz, aryl H4), 6.49 (2H, d, *J* 1.8 Hz, aryl H6), 9.74 (2H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.92 (CH_2), 55.33, 55.64 (OMe), 87.89, 94.41 (aryl CH), 124.92, 136.66, 147.41, 149.60 (aryl C), 157.60 (C=O). Mass spectrum (+ESI): *m/z* (%) 405 (M+1, 100).

***N,N*-Bis(2-amino-3,5-dimethoxyphenyl)isophthalamide (20d).** To a refluxing solution of dinitrophenyl-isophthalamide **19d** (1.0 g, 1.90 mmol) in anhydrous DMF (20 mL), 30% Pd/C (0.10 g) was added under argon followed by hydrazine monohydrate (1.80 mL) dropwise over 15 min and reflux continued for another 3 h. The solution was filtered and the filtrate was concentrated under reduced pressure. Water was added to the mixture and the resulting precipitate was filtered, washed with water and dried to yield the diaminophthalamide **20d** as a light yellow solid (0.73 g, 82%), mp 206-207 ˚C. ν_{max} (KBr): 3381, 3195, 1634, 1606, 1536, 1452, 1418, 1363, 1222, 1201, 1151, 1042, 993, 812, 698 cm^{-1}. λ_{max} (MeOH): 207 nm (ε 45,100 $cm^{-1}M^{-1}$), 249 (21,900), 312 (23,200). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 3.78 (6H, s, OMe), 3.92 (6H, s, OMe), 6.37 (2H, s, aryl H4), 6.64 (2H, s, aryl H6), 7.60-7.65 (2H, m, aryl H), 8.13-8.92 (7H,

m, 3 aryl H, 4NH), 12.89 (2H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.4, 55.8 (OMe), 97.0, 102.4, 127.3, 128.5, 130.7 (aryl CH), 124.0, 134.7, 138.0, 148.6, 150.7 (aryl C), 164.6 (C=O). Mass spectrum (+EI): *m/z* (%) 467 (M+1, 8), 466 (M, 26), 167 (100), 140 (23), 76 (20). HRMS (+ESI): $C_{24}H_{26}N_4O_6$ $[M+Na]^+$ requires 489.1744, found 489.1751.

***N,N*-Bis(2-amino-3,5-dimethoxyphenyl)terephthalamide (20e).** To a refluxing solution of the dinitrophenyl terephthalamide **19e** (0.50 g, 0.95 mmol) in absolute EtOH/THF (50 mL, 1:1), 10% Pd/C (0.05 g) was added under argon followed by hydrazine monohydrate (0.90 mL) dropwise over 5 min and reflux was continued overnight. The solution was filtered hot and the filtrate was concentrated under reduced pressure to give a precipitate which was filtered, washed with water and dried to yield the diaminoterephthalamide **20e** as a light yellow solid (0.32 g, 72%), mp >360 ˚C. ν_{max} (KBr): 3409, 3271, 1635, 1595, 1531, 1492, 1460, 1421, 1375, 1318, 1282, 1202, 1154, 1058, 895, 822, 678 cm^{-1}. λ_{max} (MeOH): 211 nm (ε 3,900 cm^{-1}M^{-1}). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.66 (6H, s, OMe), 3.79 (6H, s, OMe), 4.23 (4H, br s, NH_2), 6.45 (2H, s, aryl H4), 6.55 (2H, s, aryl H6), 8.00-8.07 (4H, m, aryl H), 9.88 (2H, br s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.78, 56.2 (OMe), 97.5, 102.8, 128.1 (aryl CH), 124.3, 125.9, 137.3, 148.9, 151.1 (aryl C), 164.7 (C=O). Mass spectrum (+EI): *m/z* (%) 468 (M+2, 46), 467 (100). HRMS (+ESI): $C_{24}H_{26}N_4O_6$ $[M+Na]^+$ requires 489.1745, found 489.1750.

2-(4,6-Dimethoxybenzimidazol-2-yl)-4,6-dimethoxybenzimidazole (21a). To a refluxing solution of dinitrophenyl oxalamide **19a** (0.5 g, 1.1 mmol) in anhydrous DMF (17 mL), 10% Pd/C (0.10 g) was added under argon followed by hydrazine monohydrate (1.5 mL) dropwise over 15 min and reflux was continued for another 2 h. The mixture was then filtered and the DMF was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 and washed with water. The organic layer was dried and the solvent removed under reduced pressure to give the aminooxalamide **20a**. Without purification, the crude product was dissolved in absolute EtOH and a few drops of 5M HCl were added. The solution was heated at reflux for 4 h, the solvent was removed until a precipitate was observed. The precipitate was collected and washed with water, 2M NaOH solution, and water to afford the bisbenzimidazole **21a** as a pale yellow solid (90 mg, 23%), mp 300-302 ˚C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (6H, s, OMe), 3.89 (6H, s, OMe), 6.32 (2H, d, *J* 2.0 Hz, aryl H5), 6.54 (2H, d, *J* 2.0 Hz, aryl H7), 8.20 (2H, br s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.8 (OMe), 87.4, 95.4 (aryl CH), 126.6, 136.8, 140.5, 150.8, 158.5 (aryl C). Mass spectrum (+EI): *m/z* (%) 355 (M+1, 20), 354 (M, 100), 339 (25), 311 (25), 296 (25), 97 (22), 83 (24), 69 (28), 57 (22). Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.0; H, 5.1; N, 15.8. Found: C, 61.2; H, 5.4; N, 15.0.

Bis(4,6-dimethoxybenzimidazol-2-yl)methane (21b). A solution of diaminophenyl malonamide **20b** (1.75 g, 4.33 mmol) in absolute EtOH (100 mL) was made acidic by 5M HCl and refluxed for 22 h. The reaction mixture was concentrated and made basic by 2M NaOH solution. The resulting solid was filtered,

washed with water and recrystallized from EtOH/H_2O as a yellow solid to yield the bisbenzimidazole **21b** (1.21 g, 76%), mp 278-280 ˚C. λ_{max} (MeOH): 209 nm (ε 38,700 $cm^{-1}M^{-1}$), 253 (9,100), 283 (7,100), 406 (2,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (6H, s, OMe), 3.88 (6H, s, OMe), 4.68 (2H, s, CH_2), 6.49 (2H, d, *J* 1.9 Hz, aryl H5), 6.67 (2H, d, *J* 1.9 Hz, aryl H7), 7.74 (2H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1 (CH_2), 56.1, 56.2 (OMe), 89.0, 96.0 (aryl CH), 121.0, 136.4, 147.1, 148.6, 158.2 (aryl C). Mass spectrum (+EI): *m/z* (%) 370 (M+2, 25), 369 (M+1, 100). HRMS (+ESI): $C_{24}H_{22}N_4O_4$ $[M+2H]^+$ requires 431.1714, found 431.1718. Anal. Calcd for $C_{19}H_{20}N_4O_4$ $0.9H_2O$: C, 59.3; H, 5.7; N, 14.6. Found: C, 59.2; H, 5.6; N, 14.5.

2-[2-(4,6-Dimethoxbenzimidazol-2-yl)propan-2-yl]-4,6-dimethoxybenzimidazole (21c). Dinitrophenyl-dimethylmalonamide **19c** (2.50 g, 5.08 mmol), absolute EtOH (70 mL), THF (20 mL) and 10% Pd/C (0.50 g) were refluxed together under nitrogen. Hydrazine monohydrate (7.5 mL) was slowly added over 15 min and the mixture refluxed for a further 2 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure. The crude residue of compound **20c** was dissolved in absolute EtOH (150 mL) and highly acidified with 16% HCl. The solution was heated at reflux for 14 h, the solvent was removed and the residue triturated with water (100 mL) and the solid collected washed with water to give the bisbenzimidazole **21c** as a white crystalline dihydrochloride salt (1.18 g, 50%), mp >300 ˚C. ν_{max} (KBr): 3616, 3150, 1640, 1531, 1285, 1222, 1203, 1154, 1032, 990 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d_6*): δ 2.14 (6H, s, Me), 3.83 (6H, s, OMe), 3.94 (6H, s, OMe), 6.70 (2H, s, aryl H5), 6.82 (2H, s, aryl H7), NH not observed. ^{13}C NMR (75 MHz, DMSO-*d_6*): δ 26.70 (Me), 56.03, 56.23 (OMe), 88.07, 97.47 (aryl CH), 117.57, 133.58, 147.63, 152.04, 159.10 (aryl C), (the C-Me carbon is presumably obscured under the DMSO). Mass spectrum (+EI): *m/z* (%) 397 (M+1, 23), 396 (100), 381 (96), 366 (15), 220 (97), 219 (63), 204 (28), 190 (20).

2-[3-(4,6-Dimethoxybenzimidazol-2-yl)phenyl]-4,6-dimethoxybenzimidazole (21d) and 2-[3-(5,7-dimethoxybenzimidazol-2-yl)phenyl]-5,7-dimethoxybenzimidazole. To a solution of diaminophthalamide **20d** (0.50 g, 1.07 mmol) in absolute EtOH (50 mL) a few drops of concentrated HCl were added and the mixture heated under reflux overnight. The reaction mixture was allowed to come to room temperature before water was added and the solution made basic with 2M NaOH solution. The resulting precipitate was filtered, washed with water and recrystallized from EtOH to yield a tautomeric mixture (1:0.38) of bisbenzimidazole **21d** as a brown powder (0.31 g, 67%), mp 210-212 ˚C. ν_{max} (KBr): 3380, 1629, 1606, 1506, 1451, 1418, 1361, 1221, 1200, 1149, 1042, 811, 700 cm^{-1}. λ_{max} (MeOH): 207 nm (ε 49,300 $cm^{-1}M^{-1}$), 239 (25,200), 249 (25,000), 314 (29,500). ^{13}C NMR (75 MHz, DMSO-*d_6*): δ 55.8, 55.9 (OMe), 87.9, 96.0, 96.1, 125.8, 127.5, 128.9 (aryl CH), 121.9, 136.0, 147.1, 147.4, 148.8, 158.4 (aryl C). Mass spectrum (+EI): *m/z* (%) 432 (M+2, 26), 431 (M+1, 100). HRMS (+ESI): $C_{24}H_{23}N_4O_4$ $[M+H]^+$ requires 431.1714, found 431.1718.

2-[3-(4,6-Dimethoxybenzimidazol-2-yl)phenyl]-4,6-dimethoxybenzimidazole (21d)

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (6H, s, OMe), 3.91 (6H, s, OMe), 6.33 (2H, s, aryl H5), 6.58 (2H, s, aryl H7), 7.61-7.63 (2H, m, aryl H), 8.08-8.10 (2H, m, aryl H), 12.89 (2H, br s, NH).

2-[3-(5,7-Dimethoxybenzimidazol-2-yl)phenyl]-5,7-dimethoxybenzimidazole

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (6H, s, OMe), 3.91 (6H, s, OMe), 6.45 (2H, s, aryl H6), 6.78 (2H, s, aryl H4), 8.21-8.23 (2H, m, aryl H), 8.84-8.94 (2H, m, aryl H), 13.03 (2H, br s, NH).

2-[4-(4,6-Dimethoxybenzimidazol-2-yl)phenyl]-4,6-dimethoxybenzimidazole (21e) and 2-[4-(5,7-dimethoxybenzimidazol-2-yl)phenyl]-5,7-dimethoxybenzimidazole. To a solution of diaminoterephthalamide **20e** (0.50 g, 1.07 mmol) in absolute EtOH (50 mL) a few drops of concentrated HCl were added and the mixture was heated under reflux overnight. The reaction mixture was allowed to come to room temperature before water was added and made basic by 2M NaOH solution. The resulting precipitate was filtered, washed with water and recrystallized from EtOH to yield a tautomeric mixture (1:0.38) of bisbenzimidazole **21e** as a brown powder (0.29 g, 63%), mp >360 ˚C. ν_{max} (KBr): 3506, 3118, 2920, 2892, 1635, 1601, 1453, 1360, 1303, 1203, 1154, 1041, 995 cm^{-1}. λ_{max} (MeOH): 208 nm (ε 11,800 cm^{-1}M^{-1}), 260 (3,600), 354 (5,400). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.9, 55.9(OMe), 87.0, 94.6, 126.6 (aryl CH), 129.3, 131.0, 136.9, 148.6, 151.6, 157.7 (aryl C). Mass spectrum (+EI): *m/z* (%) 432 (M+2, 16), 431 (M+1, 100). Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 67.0; H, 5.2; N, 13.0. Found: C, 66.7; H, 5.3; N, 13.1.

2-[4-(4,6-Dimethoxybenzimidazol-2-yl)phenyl]-4,6-dimethoxybenzimidazole (21e)

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (6H, s, OMe), 3.92 (6H, s, OMe), 6.33 (2H, d, *J* 1.8 Hz, aryl H5), 6.58 (2H, d, *J* 1.8 Hz, aryl H7), 8.20-8.32 (4H, m, aryl H), 12.76 (2H, br s, NH).

2-[4-(5,7-Dimethoxybenzimidazol-2-yl)phenyl]-5,7-dimethoxybenzimidazole

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (6H, s, OMe), 3.93 (6H, s, OMe), 6.44 (2H, s, aryl H6), 6.78 (2H, s, aryl H4), 8.20-8.32 (4H, m, aryl H), 12.91 (2H, br s, NH).

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