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. 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. These reactions make the synthesis of new classes of natural and unnatural indoles possible. Subsequently, this type of chemistry has also been investigated for the related benzofuran system by our group. 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%. 

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 by the 1H NMR spectrum in CDCl3. When the spectrum was carried out in DMSO-d6, 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 1H 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.\textsuperscript{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\textsuperscript{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-dimethoxylaniline**

![Scheme 3](image-url)
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-substitution 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](image)

**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) related to the synthesized compounds 21. In addition, these methoxy activated head-to-head 2,2'-bisbenzimidazoles 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$_2$Cl$_2$ (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$_2$O as colourless needles (12.87 g, 69%), mp 110-112 °C. $\nu_{\text{max}}$(KBr): 3313, 1686, 1642, 1600, 1536, 1508, 1456, 1314, 1289, 1258, 1201, 1177, 1106, 1065, 1028, 846, 763 cm$^{-1}$. $\lambda_{\text{max}}$(MeOH): 206 nm ($\varepsilon$ 47,200 cm$^{-1}$M$^{-1}$), 274 (20,800). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.77 (6H, s, OMe), 3.84 (3H, s, OMe), 6.25 (1H, t, $J$ 1.9 Hz, aryl H$4$), 6.89 (2H, d, $J$ 1.9 Hz, aryl H$2,6$), 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$_3$): $\delta$ 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$_2$Cl$_2$ (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$_2$O gave the trimethylacetanilide 2f as large translucent crystals (39.88 g, 86%), mp 117 °C. $R_f$ (1% MeOH/CH$_2$Cl$_2$) 0.31. $\nu_{\text{max}}$(KBr): 3316, 1655, 1616, 1555, 1479, 1451, 1419, 1208, 1156, 1059, 942, 842, 827, 687 cm$^{-1}$. $\lambda_{\text{max}}$(THF): 230 nm ($\varepsilon$ 10,000 cm$^{-1}$M$^{-1}$), 250 (13,000). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.27 (9 H, s, C(Me)$_3$), 3.71 (6 H, s, OMe), 6.19 (1 H, t, $J$ 2.3 Hz, aryl H$4$), 6.78 (2 H, d, $J$ 2.3 Hz, aryl H$2,H6$), 7.44 (1 H, bs, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 27.4 (C(Me)$_3$), 39.6 (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.

\( \text{N-(3',5'-Dimethoxyphenyl)cinnamamide (2g).} \) Cinnamoyl chloride (10.87 g, 65.28 mmol) in dry CH_{2}Cl_{2} (20 mL) at 0 °C was added dropwise with stirring to 3,5-dimethoxyaniline 1 (5 g, 32.64 mmol) in dry CH_{2}Cl_{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_{2}O. The organic layer was washed with water, brine, then dried over anhydrous Na_{2}SO_{4}, filtered and evaporated to produce a pale yellow solid. This was recrystallized from iPrOH to form the cinnamide 2g as colorless needles (7.10 g, 77%), mp 145–146 °C.

\( \text{}_{\max} \) (KBr): 3350, 1660, 1626, 1549, 1345, 1222, 1206, 1160, 1069, 1053, 976, 838, 738 cm\(^{-1}\). \( \text{1H NMR (300 MHz, CDCl}_{3}\):} \( \delta \) 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).

\( \text{13C NMR (75 MHz, CDCl}_{3}\):} \( \delta \) 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.

\( \text{N-(3',5'-Dimethoxyphenyl)-4-chlorobenzamide (2h).} \) A solution of \( p \)-chlorobenzoyl chloride (18.3 mL, 0.144 mol) in anhydrous CH_{2}Cl_{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_{2}Cl_{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_{2}CO_{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_{2}Cl_{2}) 0.53. \( \text{}_{\max} \) (KBr): 3315, 1648, 1616, 1604, 1531, 1455, 1421, 1347, 1291, 1208, 1156, 1090, 1067, 1055, 1014, 929, 895, 848, 829, 804, 675 cm\(^{-1}\). \( \lambda_{\max} \) (THF): 238 nm (\( \varepsilon = 16,400 \) cm\(^{-1}\)M\(^{-1}\)), 269 (11,400), 289 (10,100). \( \text{1H NMR (300 MHz, CDCl}_{3}\):} \( \delta \) 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, br s, NH). \( \text{13C NMR (75 MHz, CDCl}_{3}\):} \( \delta \) 55.8 (OMe), 97.6, 99.1 (aryl CH), 129.4, 128.9 (aryl 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\textsuperscript{28-30} (1 g, 5.51 mmol) in Ac₂O (10 mL) was added previously cooled HNO₃ (0.7 mL) in Ac₂O (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/H₂O (1:1) to yield the 2-nitroformanilide 3a as yellow crystals (1.12 g, 90%), mp 120-122 °C. \( \nu_{\text{max}} \) (KBr): 3335, 1715, 1700, 1600, 1550, 1320, 1270, 1240, 1180, 1160, 1120, 1080, 1070, 930, 830, 760, 720, 660 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 6.32 (1H, d, J 2.3 Hz, aryl H\(_4\)), 7.74 (1H, d, J 2.3 Hz, aryl H\(_6\)), 9.15 (1H, br s, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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\(_9\)H\(_{10}\)N\(_2\)O\(_3\): 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 acetonilide 2b\textsuperscript{31} (5 g, 25.61 mmol) in Ac₂O (65 mL) and a previously cooled solution of HNO₃ (2.4 mL) in Ac₂O (10 mL) under stirring for half an hour to yield a yellow solid which was recrystallized from EtOH/H₂O (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 Ac₂O (100 mL) in an ice-salt bath to -10 °C for 1 h. Previously cooled HNO₃ (6.5 mL) in Ac₂O (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/H₂O (1:1) to yield the 2-nitroacetanilide 3b as yellow needles (5.10 g, 65%), mp 141-142 °C. \( \nu_{\text{max}} \) (KBr): 3380, 1700, 1610, 1595, 1550, 1500, 1420, 1380. 1310, 1295, 1240, 1210, 1120, 835, 775, 750 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 2.20 (3H, s, Me), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 6.27 (1H, d, J 2.6 Hz, aryl H\(_4\)), 7.69 (1H, d, J 2.6 Hz, aryl H\(_6\)), 9.15 (1H, br s, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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\(_2\)O\(_3\): 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\textsuperscript{32} (9 g, 35.0 mmol) in Ac₂O (125 mL) was added previously cooled HNO₃ (5.5 mL) in Ac₂O (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/H2O (1:1) to yield the 2-nitrophenylbenzamide 3c as minute brown crystals (7.93 g, 75%), mp 128-130 °C. Ret (CH2Cl2) 0.64. vmax (KBr): 3317, 1681, 1666, 1608, 1542, 1502, 1456, 1422, 1323, 1271, 1210, 1170, 1141, 1076, 937, 826, 796, 686 cm⁻¹. λmax (THF): 240 nm (ε 12,500 cm⁻¹M⁻¹), 261 (15,800), 335 (5,260). 1H NMR (300 MHz, CDCl3): 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). 13C NMR (75 MHz, CDCl3): 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 C15H14N2O5: 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 CH2Cl2 (10 mL) triethylamine (2 eq., 0.70 mL) was added. A mixture of benzoyl chloride (2 eq., 0.53 mL) in CH2Cl2 (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 Na2SO4. The solvent was removed under reduced pressure and the solid was recrystallized from EtOH/H2O (1:1) to yield the 2-nitrobenzamide 3c as pale yellow needles (0.64 g, 85%).

N-[3′,5′-Dimethoxy-2′-nitrophenyl]phenylacetamide (3d). To a solution of 2-nitroaniline 9 (1.0 g, 5.10 mmol) in dry CH2Cl2 (20 mL), triethylamine (1.5 eq., 1.1 mL) was added. A mixture of phenylacetyl chloride (2 eq., 1 mL) in CH2Cl2 (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 Na2SO4. The solvent was removed under reduced pressure and the solid was recrystallized from EtOH/H2O (1:1) to yield the nitroacetamide 3d as pale yellow needles (0.95 g, 59%), mp 124-126 °C. vmax (KBr): 3300, 1665, 1590, 1530, 1510, 1340, 1220, 1200, 1160, 1120, 1040, 950, 935, 830, 720, 700 cm⁻¹. 1H NMR (300 MHz, CDCl3): δ 3.76 (2H, s, CH2), 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). 13C NMR (75 MHz, CDCl3): δ 45.5 (CH2), 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 C16H16N2O5: 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 HNO3 (0.50 mL) in Ac2O (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 Ac2O (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/H2O (1:1) to yield the 2-nitrobenzamide 3e as yellow crystals (0.97 g, 83%), mp 180-182 °C. 

\[ \text{v}_{\text{max}} \text{ (KBr): } 3379, 1688, 1613, 1557, 1491, 1454, 1311, 1285, 1262, 1180, 1123, 1030, 838 \text{ cm}^{-1}. \text{ \( \lambda_{\text{max}} \) (MeOH): } 205 \text{ nm (\( \varepsilon \) 35,800 cm}^{-1}\text{M}^{-1}\text{)}, 263 (20,300). 1H NMR (300 MHz, CDCl3): \( \delta \) 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). 13C NMR (75 MHz, CDCl3): \( \delta \) 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): \( m/\zeta \) (%) 333 (M+1, 21), 288 (M-NO2, 20), 199 (100), 153 (23). Anal. Calcd for C16H16N2O6: C, 57.8; H, 4.9; N, 8.4. Found: C, 57.8; H, 5.0; N, 8.4.

3,5-Dimethoxy-\( \alpha,\alpha,\alpha \)-trimethyl-2-nitroacetanilide (3f). A solution of trimethylacetanilide 2f (5.0 g, 21.1 mmol) in Ac2O (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 HNO3 (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 (CH2Cl2/n-hexane), to give the 2-nitroacetanilide 3f as a bright yellow powder (4.16 g, 70%), mp 98 ˚C. Rf (CH2Cl2) 0.38. \( \text{v}_{\text{max}} \) (KBr): 3385, 1689, 1609, 1563, 1500, 1450, 1285, 1234, 1207, 1174, 1120, 951, 806 cm\(^{-1}\). \( \lambda_{\text{max}} \) (THF): 242 nm (\( \varepsilon \) 12,100 cm\(^{-1}\)M\(^{-1}\)), 279 (3,770), 330 (4,770). 1H NMR (300 MHz, CDCl3): \( \delta \) 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). 13C NMR (75 MHz, CDCl3): \( \delta \) 27.8 (C(Me)3), 40.9 (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: \( m/\zeta \) (%) 282 (M, 2), 236 (100), 151 (27). Anal. Calcd for C13H18N2O5: 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 Ac2O (100 mL) was added previously cooled HNO3 (3 mL) in Ac2O (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 iPrOH to yield the 2-nitrophenylcinnamide 3g as yellow crystals (6.28 g, 80%), mp 148-148 °C. \( \text{v}_{\text{max}} \) (KBr): 3362, 1681, 1602, 1533, 1333, 1295, 1238, 1210, 1158, 1124, 1104, 981, 765, 711 cm\(^{-1}\). 1H NMR (300 MHz, CDCl3): \( \delta \) 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). 13C NMR (75 MHz, CDCl3): \( \delta \) 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_{2}O_{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_{2}O (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_{2}Cl_{2}) 0.56. \( \nu_{\text{max}} \) (KBr): 3353, 1660, 1592, 1537, 1487, 1468, 1434, 1330, 1301, 1269, 1231, 1175, 1138, 1081, 1015, 967, 907, 831, 766 cm\(^{-1}\). \( \lambda_{\text{max}} \) (THF): 247 nm (\( \varepsilon \) 17,500 cm\(^{-1}\)M\(^{-1}\)), 261 (18,600), 334 (5,610).

1H NMR (300 MHz, CDCl_{3}): \( \delta \) 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_{6}H_{4}), 7.85 (2H, d, J 8.6 Hz, 4-ClC_{6}H_{4}), 7.94 (1H, d, J 2.6 Hz, H6), 10.32 (1H, bs, NH). 13C NMR (75 MHz, CDCl_{3}): \( \delta \) 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, 150.1, 153.2 (aryl C), 168.9 (C=O). Mass spectrum (+EI): m/z (%) 336 (M, 1), 290 (48), 141 (38), 139 (100), 111 (45). Anal. Calcd for C_{15}H_{13}ClN_{2}O_{5}: C, 53.5; H, 3.9; N, 8.3. Found: C, 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_{2}Cl_{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. \( \nu_{\text{max}} \) (KBr): 3459, 3424, 3321, 3226, 1652, 1601, 1544, 1459, 1371, 1276, 1205, 1150, 1051, 800 cm\(^{-1}\). \( \lambda_{\text{max}} \) (MeOH): 211 nm (\( \varepsilon \) 52,400 cm\(^{-1}\)M\(^{-1}\)), 299 (7,700). 1H NMR (300 MHz, CDCl_{3}): \( \delta \) 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). 13C NMR (75 MHz, CDCl_{3}): \( \delta \) 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_{2}O_{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) 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 CH₂Cl₂, washed with brine, dried over anhydrous MgSO₄, and the solvent evaporated in vacuo to give the 2-aminobenzenamide 4c as an off-white powder (17.85 g, 78%), mp 173-174 °C. Rf (CH₂Cl₂) 0.23. νmax (KBr): 3459, 3353, 3252, 1636, 1597, 1578, 1531, 1498, 1487, 1471, 1430, 1284, 1202, 1174, 1149, 1053, 902, 828, 798, 714, 692 cm⁻¹. λmax (THF): 239 nm (ε 15,300 cm⁻¹M⁻¹), 312 (5,270). ¹H NMR (300 MHz, CDCl₃): δ 3.43 (2H, bs, NH₂), 3.73 (3H, s, OMe), 3.81 (3H, s, OMe), 6.31 (1H, d, J 7.1 Hz, aryl H), 6.54 (2H, d, J 7.1 Hz, aryl H), 7.43 (H, d, J 7.1 Hz, aryl H), 7.51 (1H, t, J 7.1 Hz, aryl H), 7.78 (2H, d, J 7.1 Hz, aryl H), 8.48 (1H, bs, NHCO). ¹³C NMR (75 MHz, CDCl₃): 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 C₁₅H₁₆N₂O₃: 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 CH₂Cl₂, washed with brine, and dried over MgSO₄. The organic solvent was removed under reduced pressure to yield the 2-aminobenzenamide 4e as a white solid (1.24 g, 98%), mp 154-156 °C. νmax (KBr): 3406, 3287, 1639, 1606, 1532, 1510, 1495, 1464, 1296, 1254, 1202, 1187, 1157, 1058, 1029, 852 cm⁻¹. λmax (MeOH): 207 nm (ε 47,400 cm⁻¹M⁻¹), 255 (20,600), 305 (3,200). ¹H NMR (300 MHz, CDCl₃): δ 3.72 (3H, s, OMe), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 3.99 (2H, s, NH₂), 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). ¹³C NMR (75 MHz, CDCl₃): 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): C₁₆H₁₈N₂O₄ [M+Na⁺] requires 325.1158, found 325.1150. Anal. Calcd for C₁₆H₁₈N₂O₄: 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 CH₂Cl₂, washed with brine, and dried over MgSO₄. 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. νmax (KBr): 3375, 3000, 2938, 1661, 1610, 1530, 1498, 1450, 1336, 1220, 1202, 1167, 1151, 1053, 982, 835, 766 cm⁻¹. λmax (MeOH): 208 nm (ε 40,500 cm⁻¹M⁻¹), 282 (27,800). ¹H NMR (300 MHz, CDCl₃): δ 3.32 (2H, s, NH₂), 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$_3$): $\delta$ 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$_2$O$_3$: 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$_2$O (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$_2$O (80 mL) previously cooled HNO$_3$ (1.4 mL) in Ac$_2$O (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$_2$Cl$_2$, and the extract thoroughly washed with water several times and Na$_2$CO$_3$ solution and then with brine. The organic solvent was evaporated and the residue recrystallized from EtOH/H$_2$O (1:1) to afford the 2-nitroaniline 6 as orange crystals (2.21 g, 11.16 mmol, 67%), mp 106-107 °C. $\nu$$_{\text{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$_3$): $\delta$ 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$_3$): $\delta$ 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+1, 13), 199 (M+1, 100), 183 (55), 153 (26). Anal. Calcd for C$_8$H$_{10}$N$_2$O$_4$: 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. $\nu$$_{\text{max}}$ (KBr): 3355, 3175, 1607, 1505, 1197, 1170, 1146, 1069, 994, 934, 812, 728 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C₈H₁₂N₂O₂: 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 CH₂Cl₂, the organic layer was washed with brine, dried over anhydrous MgSO₄ and solvent removed under reduced pressure to afford 1,2-diamine 7 as an oil. The oil was dissolved in HCO₂H (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/H₂O (1:1) to afford a tautomeric mixture of benzimidazole 5a as off white crystals (2.10 g, 91%), mp 204-206 °C. Rₓ (5% MeOH/CH₂Cl₂) 0.21. vₓmax (KBr): 1610, 1530, 1335, 1280, 1220, 1200, 1140, 1040, 960, 840, 810, 780 cm⁻¹. λₓmax (MeOH): 280 (ε 3,650 cm⁻¹M⁻¹).

1³C NMR (75 MHz, DMSO-d₆): 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 C₉H₁₀N₂O₂: 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, CDCl₃): 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, CDCl₃) 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 CH₂Cl₂, washed with brine, dried over anhydrous MgSO₄ 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/H₂O (1:1) to give the 2-methylbenzimidazole 5b (1.15 g, 72%) as a white powder, mp 200-202 °C. Rₓ (5% MeOH/CH₂Cl₂) 0.12. vₓmax (KBr): 1610, 1540, 1500, 1340, 1250, 1220, 1200, 1150, 1130, 1050, 1020,
980, 940, 850, 820, 780 cm\(^{-1}\). \(\lambda_{\text{max}}\) (MeOH): 282 nm (\(\varepsilon = 4,400 \text{ cm}^{-1}\text{M}^{-1}\)), 248 (6,900), 213 (19,100). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.58\) (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, aryH), 6.61 (1H, s, aryH), 7.50-6.80 (1H, bs, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.6\) (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\(_2\)O\(_2\): 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 \(N-(3',5'-\text{dimethoxy}-2'\)-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\(_2\)Cl\(_2\), 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\(_2\)Cl\(_2\)) 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\(_2\)O to give the 2-phenylbenzimidazole \(5c\) as white clusters (2.16 g, 73%), \(R_f\) (CH\(_2\)Cl\(_2\)) 0.25, mp 190-191 °C. \(\nu_{\text{max}}\) (KBr): 3196, 1628, 1603, 1508, 1467, 1455, 1361, 1223, 1202, 1154, 1047, 964, 814, 690 cm\(^{-1}\). \(\lambda_{\text{max}}\) (THF): 241 nm (\(\varepsilon = 12,800 \text{ cm}^{-1}\text{M}^{-1}\)), 255 (14,800), 309 (18,300). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 3.68\) (3H, s, OMe), 3.78 (3H, s, OMe), 6.32 (1H, d, J 2.0 Hz, aryH), 6.57 (1H, d, J 2.0 Hz, aryH), 7.31 (3H, m, phenyl), 7.62 (1H, bs, NH), 8.09 (2H, m, phenyl). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 55.5, 55.8\) (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\(_2\)O\(_2\) [M+H]\(^+\) requires 255.1128, found 255.1127. Anal. Calcd for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_2\): 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\(_2\)Cl\(_2\), 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\(_2\)O to give the 2-benzyl-4,6-dimethoxybenzimidazole \(5d\) as white crystals (0.53 g, 62%), mp 190-192 °C. \(\nu_{\text{max}}\) (KBr):
1630, 1610, 1540, 1310, 1250, 1220, 1200, 1150, 1020, 820, 790 cm\(^{-1}\). \(\lambda_{\text{max}}\) (MeOH): 283 nm (\(\varepsilon\) 6,700 cm\(^{-1}\)M\(^{-1}\)), 252 (9,000), 212 (20,800). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 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-\(d_6\)): \(\delta\) 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\(_2\)O (1:1) to yield the (4’-methoxyphenyl)benzimidazole 5e as an off white solid (0.92 g, 80%), mp 202-204 °C. \(v_{\text{max}}\) (KBr): 3380, 1643, 1612, 1579, 1504, 1469, 1361, 1302, 1268, 1224, 1190, 1151, 1024, 837, 825 cm\(^{-1}\). \(\lambda_{\text{max}}\) (MeOH): 208 nm (\(\varepsilon\) 30,200 cm\(^{-1}\)M\(^{-1}\)), 256 (15,700), 307 (18,200). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 55.2, 55.4, 55.6 (O Me), 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-\(\alpha,\alpha,\alpha\)-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\(_2\)Cl\(_2\), 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\(_2\)Cl\(_2\)) 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\(_2\)Cl\(_2\)/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\(_2\)Cl\(_2\)) 0.43. \(v_{\text{max}}\) (KBr): 3164, 3101, 1627, 1609, 1537, 1498, 1455, 1403, 1361, 1286, 1252, 1219, 1202, 1146, 1048, 998, 937, 814 cm\(^{-1}\). \(\lambda_{\text{max}}\)
(THF): 234 nm (ε 6,220 cm⁻¹ M⁻¹), 249 (7,860), 274 (3,680), 292 (1,980). ¹³C NMR (75 MHz, CDCl₃): 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).

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

¹H NMR (300 MHz, CDCl₃): 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, CDCl₃): 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 CH₂Cl₂, washed with brine and dried over anhydrous MgSO₄. 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 iPrOH to give the 2-styrylbenzimidazole 5g as a tan powder (0.35 g, 1.25 mmol, 41%), mp 218-219 °C. v 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, CDCl₃): 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). ¹³C NMR (75 MHz, CDCl₃): 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): C₁₇H₁₆N₂O₂ [M+H]+ requires 281.1285, found 281.1288. Anal. Calcd for C₁₇H₁₆N₂O₂: 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 Et₂O (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 Et₂O (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 Na₂CO₃ solution, several times with brine, then dried over anhydrous MgSO₄, and the solvent evaporated in vacuo to give an off-white solid. Purification via suction column chromatography (CH₂Cl₂), then recrystallization from iPrOH/light petroleum, gave the 4-chlorobenzenamide 10h as fine colorless needles (10.10 g, 97%), mp 123-124 °C. Rᵣ (5% MeOH/CH₂Cl₂) 0.81. νₛ (KBr): 3436, 2989, 1661, 1613, 1542, 1501, 1483, 1461, 1415, 1285, 1258, 1209, 1155, 1039, 918, 838, 744 cm⁻¹. λₛ (MeOH): 211 nm (ε 25,500 cm⁻¹M⁻¹), 224 (14,000), 286 (5,900). ¹H NMR (300 MHz, CDCl₃): δ 3.81 (3H, s, OMe), 3.89 (3H, s, OMe), 6.51 (1H, s, aryl H₃), 7.42 (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 H). ¹³C NMR (75 MHz, CDCl₃): 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, 37Cl, 5), 294 (M+1, 37Cl, 35), 293 (M+2, 35Cl, 18), 192 (M+1, 35Cl, 100). Anal. Calcd for C₁₇H₁₄ClNO₃: 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-chlorobenzenamide (11). A solution of N-(2',4'-dimethoxyphenyl)-4-chlorobenzenamide 10h (1.39 g, 4.76 mmol) and MeCOCl (0.6 mL, 8.4 mmol) in anhydrous CH₂Cl₂ (30 mL) was stirred at room temperature under nitrogen. SbCl₅ (1.2 mL, 9.5 mmol) in anhydrous CH₂Cl₂ (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, then dried over anhydrous MgSO₄, and the solvent evaporated in vacuo and the remaining solid purified via gravity column chromatography (2% MeOH/CH₂Cl₂) to give the 5'-acetylchlorobenzenamide 11 as fine pale pink needles (1.19 g, 75%), mp 175-177 °C. Rᵣ (5% MeOH/CH₂Cl₂) 0.63. νₛ (KBr): 3445, 1667, 1608, 1530, 1498, 1471, 1416, 1354, 1278, 1228, 1206, 1161, 1104, 1026, 901, 810, 751 cm⁻¹. λₛ (THF): 238 nm (ε 23,800 cm⁻¹M⁻¹), 261 (17,900), 302 (11,900). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75 MHz, CDCl₃): 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, 37Cl, 1), 335 (M, 37Cl, 9), 334 (M, 35Cl, 4), 333 (M, 35Cl, 27), 141 (38), 139 (100), 113 (20), 111 (49). Anal. Calcd for C₁₇H₁₆ClNO₄: 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 10h (3 g, 15.4 mmol) in CCl₄ (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/CH₂Cl₂), followed by recrystallization from CH₂Cl₂/light petroleum, gave the 5-bromoacetanilide
12 as colorless needles (3.37 g, 80%), mp 154-156 °C. Rf (5% MeOH/CH2Cl2) 0.51. νmax (KBr): 3229, 1655, 1597, 1537, 1508, 1470, 1437, 1373, 1324, 1285, 1203, 1173, 1056, 1025, 891, 851, 820, 701, 657 cm⁻¹. λmax (THF): 235 nm (ε 10.10 cm⁻¹M⁻¹), 252 (14,400), 299 (5,400). ¹H NMR (300 MHz, CDCl₃): 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, J 8.3 Hz, phenyl), 8.22 (1H, bs, NH), 9.14 (1H, s, H6). ¹³C NMR (75 MHz, CDCl₃): δ 24.4 (Me), 56.4, 55.8 (OMe), 6.39 (1H, s, H3), 7.57 (1H, bs, NH), 8.39 (1H, J 8.3 Hz, phenyl), 8.22 (1H, bs, NH), 9.14 (1H, s, H6). Mass spectrum (+EI): m/z (%) 275 (M⁺ 81Br, 32), 273 (M⁺ 79Br, 30), 233 (42), 231 (42), 218 (66), 216 (65), 69 (52), 43 (100). Anal. Calcd for C₁₀H₁₂BrNO₃: 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 Ac₂O (50 mL) was stirred with cooling in a salt-ice slurry. HNO₃ (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 CH₂Cl₂. The organic extract was washed several times with an aqueous saturated Na₂CO₃ solution, dried over anhydrous MgSO₄, 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. Rf (5% MeOH/CH₂Cl₂) 0.74. νmax (KBr): 3436, 1668, 1600, 1536, 1480, 1433, 1343, 1285, 1213, 1094, 1021, 911, 845, 747 cm⁻¹. λmax (THF): 240 nm (ε 20,000 cm⁻¹M⁻¹), 272 (14,500), 292 (12,900), 350 (4,230). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75 MHz, CDCl₃): 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⁺ 37Cl, 1), 338 (M⁺ 37Cl, 9), 337 (M⁺ 35Cl, 3), 336 (M⁺ 35Cl, 26), 141 (39), 139 (100), 113 (18), 111 (51). Anal. Calcd for C₁₅H₁₃ClN₂O₃: 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 Ac₂O (24 mL) was stirred with cooling in an iced water bath. HNO₃ (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 MgSO₄, and the solvent evaporated in vacuo to give an orange solid that was purified via pressure column chromatography (2% MeOH/CH₂Cl₂) to give the 5-nitroacetanilide 17 as a yellow powder (0.23 g, 52%), mp 174-175 °C. Rf (2% MeOH/CH₂Cl₂) 0.42. νmax (KBr): 3435, 3371, 1694, 1678, 1627, 1596, 1537, 1495s, 1397, 1337, 1273, 1245, 1218, 1080, 1020, 990, 825, 761 cm⁻¹. λmax (THF): 232 nm (ε 16,300 cm⁻¹M⁻¹), 250 (20,100), 354 (4,230). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75 MHz, CDCl₃): 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_{2}O_{3}0.2H_{2}O: 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_{2}Cl_{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_{2}Cl_{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_{2}Cl_{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_{2}Cl_{2}), then recrystallization from iPrOH, gave the trimethoxybenzamide 16 as colorless rectangular prisms (8.581 g, 49%), mp 193-197 °C. R\(_{f}\) (2% MeOH/CH_{2}Cl_{2}) 0.48. \( \nu \) max (KBr): 3387, 1677, 1609, 1536, 1508, 1450, 1412, 1310, 1229, 1134, 1104, 996, 831, 753 cm\(^{-1}\). \( \lambda \) max (THF): 239 nm (\( \epsilon \) 17,600 cm\(^{-1}\)M\(^{-1}\)), 260 (8,900), 294 (10,200). \(^{1}\)H NMR (300 MHz, CDCl\(_{3}\)): \( \delta \) 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\(_{3}\)): \( \delta \) 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\(_{16}\)ClN\(_{2}\)O\(_{3}\): 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\(_{2}\)O 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\(_{2}\)Cl\(_{2}\). 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\(_{2}\)Cl\(_{2}\)) 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\(_{2}\)Cl\(_{2}\)) 0.74. \( \nu \) max (KBr): 3391, 1690, 1591, 1550, 1507, 1407, 1329, 1123, 1029, 830, 747 cm\(^{-1}\). \( \lambda \) max (THF): 239 nm (\( \epsilon \) 17,000 cm\(^{-1}\)M\(^{-1}\)), 266 (16,000), 292 (7,500), 354 (2,300). \(^{1}\)H NMR (300 MHz, CDCl\(_{3}\)): \( \delta \) 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\(_{6}\)H\(_{4}\)), 7.84 (2H, d, \( J \) 9.2 Hz, 4-ClC\(_{6}\)H\(_{4}\)), 8.10 (1H, s, H6), 9.95 (1H, bs, NH). \(^{13}\)C NMR (75 MHz, CDCl\(_{3}\)): \( \delta \) 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\(_{2}\)O\(_{6}\): 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$_2$Cl$_2$, 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$_2$Cl$_2$) 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$_2$Cl$_2$) 0.14. $\nu_{\text{max}}$ (KBr): 3410, 3304, 1630, 1591, 1499, 1463, 1424, 1402, 1368, 1291, 1266, 1200, 1144, 1118, 1048, 1000, 775, 695 cm$^{-1}$. $\lambda_{\text{max}}$ (THF): 239 nm ($\varepsilon$ 12,200 cm$^{-1}$M$^{-1}$), 254 (8,320), 319 (21,400). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_2$O$_3$.0.33H$_2$O: 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$_2$Cl$_2$ (10 mL) and triethylamine (0.35 mL) a mixture of oxalyl chloride (0.11 mL, 0.5 eq) in anhydrous CH$_2$Cl$_2$ (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$_2$Cl$_2$ to afford the dinitrophenyl oxalamide 19a as yellow crystals (0.31 g, 56%), mp 298-300 °C. $\nu_{\text{max}}$ (KBr): 3300, 1710, 1610, 1550, 1330, 1290, 1240, 1210, 1170, 1120, 1080, 940, 820 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 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 (%) 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$_{18}$H$_{18}$N$_2$O$_3$·0.33H$_2$O: C, 66.2; H, 5.8; N, 9.7. Found: C, 66.2; H, 5.7; N, 9.5.

$N,N'$-Bis(3,5-dimethoxy-2-nitrophenyl)malonamide (19b). 3,5-Dimethoxy-2-nitroaniline 6 (4.0 g, 20.2 mmol) and K$_2$CO$_3$ (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. $\nu_{\text{max}}$ (KBr): 3402, 3176, 1703, 1614, 1494, 1242, 1206, 1115, 1005, 860, 715 cm$^{-1}$. $\lambda_{\text{max}}$ (MeOH): 209 nm (ε 65,700 cm$^{-1}$M$^{-1}$), 240 (25,000), 346 (8,400). $^1$H NMR (300 MHz, acetone-d$_6$): $\delta$ 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$_6$): $\delta$ 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$_4$O$_{10}$: 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$_2$CO$_3$ (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 (2×300 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. $\nu_{\text{max}}$ (KBr): 3591, 3080, 1695, 1599, 1301, 1151, 1100, 964, 847, 800 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_4$O$_{10}$: 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$_2$CO$_3$ (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 189 °C. $\nu_{\text{max}}$ (KBr): 3328, 3164, 1661, 1627, 1558, 1456, 1420, 1326, 1203, 1158, 1061, 973, 831, 745, 676 cm$^{-1}$. $\lambda_{\text{max}}$ (MeOH): 208 nm (ε 87,200 cm$^{-1}$M$^{-1}$), 225 (53,000), 316 (26,800). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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_{4}O_{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_{2}CO_{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. \( \lambda_{\text{max}} \) (KBr): 3362, 2945, 1722, 1695, 1605, 1556, 1493, 1454, 1419, 1280, 1206, 1119, 1069, 939, 838, 719 cm\(^{-1}\). \( \lambda_{\text{max}} \) (MeOH): 205 nm (ε 64,600 cm\(^{-1}\)M\(^{-1}\)). \( \nu_{\text{max}} \) (KBr): 3362, 3020, 2945, 2831, 1632, 1605, 1556, 1493, 1454, 1419, 1280, 1206, 1119, 1069, 939, 838, 719 cm\(^{-1}\). \( \nu_{\text{max}} \) (MeOH): 3362, 3020, 2945, 2831, 1632, 1605, 1556, 1493, 1454, 1419, 1280, 1206, 1119, 1069, 939, 838, 719 cm\(^{-1}\). \( \lambda_{\text{max}} \) (MeOH): 205 nm (ε 64,600 cm\(^{-1}\)M\(^{-1}\)). \( \lambda_{\text{max}} \) (KBr): 3020, 2945, 2831, 1632, 1605, 1556, 1493, 1454, 1419, 1280, 1206, 1119, 1069, 939, 838, 719 cm\(^{-1}\). \( \lambda_{\text{max}} \) (MeOH): 205 nm (ε 64,600 cm\(^{-1}\)M\(^{-1}\)). 1H 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 H\(_{4}, \text{H}_{6}\)), 10.54 (2H, br s, NH). 13C 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).

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\(_{2}\)Cl\(_{2}\), 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. \( \nu_{\text{max}} \) (KBr): 3112, 3000, 2985, 2831, 1634, 1603, 1496, 1450, 1357, 1311, 1223, 1192, 1043, 1027, 993, 931 cm\(^{-1}\). \( \lambda_{\text{max}} \) (MeOH): 205 nm (ε 64,600 cm\(^{-1}\)M\(^{-1}\)). 1H 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 H\(_{4}\)), 6.49 (2H, d, \( J = 1.8 \) Hz, aryl H\(_{6}\)), 9.74 (2H, br s, NH). 13C 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 dinitrophenylisophthalamide 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. \( \nu_{\text{max}} \) (KBr): 3381, 3195, 1634, 1606, 1536, 1452, 1418, 1363, 1222, 1201, 1151, 1042, 993, 812, 698 cm\(^{-1}\). \( \lambda_{\text{max}} \) (MeOH): 207 nm (ε 45,100 cm\(^{-1}\)M\(^{-1}\)), 249 (21,900), 312 (23,200). 1H NMR (300 MHz, DMSO-\( d_{6} \)): δ 3.78 (6H, s, OMe), 3.92 (6H, s, OMe), 6.37 (2H, s, aryl H\(_{4}\)), 6.64 (2H, s, aryl H\(_{6}\)), 7.60–7.65 (2H, m, aryl H\(_{4}\)), 7.60–7.65 (2H, m, aryl H\(_{6}\)), 8.13–8.92 (7H,
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 diamino terephthalamide 20e as a light yellow solid (0.32 g, 72%), mp >360 °C.

$\max (\text{KBr}): 3409, 3271, 1635, 1595, 1531, 1492, 1460, 1421, 1375, 1318, 1282, 1202, 1154, 1058, 895, 822, 678 \text{ cm}^{-1}$. $\max (\text{MeOH}): 211 \text{ nm} (\varepsilon 3,900 \text{ cm}^{-1} \text{M}^{-1})$. $\text{H NMR (300 MHz, DMSO-}d_6): \delta 3.66 \text{ (6H, s, OMe)}, 3.79 \text{ (6H, s, OMe)}, 4.23 \text{ (4H, br s, NH$_2$)}, 6.45 \text{ (2H, s, aryl H4)}, 6.55 \text{ (2H, s, aryl H6)}, 8.00-8.07 \text{ (4H, m, aryl H)}, 9.88 \text{ (2H, br s, NH)}$. $\text{C NMR (75 MHz, DMSO-}d_6): \delta 55.4, 55.8 \text{ (OMe)}, 97.0, 102.4, 127.3, 128.5, 130.7 \text{ (aryl CH)}, 124.0, 134.7, 138.0, 148.6, 150.7 \text{ (aryl C)}, 164.6 \text{ (C=O)}. \text{ Mass spectrum (+EI): m/z (%) 467 (M+1, 8), 466 (M, 26), 167 (100), 140 (23), 76 (20). HRMS (+ESI): C$_{24}$H$_{26}$N$_4$O$_6$ [M+Na]$^{+}$ requires 489.1744, found 489.1751.

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$_2$Cl$_2$ 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. $\text{H NMR (300 MHz, DMSO-}d_6): \delta 3.77 \text{ (6H, s, OMe)}, 3.89 \text{ (6H, s, OMe)}, 6.32 \text{ (2H, d, J 2.0 Hz, aryl H5)}, 6.54 \text{ (2H, d, J 2.0 Hz, aryl H7)}, 8.20 \text{ (2H, br s, NH)}$. $\text{C NMR (75 MHz, DMSO-}d_6): \delta 55.8 \text{ (OMe)}, 87.4, 95.4 \text{ (aryl CH)}, 126.6, 136.8, 140.5, 150.8, 158.5 \text{ (aryl C)}. \text{ Mass spectrum (+EI): m/z (%) 355 (M+1, 20), 354 (M, 100), 339 (25), 311 (25), 296 (25), 97 (22), 83 (24), 69 (28), 57 (22). Anal. Calcd for C$_{18}$H$_{18}$N$_4$O$_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$_2$O as a yellow solid to yield the bisbenzimidazole 21b (1.21 g, 76%). mp 278-280 °C. $\lambda_{\text{max}}$ (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$_4$O$_4$ [M+2H]$^+$ requires 431.1714, found 431.1718. Anal. Calcd for C$_{19}$H$_{20}$N$_4$O$_4$·0.9H$_2$O: C, 59.3; H, 5.7; N, 14.6. Found: C, 59.2; H, 5.6; N, 14.5.

2-[2-(4,6-Dimethoxybenzimidazol-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. $\nu_{\text{max}}$ (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), 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 (%) 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. $\nu_{\text{max}}$ (KBr): 3380, 1629, 1606, 1506, 1451, 1418, 1361, 1221, 1200, 1149, 1042, 811, 700 cm$^{-1}$. $\lambda_{\text{max}}$ (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$_4$O$_4$ [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-$d_6$): $\delta$ 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-$d_6$): $\delta$ 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. $\nu_{\text{max}}$ (KBr): 3506, 3118, 2920, 2892, 1635, 1453, 1360, 1203, 1154, 1041, 995 cm$^{-1}$. $\lambda_{\text{max}}$ (MeOH): 208 nm ($\varepsilon$ 11,800 cm$^{-1} \cdot $M$^{-1}$), 260 (3,600), 354 (5,400).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 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$_4$O$_4$: C, 67.0; H, 5.2; N, 13.0. Found: C, 66.7; H, 5.3; N, 13.1.

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