Synthesis and characterisation of peripherally functionalised dendritic molecules

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A number of peripherally functionalised dendritic molecules were synthesised in almost quantitative yield by a synthetic method involving the reaction between amines and isocyanates. The peripheral functional groups were incorporated by preparing a number of branched subunits, based on tris(hydroxymethyl)aminomethane (TRIS), **1**, possessing three nitro, methoxy, methyl or maleimide terminal functionalities. Attachment of these branched units to the core molecules 4,4′-methylenebis(phenyl isocyanate) **13** and 1,3,5-benzene triisocyanate **20** afforded the corresponding dendritic molecules possessing 6 or 9 peripheral functional groups. Functional group conversions on the dendritic molecules have been successfully carried out, including hydrogenation of the terminal nitro to the corresponding amine and cleavage of the methoxy ether to give the corresponding phenol.

Introduction

A rising demand for well-defined, functional materials for nano-scale applications has stimulated the development of synthetic procedures for the efficient assembly of dendritic and polymeric species.[1] Several synthetic approaches to these systems feature architectural control while still maintaining flexibility in the incorporation of functional groups.[2] However, many approaches to dendrimer syntheses, particularly in later generations, require high monomer loading and involve prolonged, repetitive, chromatographic separations, generating considerable waste.[3] In an attempt to overcome this problem a growing number of synthetic approaches are utilising facile coupling techniques for the assembly of macromolecular dendritic and polymeric structures.[4] Recently, several urea-based syntheses have been reported for the divergent growth of dendrimers[5–7] and other macro-molecular structures.[8] Here we report a highly efficient, facile approach for the modular synthesis of a diverse range of peripherally functionalised structures that can serve as scaffolds for the assembly of more complex macromolecular structures for use in nanotechnology, biological and materials sciences. The syntheses utilise the well-documented reaction between an isocyanate and an amine and afford peripherally functionalised nanoparticles in excellent yields and purity.

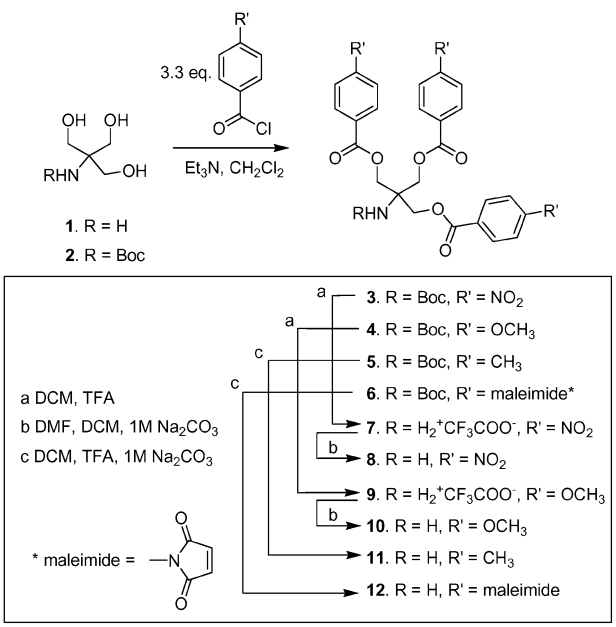
Results and discussion

Synthetic strategy

The synthetic strategy utilised in this body of work was based on the preparation of a number of branched synthetic building blocks possessing differing terminal functionality. These dendrons were then attached to bi- and tri-functional core molecules *via* urea linkages, by utilising the facile reaction occurring between amines and isocyanates. Such a modular strategy provides ample opportunity for tailoring of the final molecules for specific applications and properties.

Synthesis of branched dendrons with peripheral functionality

The synthesis of the branched dendrons, bearing three terminal residues and based on the inexpensive starting material tris(hydroxymethyl)aminomethane (TRIS) **1**, involved the coupling of 3.3 equivalents of an appropriately *para*-substituted benzoic acid chloride with Boc protected TRIS **2** in dichloromethane (DCM) in the presence of triethylamine (Scheme 1).



Scheme 1 Synthesis of the branched dendrons.

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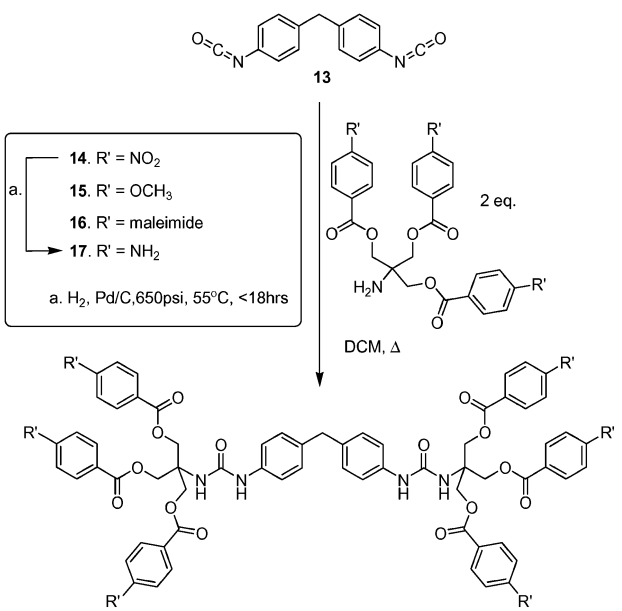
The *p*-nitro, *p*-methoxy and *p*-methyl benzoyl chloride starting materials were obtained commercially, whilst *N*-(4-carboxyphenyl)maleimide was synthesised according to literature procedures.[9] Conversion of *N*-(4-carboxyphenyl)-maleimide to the required acid chloride was carried out immediately prior to use *via* standard procedures using thionyl chloride. Initial synthesis of the maleimide 3-mer dendron (*N*-(*tert*-butyloxycarbonyl)-1,1,1-tris(4-maleimidobenzoyloxy-methyl) methylamine) **6** resulted in low yields due to unwanted polymerisation. Subsequent procedures utilising *tert*-butylcatechol to suppress polymerisation[9] resulted in higher yields being obtained. The Boc protected dendrons **3–6** were synthesised in yields ranging from 41–92%. Deprotection of the Boc protected dendrons **3** and **4** in DCM with trifluoroacetic acid (TFA), followed by the addition of 1 M sodium carbonate afforded the TFA salts **7** and **9**, respectively. The corresponding free base amines **8** and **10** were obtained on further treatment of the TFA salts with sodium carbonate. Deprotection of the Boc protected dendrons **5** and **6** afforded the free amines **11** and **12** directly after treatment with sodium carbonate.

Synthesis of functionalised branched molecules containing 6- and 9-peripheral functionalities

The modular strategy devised for the synthesis of branched molecules containing 6- and 9-peripheral functionalities provides for flexibility in the level of complexity available for elaboration, as well as increasing the variety of peripheral functional groups that could be incorporated. Initial investigations were carried out on the commercially available bi-functional 4,4′-methylenebis(phenyl isocyanate) **13** as the core unit. The synthetic methodology for the assembly of these linear 6-mer systems is shown in Scheme 2.

The success of this system can be best illustrated through the resultant NMR spectra of the 'crude' 6-nitro species as seen in Fig. 1. The symmetry of the fully functionalised dendritic system is evidenced in the NMR spectrum. Less symmetrical species, suggesting incomplete reactions, were not observed in the crude products isolated in all cases. Formation of the urea linkages were confirmed through two-dimensional NMR experiments and the corresponding cross peaks can be clearly identified in the gHMBC spectrum (Fig. 2).



Scheme 2 Synthesis of the 6-mer macromolecules.

1,3,5-Benzene triisocyanate **20** was selected as the tri-functional core unit for the synthesis of the more radially distributed 9-mer systems,. This material was prepared, according to a literature procedure,[7] from the corresponding 1,3,5-benzenetricarbonyl triazide precursor **19**, *via* a Curtius rearrangement. Once prepared the acylazide precursor **19** was stored at −20 °C until required, as this compound is reported to be explosive under heat or pressure in the solid state.[8] The synthetic methodology for the assembly of the 9-mer systems is shown in Scheme 3.

In most cases the products precipitated from the reaction mixture after 18 h and were isolated simply by filtration. ^{1}H NMR analysis of the reaction products for the formation of the nitro 6-mer **14** (Scheme 2) showed the formation of spectroscopically pure product in a 75% yield. However, the use of the trifunctional core **20** to assemble the analogous 9-mer nitro species **21** resulted in poor yields. Further investigation found that the application of gentle heat to the reaction afforded required compound **21** in a 92% yield (Scheme 3). Consequently, subsequent reactions to construct the 6-mer and 9-mer species were carried out in refluxing DCM. Formation of the methoxy **15** and maleimido **16** functionalised 6-mers recorded yields of 74 and 94% (Scheme 2), whilst the construction of the methoxy **22**, methyl **23** and maleimide **24** terminated 9-mers achieved yields of 96, 97, and 99%, respectively (Scheme 3). Solubility of both the 6-mer and 9-mer species varies greatly with varying external functionality. In all cases the methoxy and maleimido functionalised molecules were soluble in dichloromethane and were isolated *via* solvent removal at reduced pressure.

Conversion of the peripheral nitro functionalised species **14** and **21** to the corresponding amines occurred smoothly *via* hydrogenation using 5% Pd/C under elevated temperatures and pressure (DMF, 55 °C, 600 psi) and afforded yields of the polyamine 6-mer **17** in 62% yield and the 9-mer **25** in 60% yield, respectively. Similarly, conversion of the methoxy protected 9-mer **22**, to the phenolic compound **26** ($AlBr_3$, dodecane thiol, DCM) afforded the 9-mer polyphenol **26** in 87% yield.

Conclusions

We have demonstrated the facile assembly of highly monodisperse branched molecules possessing a range of peripheral functionalities, based upon the high yielding coupling reaction occurring between amines and isocyanates. The uniform attachment of the dendrons to the bi- and tri-functionalised cores is highly efficient and yields compounds of high purity due to the quantitative reaction between the amines on the branched dendrons and the isocyanates present on the core molecules. Our investigations are continuing into the application of these molecules as a basis for the assembly of more complex macromolecular structures for applications in biological and materials science.

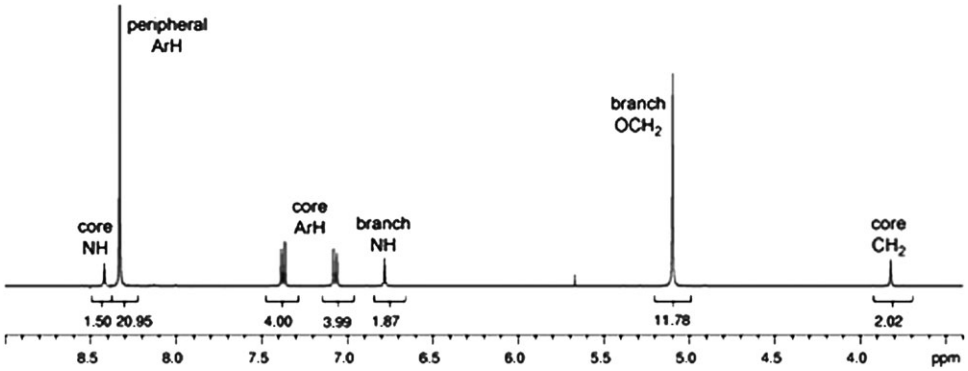


Fig. 1 ^{1}H NMR spectrum (400 MHz, 298 K, CD_3COCD_3–CD_3SOCD_3) of the crude 6-mer, **14**.

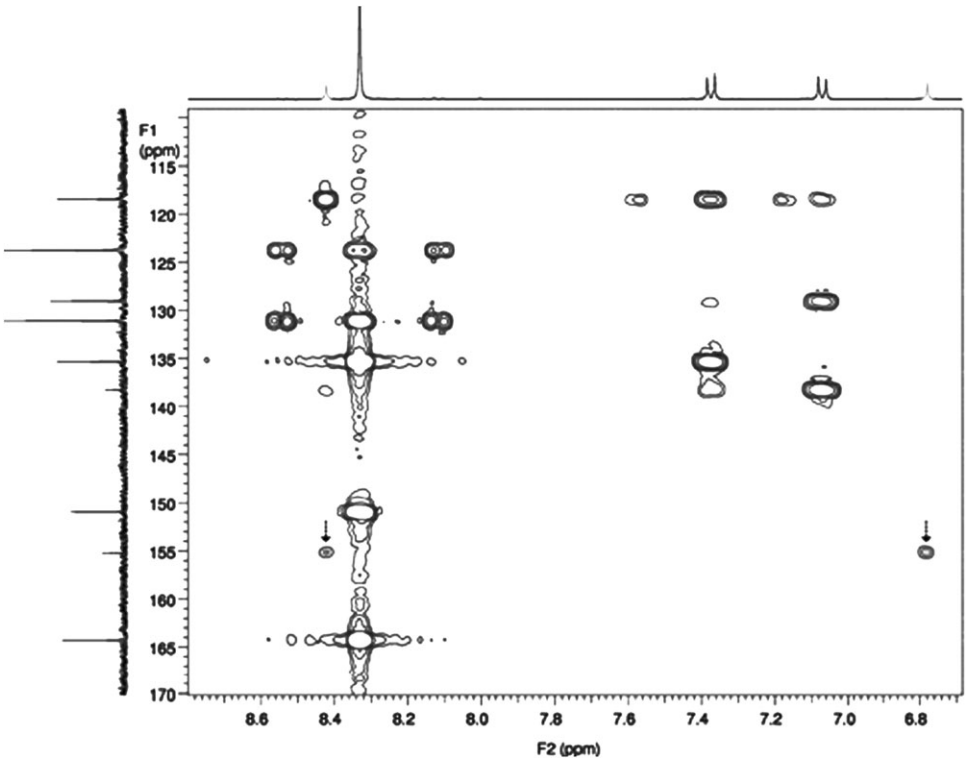


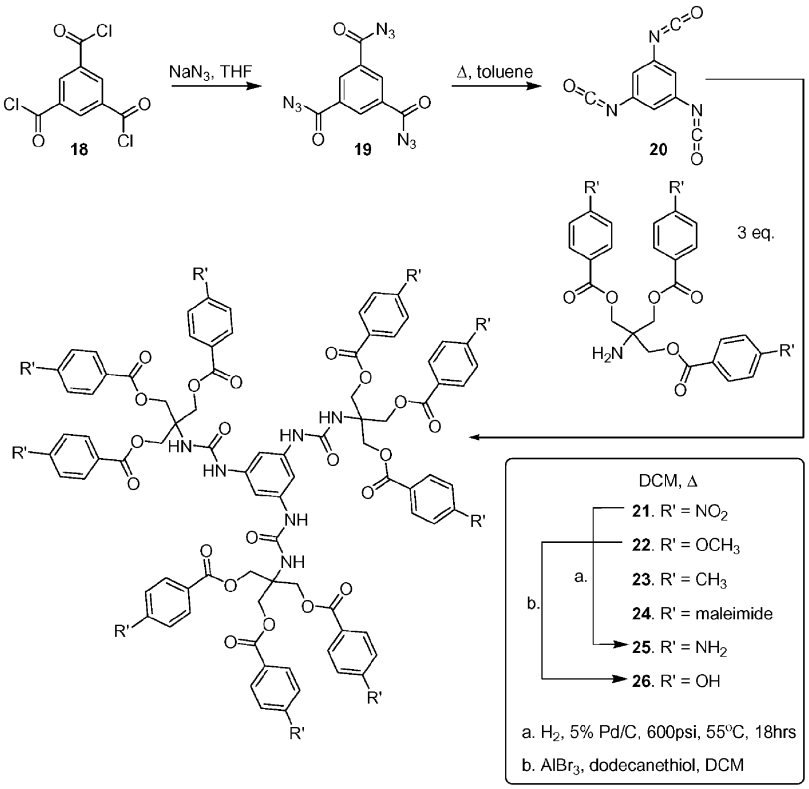
Fig. 2 Expansion of the ^{1}H/^{13}C gHMBC spectrum of the 6-mer, **14** (400 MHz, 298 K, CD_3COCD_3–CD_3SOCD_3). Basic ^{1}H and ^{13}C{^{1}H} spectra are provided as axes references. Crosspeaks correlating the NH protons and the carbon of the central carbonyl of the urea linkage are highlighted.

Experimental

General methods and materials

Anhydrous solvents were prepared according to literature methods.[10] Most reagents and starting materials were obtained from commercial sources (Sigma-Aldrich) and used without further purification. 4-Maleimidobenzoic acid[9] and 1,3,5-benzenetricarbonyl triazide[7] **19** were prepared according to published procedures. All reactions were performed in flame-dried or oven-dried glassware under an inert atmosphere of nitrogen. In all cases the isocyanate was prepared immediately prior to coupling with the appropriate amine. Analytical TLC was carried out on Merck aluminium TLC plates coated with silica gel 60 F254 (0.2 mm) and visualised by ultraviolet light (254 nm) or in an iodine vapour tank. Chromatographic separations were carried out by column chromatography with Merck silica gel 60 Å (230–400 mesh) as the stationary phase.

NMR spectra were recorded on a Varian Unity INOVA spectrometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) chemical shifts were referenced to the residual solvent peaks. gCOSY, gHSQC and gHMBC spectra were acquired using the standard sequences contained in the VNMR6.1C software package. FTIR spectra were recorded in the range of 4000–400 cm^{-1} on a Thermo Nicolet-Nexus FTIR spectrometer. Melting points were measured using the capillary method on a GallenKamp Variable Temperature Apparatus and are uncorrected. Mass spectra were recorded on a Fisons VG-Platform II spectrometer, using positive and negative mode



Scheme 3 Synthesis of the 9-mer branched molecules.

electrospray as the ionisation technique and Mass Lynx Version I (IBM) software to acquire and process ESMS data. Lithium was added to ESMS scans as LiBr. HRMS were carried out by the Mass Spectrometry Facility, Griffith University on a Bruker Daltonics Apex III 4.7e Fourier Transform Mass Spectrometer, fitted with an Apollo API source and are within 2.5 ppm. Elemental analyses were carried out by the Microanalytical Service, Department of Chemistry at the University of Queensland, Brisbane.

Synthesis

***N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(hydroxymethyl)methylamine 2.** Tris(hydroxylmethyl)aminomethane (**1**) (11.7 g, 97 mmol) was added as a solid to a solution of di-*tert*-butyl dicarbonate (21.0 g, 96 mmol) in THF (200 ml) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 4 days. The resulting precipitate was filtered off and washed thoroughly with cold THF then dried under high vacuum to give a white powder (15.1 g, 73% yield) as a spectroscopically pure product; mp 144–146 °C (lit.,[11] 147 °C). ESMS (−ve) 220 (M^-, 20%); ESMS (+ve) 222 (M^+, 15%), 228 (MLi^+, 95%). ^{1}H NMR (DMSO-d$_6$) δ 5.76 (br. s, 1H, N*H*), 4.49 (br. t, 3H, O*H*), 3.51 (d, 6H, CH_2), 1.37 (s, 9H, CH_3). ^{13}C NMR[12] (DMSO-d$_6$) δ 155.03 (*C*=O), 77.83 (C_q–CH$_3$), 60.45 (*C*H$_2$), 60.24 (C_q–CH$_2$), 28.22 (*C*H$_3$).

***N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(4-nitrobenzoyloxy-methyl) methylamine 3.** A solution of 4-nitrobenzoyl chloride (14.0 g, 74.6 mmol) dissolved in dichloromethane (30 ml) was added dropwise, under an atmosphere of nitrogen, to a solution of **2** (5.0 g, 23 mmol) and Et$_3$N (11 ml, 79 mmol) in dry dichloromethane (100 ml). The reaction was gently refluxed for 20 hours, then cooled to room temperature and filtered to remove the precipitated triethylamine hydrochloride. The organic solution was washed with saturated aqueous NaHCO$_3$ (3 × 150 ml) and saturated aqueous NaCl (5 × 150 ml), dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (4% ethyl acetate–dichloromethane) affording an ivory colored solid (13.2 g, 87% yield); mp 147.5–149 °C. ESMS (+ve) 691 (MNa^+, 65%), 675 (MLi^+, 30%). IR(KBr, pellet, cm^{-1}) 3391 m, 1725 s, 1526 s, 1349 m, 1276 s. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.29 (m (AA′), 6H, Ar–*H*), 8.18 (m (BB′), 6H, Ar–*H*), 7.51 (br. s, 1H, N*H*), 4.81 (s, 6H, CH_2), 1.34 (s, 9H, CH_3). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 163.84 (*C*O$_2$R), 154.74 (NH–*C*=O), 150.30 (Ar*C*–NO$_2$), 134.68 (Ar*C*–CO$_2$H), 130.74 (Ar*C*–H), 123.76 (Ar*C*–H), 78.79 (C_q–CH$_3$), 63.78 (*C*H$_2$), 56.57 (C_q–CH$_2$), 28.01 (C–*C*H$_3$). Anal. calcd for $C_{30}H_{28}N_4O_{14}$: C, 53.89; H, 4.22; N, 8.38. Found: C, 54.12; H, 4.35; N, 8.23%.

***N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(4-methoxybenzoyloxy-methyl)methylamine 4.** This compound was prepared by a procedure analogous to that used for the preparation of **3** using *p*-anisoyl chloride (12.7 g, 75 mmol) and **2** (5.0 g, 23 mmol). The crude product was purified by column chromatography (2% ethyl acetate–CH$_2$Cl$_2$) affording a white foamy solid (13.0 g, 92% yield); mp 136 °C. ESMS (+ve) 630 (MLi^+, 100%), 647 (MNa^+, 100%). IR(KBr, pellet, cm^{-1}) 3364 m, 2976 w, 1718 s, 1697 s, 1606 s, 1255 s. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 7.91 (m (AA′), 6H, Ar–*H*), 7.34 (br. s, 1H, N*H*) 7.00 (m (XX′), 6H, Ar–*H*), 4.65 (s, 6H, CH_2), 3.82 (s, 9H, O–CH_3), 1.34 (s, 9H, C–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.93 (*C*O_2R), 163.24 (Ar*C*–OCH_3), 154.69 (NH–*C*=O), 131.37 (Ar*C*–H), 121.53 (Ar*C*–CO_2R), 113.93 (Ar*C*–H), 78.47 (C_q–CH_3), 62.85 (*C*H_2), 56.77 (C_q–CH_2), 55.48 (O–*C*H_3), 28.04 (C–*C*H_3). Anal. calcd for $C_{33}H_{37}NO_{11}$: C, 63.55; H, 5.98; N, 2.25. Found: C, 63.64; H, 6.01; N, 2.21%.

***N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(4-methylbenzoyloxymethyl)methylamine 5.** This compound was prepared by a procedure analogous to that used for the preparation of **3** using *p*-toluoyl chloride (11.7 g, 10.0 ml, 76 mmol) and **2** (5.0 g, 23 mmol). The crude product was purified by column chromatography (gradient elution 50–65% dichloromethane–hexane) to yield a white solid (12.00 g, 20.8 mmol, 92%); mp 129–131 °C. ESMS (+ve) 582 (MLi^+, 100%), 598 (MNa^+, 100%). IR(KBr, pellet, cm^{-1}) 3378 m, 2977 w, 1726 s, 1704 s, 1271 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (m (AA′), 6H, Ar–*H*), 7.38 (br. s, 1H, N*H*), 7.28 (m (XX′), 6H, Ar–*H*), 4.67 (s, 6H, CH_2), 2.36 (s, 9H, Ar–CH_3), 1.33 (s, 9H, C–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.25 (*C*O_2R), 154.69 (NH–*C*=O), 143.78 (Ar*C*–CH_3), 129.29 (Ar*C*–H), 129.20 (Ar*C*–H), 126.61 (Ar*C*–CO_2R), 78.49 (*Cq*–CH_3), 62.96 (*C*H_2), 56.73 (*Cq*–CH_2), 28.03 (C–*C*H_3), 21.13 (ArC–*C*H_3). Anal. calcd for $C_{33}H_{37}NO_8$: C, 68.85; H, 6.48; N, 2.43. Found: C, 69.12; H, 6.46; N, 2.42%.

***N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(4-maleimidobenzoyloxymethyl)methylamine 6.** 4-Maleimidobenzoic acid (12.0 g, 55.35 mmol) was gently refluxed in thionyl chloride (45 ml) with *tert*-butyl catechol (0.01 g) and stirred for 2 hours under an atmosphere of nitrogen. The solution was cooled to room temperature, the excess thionyl chloride removed *in vacuo* and the resulting solid dried under high vacuum. This solid was gradually added, under an atmosphere of N_2, to a solution of **2** (3.7 g, 16.8 mmol), *tert*-butyl catechol (0.01 g) and Et_3N (20 ml, 144 mmol) in dichloromethane (200 ml). The reaction was heated gently for 18 hours then cooled to room temperature and filtered. The solution was washed with saturated aqueous $NaHCO_3$ (3 × 150 ml) and saturated aqueous NaCl (5 × 150 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate–dichloromethane) and dried under high vacuum (6.9 g, 8.4 mmol, 50%); mp 113–116 °C. ESMS (+ve) 825 (MLi^+, 100%), 841 (MNa^+, 45%). IR(KBr, pellet, cm^{-1}) 3376 w, 3102 w, 2977 w, 1716 s, 1267 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (m (AA′), 6H, Ar–*H*), 7.48 (m (XX′), 6H, Ar–*H*), 7.43 (br. s, 1H, N*H*), 7.22 (s, 6H, *HC*=C*H*), 4.76 (s, 6H, CH_2), 1.36 (s, 9H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.43 (*C*=ONC=O), 164.66 (*C*O_2R), 154.71 (NH–*C*=O), 135.95 (Ar*C*–NR), 134.86 (RH*C*=*C*HR), 129.90 (Ar*C*–H), 128.02 (Ar*C*–CO_2R), 126.19 (Ar*C*–H), 78.57 (*Cq*–CH_3), 63.31 (*C*H_2), 56.75 (*Cq*–CH_2), 28.05 (C–*C*H_3). Anal. calcd for $C_{42}H_{34}N_4O_{14}$: C, 61.61; H, 4.19; N, 6.84. Found: C, 61.76; H, 4.24; N, 6.87%.

1,1,1-Tris(4-nitrobenzoyloxymethyl)methylamine trifluoroacetic acid salt 7. *N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(4-nitrobenzoyloxy-methyl)methylamine (**3**) (3.5 g, 5.3 mmol) was dissolved in the minimum amount of dichloromethane then trifluoroacetic acid (3 ml) was added and the solution was refrigerated for 18 hours. The organic solution was poured into 1 M aqueous Na_2CO_3 and the resulting white precipitate was collected by filtration and dried (3.59 g, 99% yield); mp 158–159 °C. ESMS (−ve) 113 (CF_3COO^-, 95%). ESMS (+ve) 569 (M^+, 100%). IR(KBr, pellet, cm^{-1}) 1742 s, 1729 s, 1267 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (br. s, 3H, NH_3^+), 8.36 (m (AA′BB′), 12H, Ar–*H*), 4.81 (s, 6H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.79 (*C*O_2R), 150.55 (Ar*C*–NO_2), 134.16 (Ar*C*–CO_2R), 131.25 (Ar*C*–H), 123.68 (Ar*C*–H), 63.66 (*C*H_2), 56.38 (*Cq*). Anal. calcd for $C_{27}H_{21}F_3N_4O_{14}\cdot H_2O$: C, 46.29; H, 3.31; N, 8.00. Found: C, 46.01; H, 2.95; N, 7.95%.

1,1,1-Tris(4-nitrobenzoyloxymethyl)methylamine 8. **7** (9.5 g, 13.9 mmol) was dissolved in DMF (100 ml) then dichloromethane (200 ml) was added. This organic solution was washed with 1 M Na_2CO_3 (2 × 150 ml) and water (2 × 150 ml), then dried ($MgSO_4$), filtered and evaporated to yield the free amine (5.7 g, 72% yield); mp 152–153 °C. ESMS (+ve) 569 (M^+, 100%). IR(KBr, pellet, cm^{-1}) 1725 s, 1266 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (m (AA′BB′), 12H, Ar–*H*), 4.52 (s, 6H, CH_2), 2.34 (br. s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.04 (*C*O_2R), 150.22 (Ar*C*–NO_2), 134.74 (Ar*C*–CO_2R), 130.82 (Ar*C*–H), 123.65 (Ar*C*–H), 67.31 (*C*H_2), 54.25 (C_q). Anal. calcd for $C_{25}H_{20}N_4O_{12}$: C, 52.82; H, 3.55; N, 9.86. Found: C, 52.65; H, 3.49; N, 9.81%.

1,1,1-Tris(4-methoxybenzoyloxymethyl)methylamine trifluoroacetic acid salt 9. This compound was prepared by a procedure analogous to that used for the preparation of **7** using *N*-(*tert*-butyloxycarbonyl)-1,1,1-tris(4-methoxybenzoyloxymethyl)methylamine **4** (5.9 g, 9.5 mmol), dichloromethane (20 ml) and trifluoroacetic acid (4 ml) (5.9 g, 98% yield); mp 150–151 °C. ESMS (−ve) 113 (CF_3COO^-, 50%). ESMS (+ve) 524 (M^+, 100%). IR(KBr, pellet, cm^{-1}) 1731 s, 1713 s, 1259 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (br. s, 3H, NH_3^+), 8.09 (m (AA′), 6H, Ar–*H*), 7.03 (m (XX′), 6H, Ar–*H*), 4.65 (s, 6H, CH_2), 3.84 (s, 9H, O–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.88 (*C*O_2R), 163.55 (Ar*C*–OCH_3), 131.96 (Ar*C*–H), 120.92 (Ar*C*–CO_2R), 113.93 (Ar*C*–H), 63.04 (*C*H_2), 56.49 (C_q), 55.56 (O–*C*H_3). Anal. calcd for $C_{30}H_{30}F_3NO_{11}.2[H_2O]$: C, 53.49; H, 5.09; N, 2.16. Found: C, 53.93; H, 4.50; N, 2.16%.

1,1,1-Tris(4-methoxybenzoyloxymethyl)methylamine 10. This compound was prepared by a procedure analogous to that used for the preparation of **8** using **9** (4.2 g, 6.7 mmol), DMF (50 ml) and dichloromethane (250 ml) (2.8 g, 80% yield); mp 93 °C. ESMS (+ve) 524 (M^+, 90%). IR(KBr, pellet, cm^{-1}) 3389 m, 2964 m, 1705 s, 1605 s, 1256 s. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m (AA′), 6H, Ar–*H*), 6.88 (m (XX′), 6H, Ar–*H*), 4.48 (s, 6H, CH_2), 3.83 (s, 9H, CH_3), 1.79 (br. s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.94 (*C*O_2R), 163.79 (Ar*C*–OCH_3), 131.91 (Ar*C*–H), 121.99 (Ar*C*–CO_2R), 113.89 (Ar*C*–H), 66.28 (*C*H_2), 55.58 (*C*H_3), 55.18 (*C*q). Anal. calcd for $C_{28}H_{29}NO_9$: C, 64.24; H, 5.58; N, 2.68. Found: C, 64.12; H, 5.61; N, 2.65%.

1,1,1-Tris(4-methylbenzoyloxymethyl)methylamine 11. *N*-(*tert*-Butyloxycarbonyl)-1,1,1-tris(4-methylbenzoyloxymethyl)methylamine **5** (5.4 g, 9.4 mmol) was dissolved in dichloromethane (50 ml), trifluoroacetic acid (5 ml) was added and the solution was refrigerated for 18 hours. The organic solution was washed with 1 M Na_2CO_3 (2 × 150 ml) and water (2 × 150 ml), then dried ($MgSO_4$), filtered and evaporated to yield the free amine (3.5 g, 77% yield); mp 119 °C. ESMS (+ve) 476 (M^+, 100%), 483 (MLi^+, 35%). IR(KBr, pellet, cm^{-1}) 3387 m, 2949 w, 1727 s, 1714 s, 1261 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (m (AA′), 6H, Ar–*H*), 7.26 (m (XX′), 6H, Ar–*H*), 4.39 (s, 6H, CH_2), 2.36 (s, 9H, ArC–CH_3), 2.14 (br. s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.47 (*C*O_2R), 143.67 (Ar*C*–CH_3), 129.33 (Ar*C*–H), 129.18 (Ar*C*–H), 126.66 (Ar*C*–CO_2R), 66.58 (*C*H_2), 54.26 (C_q–CH_2), 21.14 (ArC–*C*H_3). Anal. calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.76; H, 6.14; N, 2.98%.

1,1,1-Tris(4-maleimidobenzoyloxymethyl)methylamine 12. This compound was prepared by a procedure analogous to that used for the preparation of **11** using *N*-(*tert*-butyloxycarbonyl)-1,1,1-tris(4-maleimidobenzoyloxymethyl)methylamine **6** (1.1 g, 1.3 mmol), dichloromethane (20 ml) and trifluoroacetic acid (1 ml) (0.84 g, 90% yield); mp 111 °C. ESMS (+ve) 719 (M^+, 100%), 725 (MLi^+, 30%). IR(KBr, pellet, cm^{-1}) 3475 w, 3102 w, 1716 s, 1265 s. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.13 (m (AA′), 6H, Ar–*H*), 7.49 (m (XX′), 6H, Ar–*H*), 7.06 (s, 6H, *H*C═C*H*), 4.63 (s, 6H, CH_2). ^{13}C NMR (100 MHz, acetone-*d*6) δ 170.19 (*C*═ON*C*═O), 165.99 (*C*O_2R), 137.30 (Ar*C*–NR), 135.61 (RH*C*═*C*HR), 131.02 (Ar*C*–H), 129.59 (Ar*C*–CO_2R), 126.80 (Ar*C*–H), 68.10 (*C*H_2), 55.65 (C_q–CH_2). Anal. calcd for $C_{37}H_{26}N_4O_{12}$: C, 61.84; H, 3.65; N, 7.80. Found: C, 61.62; H, 3.74; N, 7.59%.

(*N*′,*N*‴-Bis(1,1,1-tris(4-nitrobenzoyloxymethyl)methyl))-4,4′-methylenebis(phenylurea) 14. 1,1,1-Tris(4-nitrobenzoyloxymethyl)methylamine **8** (2.5 g, 4.4 mmol) was dissolved in dry dichloromethane (35 ml) and added to a stirred solution of 4,4′-methylenebis(phenyl isocyanate) **13** (0.6 g, 2.2 mmol) in dichloromethane (20 ml). The reaction mixture was stirred under an atmosphere of nitrogen at RT for 18 hours. The product was isolated by filtration as an off-white solid (2.3 g, 75%); mp 149–151 °C. ESMS (+ve) 1409 (MNa^+, 50%), 1393 (MLi^+, 60%). IR(KBr, pellet, cm^{-1}) 3385 m, 3111 w, 1731 s, 1525 s, 1265 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (br s, 2H, N*H*), 8.20 (m (AA′), 12H, Ar–*H*), 8.16 (m (MM′), 12H, Ar–*H*), 7.19 (m (AA′), 4H, core-Ar–*H*), 6.97 (m (MM′), 4H, core-Ar–*H*), 6.74 (br s, 2H, N*H*), 4.86 (s, 12H, CH_2), 3.69 (br s, 2H, core-CH_2). ^{13}C NMR(100 Mhz, DMSO-d_6) δ 163.88 (*C*O_2R), 154.69 (NH*C*═ONH), 150.28 (Ar*C*–NO_2), 137.55 (core-Ar*C*–NHR), 134.82 (core-Ar*C*–H),134.55 (Ar*C*–CO_2R), 130.77 (*p*-NO_2-Ar*C*–H), 128.8 (core-Ar*C*–CH_2), 123.73 (*p*-NO_2-Ar*C*–H), 118.14 (core-Ar*C*–H), 64.51(*C*H_2), 56.65 (C_q), 39.51 coincident with residual solvent (core-*C*H_2). Anal. calcd for $C_{65}H_{50}N_{10}O_{26}$: C, 56.28; H, 3.63; N, 10.10. Found: C, 56.30; H, 3.65; N, 9.85%.

(*N*′,*N*‴-Bis(1,1,1-tris(4-methoxybenzoyloxymethyl)methyl))-4,4′-methylenebis(phenylurea) 15. This compound was prepared by a procedure analogous to that used for the preparation of **14** using 1,1,1-tris(4-methoxybenzoyloxymethyl)methylamine **4** (0.5 g, 0.7 mmol), dichloromethane (10 ml), 4,4′-methylenebis(phenyl isocyanate) **13** (0.09 g, 0.35 mmol) for 24 h. The product was isolated by filtration as a white solid (0.33 g, 74%); mp 94.4–95 °C. ESMS (+ve) 1320 (MNa^+, 50%), 1303 (MLi^+, 45%). IR(KBr, pellet, cm^{-1}) 3377 m, 3005 w, 2960 m, 2838 m, 1713 s, 1257 s. ^{1}H NMR(400 MHz, DMSO-d_6) δ 8.58 (br s, 2H N*H*), 7.90 (m (AA′), 12H, Ar–*H*), 7.24 (m (AA′), 4H, core-Ar–*H*), 7.02 (m (MM′), 4H, core-Ar–*H*), 6.97 (m (AA′), 12H, Ar–*H*), 6.67 (br. s, 2H, N*H*), 4.74 (s,12H, CH_2), 3.80 (s,18H, CH_3), 3.75 (br. s, 2H, core-CH_2) ^{13}C NMR(100 MHz, DMSO-d_6) δ 164.95 (*C*O_2R), 163.26 (Ar*C*–OCH_3), 154.68 (NH*C*═ONH), 137.68 (core-Ar*C*–NHR), 134.67 (Ar*C*–CO_2R), 131.39 (core-Ar*C*–H), 128.80 (core-Ar*C*–CH_2), 121.37 (*p*-CH_3O–Ar*C*–H), 118.02 (core-Ar*C*–NHR), 113.95 (*p*-CH_3O–Ar*C*–H), 63.62 (*C*H_2), 56.79 (C_q), 55.47 (*C*H_3), 39.51 (core-*C*H_2). Anal. calcd for $C_{71}H_{68}N_4O_{20}$: C, 65.73; H, 5.28; N, 4.32. Found: C, 65.27; H, 5.25; N, 4.03%.

(*N*′,*N*‴-Bis(1,1,1-tris(4-maleimidobenzoyloxymethyl)methyl))-4,4′-methylenebis(phenylurea) 16. This compound was prepared by a procedure analogous to that used for the preparation of **14** using 1,1,1-tris(4-maleimidobenzoyloxymethyl) methylamine **6** (0.8 g, 1.1 mmol), dichloromethane (15 ml) and added to a stirred solution of 4,4′-methylenebis(phenyl isocyanate) (0.14 g, 0.55 mmol) **13** for 48 hours. The solvents were removed *in vacuo* to give the product as a bright yellow solid (0.85 g, 92%); mp 153.5 °C. ESMS (+ve) 1710 (MNa^+, 70%), 1694 (MLi^+, 20%). IR(KBr, pellet, cm^{-1}) 3475 w, 3381 m, 3100 m, 2960 w, 1716 s, 1265 s. ^{1}H NMR(400 MHz, DMSO-d_6) δ 8.57 (br.s, 2H, N*H*), 8.05 (m (AA′), 12H, Ar–*H*), 7.45 (m (XX′), 12H, Ar–*H*), 7.26 (m (AA′), 4H, core-Ar–*H*), 7.20 (s, 12H, *H*C═C*H*), 6.69 (br. s, 2H, N*H*), 4.87 (s,12H, CH_2), 3.75 (br. s, 2H, core-CH_2). ^{13}C NMR(100 Mhz, DMSO-d_6) δ 169.40 (O═*C*N*C*═O), 164.70 (*C*O_2R), 154.72 (NH*C*═ONH), 137.61 (core-Ar*C*–H), 135.95 (Ar*C*–NR_2), 134.83 (RH*C*═*C*HR), 134.73 (Ar*C*–CO_2R), 129.91 (*p*-maleimide-Ar*C*–H), 128.83 (core-Ar*C*–CH_2), 127.88 (core-Ar*C*–H), 126.15 (*p*-maleimide-Ar*C*–H), 118.19 (core-Ar*C*–NHR), 64.16 (*C*H_2), 56.76 (C_q), 39.51 coincident with residual solvent (core-*C*H_2). Anal. calcd for $C_{89}H_{62}N_{10}O_{26}$: C, 63.35; H, 3.70; N, 8.30. Found: C, 62.46; H, 3.72; N, 7.96%.

(*N*′,*N*‴-Bis(1,1,1-tris(4-aminobenzoyloxymethyl)methyl))-4,4′-methylenebis(phenylurea) 17. (*N*′,*N*‴-Bis(1,1,1-tris(4-nitrobenzoyloxymethyl)methyl)-4,4′-methelenebis(phenylurea) **14** (1.8 g, 1.29 mmol) was dissolved in dry DMF (18 ml) and 0.18 g of 5% Pd/C was added. The reaction mixture was pressurised with H_2 gas (650 psi) and heated to 55 °C for 18 hours. The solution was filtered and evaporated under reduced pressure to give a brown residue. The residue was triturated with diethyl ether (3 × 20 ml) and dichloromethane added to precipitate the product as a dark yellow solid. The powder was collected by filtration and dried under high vacuum to yield (0.97 g, 0.8 mmol, 62%); mp 164–165.6 °C. ESMS (+ve) 1229 (MNa^+, 100%), 1213 (MLi^+, 100%). (HRMS) Found 1207.4490. $C_{64}H_{63}N_{10}O_{14}$(+) requires 1207.4519. IR(KBr, pellet, cm^{-1}) 3365 m, 3955 w, 2358 w,

1698 s, 1601 s. ^{1}H NMR(400 MHz, DMSO-d_6) δ 8.55 (br. s, 2H, N*H*), 7.65 (m (AA′), 12H, Ar–*H*), 7.23 (m (AA′), 4H, core-Ar–*H*), 7.02 (m (XX′), 4H, core-Ar–*H*), 6.53 (m (XX′), 12H, Ar–*H*), 6.50 (br. s, 2H, N*H*), 5.99 (br. s, 12H, Ar–NH_2), 4.60 (s, 12H, CH_2), 3.75 (br. s, 2H, core-CH_2). ^{13}C NMR(100 MHz, DMSO-d_6) δ 165.45 (*C*O_2R), 154.67 (NH*C*=ONH), 153.71 (Ar*C*–NH_2), 137.74 (core-Ar*C*–H), 134.54 (Ar*C*–CO_2), 131.28 (core-Ar*C*–H), 128.83 (core-Ar*C*–CH_2), 117.96 (core-Ar*C*–NHR), 115.21 (*p*-NH_2–Ar*C*–H), 112.59 (*p*-NH_2–Ar*C*–H), 62.88 (*C*H_2), 56.94 (C_q), 39.51 coincident with residual solvent (core-*C*H_2).

1,3,5-Tris((1,1,1-tris(4-nitrobenzoyloxymethyl)methylamino) carbonylamino)benzene 21. 1,3,5-Benzenetricarbonyl triazide **19** (0.09 g, 0.3 mmol) was dissolved in dry toluene (5 ml) and refluxed for one hour under an atmosphere of nitrogen. The reaction was allowed to cool, the toluene was removed on a rotary evaporator and 1,1,1-tris(4-nitrobenzoyloxymethyl)-methylamine **8** (0.52 g, 0.9 mmol) dissolved in CH_2Cl_2 (10 ml) was added under an atmosphere of nitrogen. The reaction mixture was gently refluxed for 16 hours and cooled to room temperature. The resulting precipitate was collected by filtration affording a yellow powder (0.53 g, 92% yield); mp 143–145° C. (ESMS+) 1929 (MNa^+, %). Anal. calcd for $C_{84}H_{63}N_{15}O_{39}$: C, 52.92; H, 3.33; N, 11.02. Found: C, 52.79; H, 3.41; N, 10.84%. IR(KBr, pellet, cm^{-1}) 3397 m, 1733 s. ^{1}H NMR (400 MHz, acetone-d_6) 8.23 (m (AA′BB′), 36H, *p*-NO_2-Ar–*H*), 8.08 (br. s, 3H, N*H*), 7.22 (s, 3H, core-Ar–*H*), 6.43 (br. s, 3H, N*H*), 5.07 (s, 18H, CH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.03 (*C*O_2R), 155.67 (NH*C*=ONH), 151.70 (Ar*C*–NO_2), 141.47 (Ar*C*–NHR), 135.96 (Ar*C*–CO_2R), 131.83 (p-NO_2–Ar*C*–H), 124.51 (*p*-NO_2–Ar*C*–H), 103.43 (core-Ar*C*–H), 65.73 (CH_2), 58.50 (C_q).

1,3,5-Tris((1,1,1-tris(4-methoxybenzoyloxymethyl)methylamino) carbonylamino)benzene 22. This compound was prepared by a procedure analogous to that used for the preparation of **21** using 1,3,5-benzenetricarbonyl triazide **19** (0.15 g, 0.52 mmol) and dry toluene (7 ml), 1,1,1-tris(4-methoxybenzoyloxymethyl)methylamine **10** (0.82 g, 1.56 mmol) and dichloromethane (15 ml). The reaction mixture was gently refluxed for 16 hours and cooled to room temperature. The solvent was removed by rotary evaporation to yield a white solid (0.89 g, 0.50 mmol, 96%); mp 114–115 °C. (ESMS+) 1778 (MLi^+, 100%), 1794 (MNa^+, 100%). Anal. calcd for $C_{93}H_{90}N_6O_{30}$: C, 63.05; H, 5.12; N, 4.74. Found: C, 63.09; H, 5.29; N, 4.74%. IR(KBr, pellet, cm^{-1}) 3384 m, 2962 w, 1717 s, 1258 s. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.15 (s, 3H, N*H*), 7.97 (m (AA′), 18H, *p*-CH_3O–Ar–*H*), 7.30 (s, 3H, core-Ar–*H*), 6.96 (m (XX′), 18H, *p*-CH_3O–Ar–*H*), 6.28 (s, 3H, N*H*), 4.90 (s, 18H, CH_2), 3.86 (s, 27H, CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.17 (*C*O_2R), 164.73 (Ar*C*–OCH_3), 155.61 (NH*C*=ONH), 141.70 (Ar*C*–NHR), 132.55 (*p*-CH_3O–Ar*C*–H), 123.02 (Ar*C*–CO_2R), 114.73 (*p*-CH_3O–Ar*C*–H), 102.56 (core-Ar*C*–H), 64.87 (*C*H_2), 58.57 (*Cq*), 56.01 (*C*H_3).

1,3,5-Tris((1,1,1-tris(4-methylbenzoyloxymethyl)methylamino) carbonylamino)benzene 23. This compound was prepared by a procedure analogous to that used for the preparation of **22** using 1,3,5-benzenetricarbonyl triazide **19** (0.09 g, 0.3 mmol) and dry toluene (5 ml), 1,1,1-tris(4-methylbenzoyloxymethyl)-methylamine **11** (0.43 g, 0.9 mmol) and dichloromethane (10 ml) (0.47 g, 0.29 mmol, 97%); mp 111–112 °C. (ESMS+) 1634 (MLi^+, 100%), 1650 (MNa^+, 100%). Anal. calcd for $C_{93}H_{90}N_6O_{21}$: C, 68.62; H, 5.57; N, 5.16. Found: C, 68.63; H, 5.78; N, 5.02%. IR(KBr, pellet, cm^{-1}) 3392 m, 1718 s, 1268 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 3H, N*H*), 7.91 (m (AA′), 18H, *p*-CH_3–Ar–*H*), 7.28 (s, 3H, core-Ar–*H*), 7.25 (m (XX′), 18H, *p*-CH_3–Ar–*H*), 6.30 (s, 3H, N*H*), 4.93 (s, 18H, CH_2), 2.37 (s, 27H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.49 (*C*O_2R), 155.58 (NH*C*=ONH), 144.90 (Ar*C*–CH_3), 141.64 (Ar*C*–NHR), 130.52 (*p*-CH_3–Ar*C*–H), 130.10 (*p*-CH_3-Ar*C*–H), 128.08 (Ar*C*–CO_2R), 102.57 (core-Ar*C*–H), 64.94 (*C*H_2), 58.53 (C_q), 21.66 (*C*H_3).

1,3,5-Tris((1,1,1-tris(4-maleimidobenzoyloxymethyl)methylamino)carbonylamino)benzene 24. This compound was prepared by a procedure analogous to that used for the preparation of **22** using 1,3,5-benzenetricarbonyl triazide **19** (0.04 g, 0.15 mmol) and dry toluene (3 ml), 1,1,1-tris(4-maleimidobenzoyloxymethyl)methylamine **12** (0.32 g, 0.45 mmol) and dichloromethane (10 ml) to yield a yellow solid (0.35 g, 0.15 mmol, 99%); mp 200 °C. IR(KBr, pellet, cm^{-1}). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (br. s, 3H, N*H*), 8.04 (m (AA′), 18H, Ar–*H*), 7.44 (m (XX′), 18H, Ar–*H*), 7.22 (s, 3H, core-Ar–*H*), 7.19 (s, 18H, *H*C=C*H*), 6.53 (br. s, 3H, N*H*), 4.87 (s, 18H, CH_2). ^{3}C NMR (100 MHz, DMSO-d_6) δ 169.4 (*C*=ONC=O), 164.69 (*C*O_2R), 154.55 (NH*C*=ONH), 140.43 (core-Ar*C*–NHR), 135.96 (Ar*C*–NR_2), 134.83 (RH*C*=*C*HR), 129.93 (*p*-maleimide-Ar*C*–H), 127.85 (Ar*C*–CO_2R), 126.15 (*p*-maleimide-Ar*C*–H), 100.57 (core-Ar*C*–H), 64.20 (*C*H_2), 56.70 (C_q). Anal. calcd for $C_{120}H_{81}N_{15}O_{39}.H_2O$: C, 60.69; H, 3.52; N, 8.85. Found: C, 60.43; H, 3.71; N, 8.71%.

1,3,5-Tris((1,1,1-tris(4-aminobenzoyloxymethyl)-methylamino) -carbonylamino)benzene 25. 1,3,5-Tris((1,1,1-tris(4-nitrobenzoyloxymethyl)methylamino) carbonyl-amino)benzene **21** (400 mg, 0.2 mmol) was dissolved in dry DMF (5 ml) and 0.04 g of 5% Pd/C was added. The reaction mixture was pressurised with H_2 gas (650 psi) and heated to 55 °C for 15 hours. The solution was filtered and evaporated under reduced pressure to give a brown oil that was solidified by the addition of dichloromethane, collected by filtration and dried under high vacuum to yield a yellow solid (0.21 g, 0.13 mmol, 65%); mp 258–260 °C. (HRMS) Found 1636.5692. $C_{84}H_{82}N_{15}O_{21}$(+) requires 1636.5804. IR(KBr, pellet, cm^{-1}) 3368 m, 1700 s, 1602 s, 1268 s. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (br, s, 3H, N*H*), 7.65 (m (AA′), 18H, Ar–*H*), 7.15 (s, 3H, core-Ar–*H*), 6.53 (m (XX′), 18H, Ar–*H*), 6.37 (br, s, 3H, N*H*), 5.98 (s, 18H, NH_2), 4.60 (s, 18H, CH_2). ^{13}C NMR (100 MHz) δ 165.44 (*C*O_2R), 154.48 (NH*C*=ONH), 153.70 (Ar*C*–NH_2), 140.51 (core-Ar*C*–NHR), 131.29 (*p*NH_2–Ar*C*–H), 115.18 (*p*NH_2–Ar*C*–H), 112.62 (core-Ar*C*–H), 62.89 (*C*H_2), 56.87 (C_q).

1,3,5-Tris((1,1,1-tris(4-hydroxybenzoyloxymethyl)methylamino) carbonylamino)benzene 26. A solution of aluminium bromide (1.01 g, 3.8 mmol) and dodecanethiol (2 ml) in dry DCM (7 ml) was cooled in an ice bath under an atmosphere of N_2. 1,3,5-Tris((1,1,1-tris(4-

methoxybenzoyloxymethyl)methylamino)carbonylamino)benzene **22** (0.25 g, 0.14 mmol) was added as a solid and the reaction warmed to room temperature and stirred for 16 hours. The reaction mixture was poured into water (250 ml) and acidified with 1 M HCl. The aqueous solution was extracted with DCM (200 ml) that was set aside then the aqueous layer was filtered to collect the precipitated white solid (0.20 g, 0.12 mmol, 87%); mp 168–169 °C. (HRMS [M-2H]$^{2-}$) Found 821.2094. $C_{84}H_{70}N_6O_{30}(-2)$ requires 821.2073 IR(KBr, pellet, cm^{-1}) 3383 br, 1698 s, 1608 s, 1270 s. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.35 (s, 9H, O*H*), 8.74 (s, 3H, N*H*), 7.82 (m (AA′), 18H, *p*-OH–Ar–*H*), 7.17 (s, 3H, core-Ar–*H*), 6.80 (m (XX′), 18H, *p*-OH–Ar–*H*), 6.46 (s, 3H, N*H*), 4.70 (s, 18H, CH_2). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 165.15 (*C*O$_2$R), 162.20 (Ar*C*–OH), 154.51 (NH*C*═ONH), 140.50 (core-Ar*C*–NHR), 131.66 (*p*-OH-Ar*C*–H), 119.80 (Ar*C*–CO$_2$R), 115.35 (*p*OH–Ar*C*–H), 100.15 (core-Ar*C*–H), 63.51 (*C*H$_2$), 56.76 (C_q).

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