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Dendroid Peptide Structural Mimetics of ω-Conotoxin MVIIA based on a 2(1*H*)-Quinolinone Core

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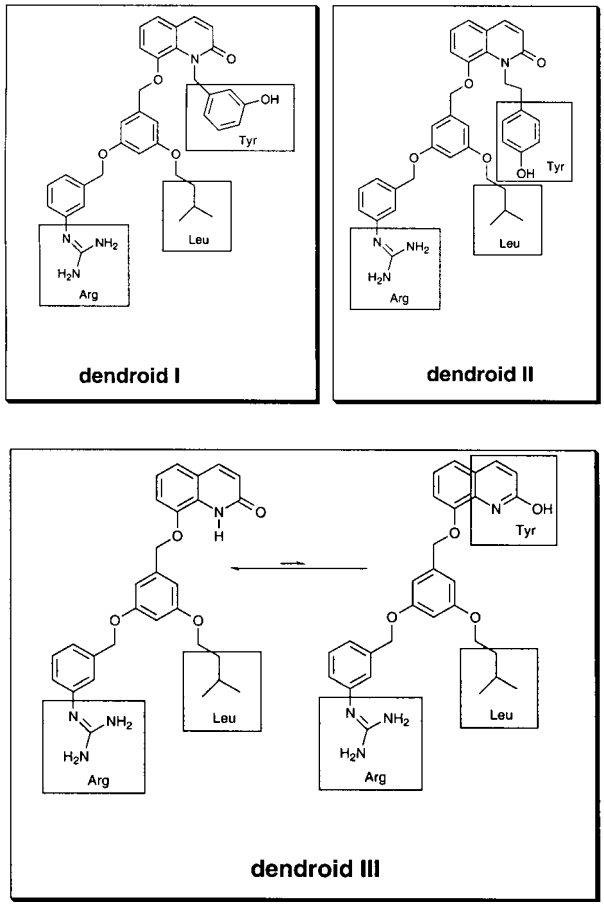
Abstract—Three mimetics of the peptide ω-Conotoxin MVIIA have been synthesised following the dendroid approach. The three key central amino acids of the natural peptide are mimicked by phenylguanidine (arginine), isopentyl (leucine) and aryl alcohol (tyrosine) attached to a quinolinone core at the 1- and 8-positions. The derivatives are designed to position these key groups in similar spatial orientation to that of the natural peptide in a structure that will have limited conformational flexibility. Key steps of the syntheses involve selective *N*-alkylation of quinolinone derivatives and guanylation of aryl amines.

Introduction

ω-Conotoxin MVIIA, which is isolated from the venom of the cone shell conus magnus,[1] is a 25 amino-acid residue containing peptide with three disulfide bonds. It is a promising new drug for the treatment of severe neuropathic pain[2] whose analgesic effect is derived from a highly selective modulation of N-type neuronal calcium ion channels.[3] The synthetic equivalent SNX-III (ziconotide) has demonstrated therapeutic benefit in animal models of traumatic brain injury, focal cerebral ischemia and pain.[4] However, total synthesis of SNX-III is time consuming and expensive, and the drug cannot be administered orally. Recent progress in the area of small molecule N-type calcium channel blockers has been reviewed.[5]

Our strategy for the synthesis of conotoxin mimetics follows the 'dendroid' approach.[6,7] This strategy involves placement of mimetics of the key residues around a central core. The overall structure has intermediate conformational freedom and allows the key groups to adopt similar spatial orientations to that found in the natural product (based on the 3D structure of ω-conotoxin MVIIA[8]).

The three key central amino acids important for SNX-III binding to ion channels are leucine, tyrosine and arginine. Based on this information, and the 3D structure, we chose dendroids **I**–**III** as synthetic targets.



Keywords: quinolinones; peptide mimetics; guanidines; calcium ion channels.

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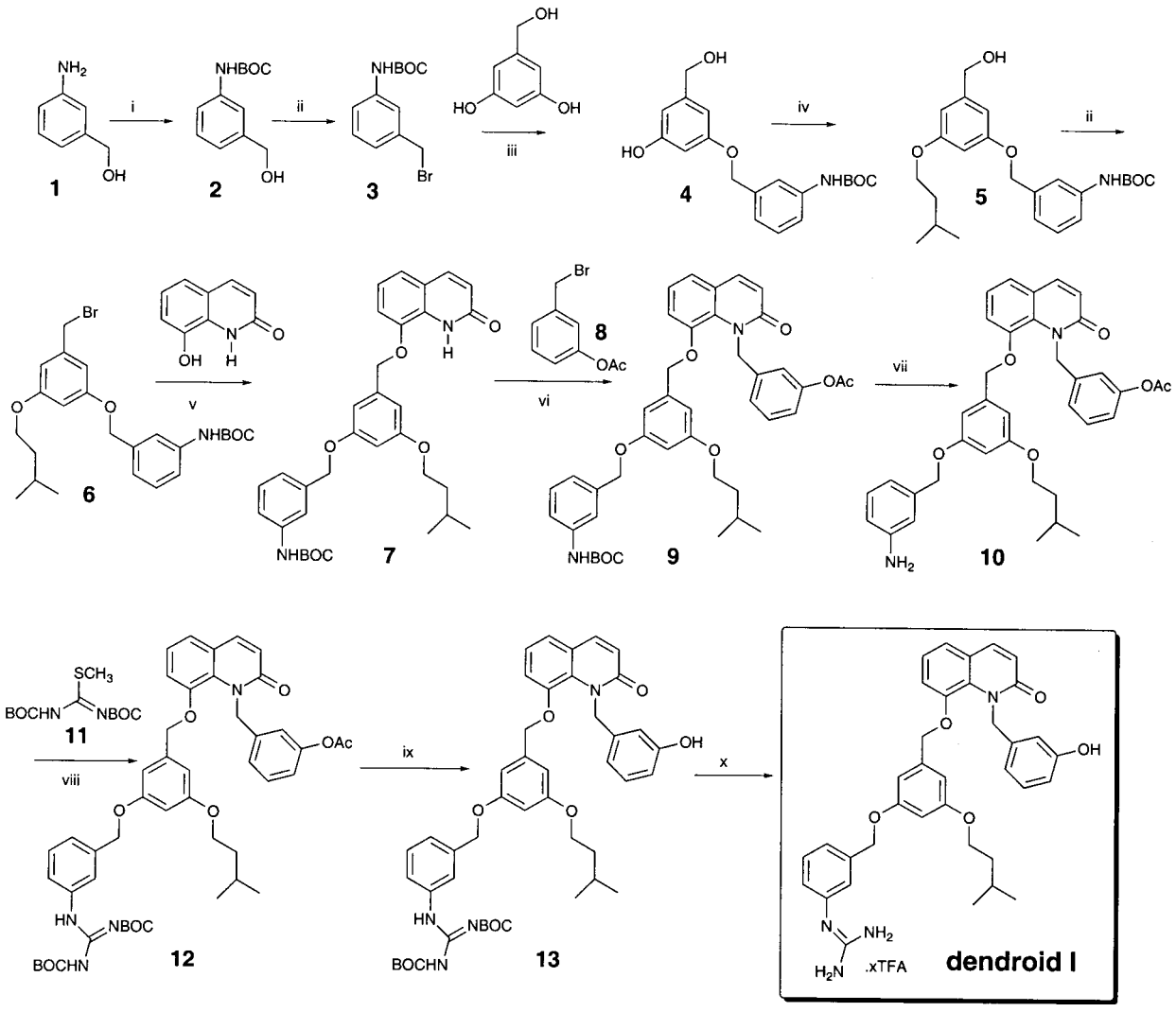


Scheme 1. Synthesis of dendroid **I**: (i) BOC_2O, THF, reflux, 4 h; (ii) CBr_4, PPh_3, CH_2Cl_2, 0°C, 1 h; (iii) K_2CO_3, acetone, reflux, 5 h; (iv) *i*-pentyl bromide, K_2CO_3, 18-crown-6, acetone, reflux, 5 h; (v) K_2CO_3, acetone, reflux, 15 h; (vi) KOH, TBAI, toluene, 50°C, 4 h; (vii) TFA, CH_2Cl_2, rt, 2 h; (viii) $HgCl_2$, Et_3N, DMF, 0°C, 3 h then rt, 2 h; (ix) K_2CO_3, MeOH, rt, 1 h; (x) TFA, CH_2Cl_2, rt, 5 h.

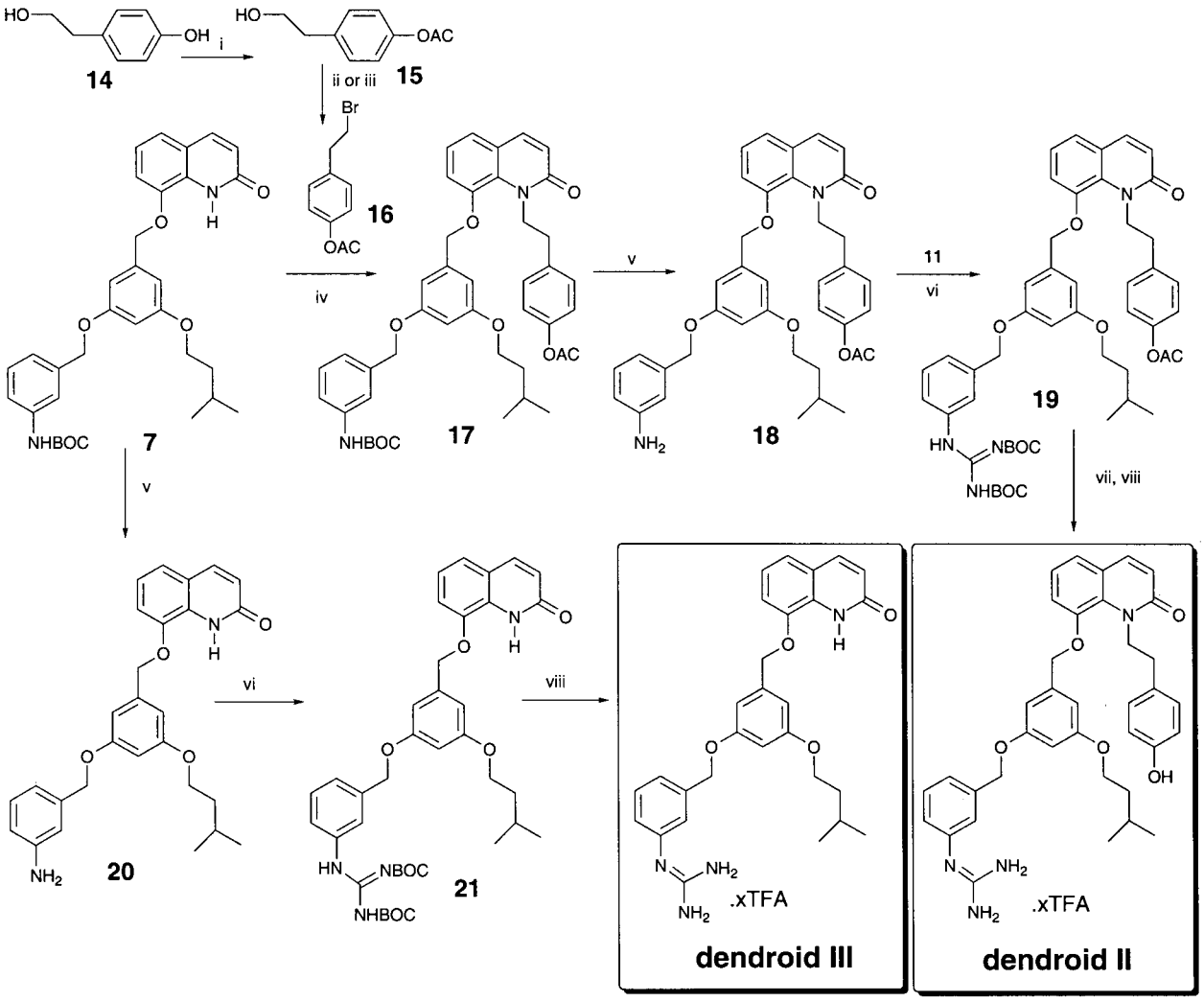
8-Hydroxy-2-(1*H*)-quinolinone was chosen as core because we anticipate that steric crowding will impede conformational freedom and give non-planar structures. Furthermore, we expected it to be straightforward to perform sequential alkylations on the 8-hydroxyl and nitrogen. In all cases arginine was mimicked by phenyl guanidine and leucine by isopentyl. In dendroids **I** and **II** tyrosine was mimicked by phenols, whereas in **III** it is mimicked by the 2-hydroxyquinoline tautomer.

Results and Discussion

Synthesis of dendroid I

The synthesis of dendroid **I** is outlined in Scheme 1. 3-Aminobenzyl alcohol was BOC-protected and brominated following literature procedures[9] to give benzyl bromide **3**. Compound **3** was treated with 4 equiv. of 3,5-dihydroxybenzyl alcohol and potassium carbonate in refluxing acetone to give the monoalkylated product **4** in 41% yield. Alkylation of the second phenolic hydroxyl group of **4** with isopentyl bromide also employed potassium carbonate in refluxing acetone but required addition of 18-C-6 catalyst to achieve a reasonable reaction rate. Bromination of benzyl alcohol **5** was best achieved using CBr_4/PPh_3 in dichloromethane to give benzyl bromide **6**. 8-Hydroxy-2-(1*H*)-quinolinone was then alkylated (on the 8-hydroxyl) with **6** by treatment with potassium carbonate in refluxing acetone to give intermediate **7** in 85% yield.

3-Hydroxybenzyl alcohol was selectively acetylated on the phenolic hydroxyl (ice cold acetic anhydride/KOH[10]) before conversion of the benzyl alcohol to the corresponding bromide (by treatment with PBr_3) to give **8** in an overall yield of 44%. Selective *N*-alkylation of **7** with 3-acetoxybenzyl bromide **8** was achieved using similar conditions to the most selective found in our model studies[11] (toluene/KOH/TBAI) to give **9** in 38% yield. The N- vs. O-selectivity ratio was determined to be 2.3:1 (by analysis of the ^{1}H NMR spectrum of the crude mixture), similar to that observed in the model studies. The low yield was due to slow reaction of the bromide **8**, leading to incomplete reaction (30% of the starting material was recovered). The BOC protecting group on **9**



Scheme 2. Syntheses of dendroids **II** and **III**: (i) KOH(aq), Ac_2O, 0°C, 45 min; (ii) PBr_3, toluene, 0°C, 1.5 h; (iii) CBr_4, PPh_3, CH_2Cl_2, 0°C, 1 h; (iv) KOH, TBAI, toluene, 50°C, 4 h; (v) TFA, CH_2Cl_2, rt, 2 h; (vi) $HgCl_2$, Et_3N, DMF, 0°C, 3 h then rt, 2 h; (vii) K_2CO_3, MeOH, rt, 1 h; (viii) TFA, CH_2Cl_2, rt, 5 h.

was removed by treatment with TFA in dichloromethane at room temperature to give the free aniline **10** in 90% yield. Guanylation of **10** with 1,3-bis-BOC-2-methyl-2-thiopseudourea **11** in the presence of mercury chloride gave bis-BOC protected guanidine **12** in 86% yield. The ^1H and ^{13}C NMR spectra imply that **12** exists essentially as a single tautomer.

The acetate protecting group on **12** was removed under mild conditions by stirring with potassium carbonate in methanol at room temperature (75%). Finally the BOC protecting groups on guanidine **13** were removed by treatment with TFA in dichloromethane to give dendroid **I** as its TFA salt (76%). Attempts to prepare the HCl salt of dendroid **I** using a literature procedure[12] (treatment of **13** with tin chloride in ethyl acetate) were unsuccessful. Treatment of **13** with 1 M HCl in ether[13] caused partial reaction to afford a mixture of starting material and products from removal of one and both BOC protecting groups. Further reaction, however, was prevented by precipitation.

Synthesis of dendroids II and III

Dendroids **II** and **III** were synthesised from intermediate **7** following similar *N*-alkylation (in the case of dendroid **II**), deprotection and guanylation procedures to those employed for the synthesis of dendroid **I**, as shown in Scheme 2.

Conclusions

Three mimetics of the peptide ω-Conotoxin MVIIA have been synthesised in which a quinolinone core is elaborated at the 1- and 8-positions to generate a dendroid structure which incorporates a phenylguanidine (arginine), isopentyl (leucine) and an aryl alcohol (tyrosine).

Experimental

Column chromatography was carried out with Merck Kieselgel 60 (70–230 mesh). NMR spectra were measured on a Varian Gemini 2000 instrument using TMS as internal standard. IR spectra were recorded on a Perkin–Elmer FTIR 1720 instrument. Routine mass spectra (EI) were performed on a Kratos MS 25 mass spectrometer. Melting points are uncorrected.

3-(3′-*N*-BOC-Aminobenzyloxy)-5-hydroxybenzyl alcohol 4. A mixture of 3,5-dihydroxybenzyl alcohol (25.78 g, 4 equiv.), 3-*N*-BOC-aminobenzyl bromide (13.16 g, 46 mmol) and potassium carbonate (12.71 g, 2 equiv.) were stirred in refluxing acetone (300 ml) for 5 h under nitrogen. After cooling to room temperature the mixture was concentrated in vacuo and the residue treated with water (400 ml) and extracted with dichloromethane (600 ml then 2×100 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated to give the crude product as an amorphous solid which was purified by column chromatography (silica, CH_2Cl_2/methanol 0–2%) to give a white solid which was recrystallised from acetone/light petroleum (6.51 g, 41%). Mp 149.3–150.8°C; CHN Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.16; H, 6.69; N, 3.96; IR (nujol) ν_{max} 3300, 1697, 1600, 1537 cm^{-1}; ^1H NMR (300 MHz, Acetone-d_6) δ_H, 1.48 (9H, s), 4.21 (1H, brs), 4.54 (2H, s), 5.02 (2H, s), 6.36–6.38 (1H, m), 6.48–6.49 (1H, m), 6.54–6.55 (1H, m), 7.07–7.09 (1H, m), 7.28 (1H, t, *J*=8 Hz), 7.50 (1H, d, *J*=8 Hz), 7.68 (1H, s), 8.29 (1H, brs), 8.44 (1H, brs); ^{13}C NMR (75 MHz, acetone-d_6) δ_C, 28.55, 64.73, 70.41, 80.13, 101.67, 105.15, 107.15, 118.19, 118.57, 122.27, 129.76, 139.39, 140.93, 146.04, 153.98, 159.49, 161.21; LRMS (EI): 245 (2%), 106 (9%), 41 (100%).

3-(3′-*N*-BOC-Aminobenzyloxy)-5-*i*-pentyloxybenzyl alcohol 5. A mixture of 3-(3′-*N*-BOC-aminobenzyloxy)-5-hydroxybenzyl alcohol **4** (9.84 g, 28.5 mmol), *i*-pentyl bromide (10.70 ml, 3 equiv.), potassium carbonate (7.87 g, 2 equiv.) and 18-crown-6 (1.51 g, 0.2 equiv.) was stirred in refluxing acetone (220 ml) for 5 h under nitrogen. After cooling to room temperature the mixture was concentrated in vacuo and the residue treated with water (100 ml) and extracted with ethyl acetate (150 ml then 2×60 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated to give the crude product as an amorphous off-white solid which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:10 to 1:3) to give **5** as white solid (10.90 g, 92%). Mp 96.9–97.7°C; CHN Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.51; H, 8.05; N, 3.27; IR (nujol) ν_{max} 3410, 3230, 1695, 1595, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.94 (6H, d, *J*=6.8 Hz), 1.51 (9H, s), 1.64 (2H, q, *J*=6.8 Hz), 1.76–1.83 (1H, m), 2.14 (1H, t, *J*=6.0 Hz), 3.94 (2H, t, *J*=6.8 Hz), 4.58 (2H, d, *J*=6.0 Hz), 4.98 (2H, s), 6.43 (1H, t, *J*=2.4 Hz), 6.51–6.52 (1H, m), 6.55–6.56 (1H, m), 6.66 (1H, brs), 7.05–7.09 (1H, m), 7.26–7.29 (2H, m), 7.44 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.39, 24.86, 28.15, 37.77, 65.10, 66.36, 69.69, 80.53, 100.89, 105.19, 105.55, 117.51, 118.05, 121.97, 129.19, 137.94, 138.64, 143.42, 152.86, 160.05, 160.52; LRMS (EI): 415 (M^+, 4%), 359 (2%), 315 (14%), 106 (100%).

3-(3′-*N*-BOC-Aminobenzyloxy)-5-*i*-pentyloxybenzyl bromide 6. Carbon tetrabromide (5.72 g, 1.5 equiv.) was added portionwise over 20 min to a stirred solution of 3-(3′-*N*-BOC-aminobenzyloxy)-5-*i*-pentyloxybenzyl alcohol **5** (4.78 g, 11.5 mmol) and triphenyl phosphine (4.52 g, 1.5 equiv.) in dry dichloromethane (80 ml) at 0°C under nitrogen. The resulting pale yellow solution was stirred at 0°C for a further 1 h and then concentrated in vacuo. The residue was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:30 to 1:15) to give **6** as white needles (4.77 g, 87%). Mp 78.7–79.9°C; CHN Calcd for $C_{24}H_{32}NO_4Br$: C, 60.25; H, 6.74; N, 2.93; Br, 16.70. Found: C, 60.53; H, 6.74; N, 2.79; Br, 16.41; IR (nujol) ν_{max} 3260, 1680, 1595, 1535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.95 (6H, d, *J*=6.6 Hz), 1.52 (9H, s), 1.65 (2H, q, *J*=6.6 Hz), 1.73–1.86 (1H, m), 3.95 (2H, t, *J*=6.6 Hz), 4.40 (2H, s), 4.99 (2H, s), 6.45 (1H, t, *J*=2.1 Hz), 6.54–6.55 (1H, m), 6.57–6.58 (2H, m), 7.07–7.10 (1H, m), 7.28–7.32 (2H, m), 7.46 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.63, 25.09, 28.39, 33.73, 37.98, 66.66, 70.05, 80.76, 101.98, 107.83, 108.19, 117.60, 118.28, 122.18, 129.48, 137.98, 138.94, 139.89, 152.98, 160.25, 160.71; LRMS (EI): 479 (M^+, 2%), 477 (M^+, 2%), 342 (2%), 298 (3%), 106 (18%), 82 (41%), 80 (41%), 41 (100%).

8-[3′-(*i*-Pentyloxy)-5′-(3″-*N*-BOC-aminobenzyloxy)benzyloxy]-2-[1*H*]-quinolinone 7. A mixture of 3-(3′-*N*-BOC-aminobenzyloxy)-5-*i*-pentyloxybenzyl bromide **6** (9.09 g, 19 mmol), 8-hydroxy-2(1*H*)-quinolinone (3.06 g, 19 mmol) and potassium carbonate (5.25 g, 2 equiv.) were stirred overnight in refluxing acetone (200 ml). After cooling to room temperature the mixture was concentrated in vacuo and the residue treated with water (300 ml) and extracted with dichloromethane (600 ml then 100 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated to give the crude product as a brown oil which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:4 to 1:1.5) to give **7** as a white solid (8.97 g, 85%). Mp 152.7–153.9°C; CHN Calcd for $C_{33}H_{38}N_2O_6$: C, 70.95; H, 6.86; N, 5.01. Found: C, 70.92; H, 6.84; N, 5.01; IR (nujol) ν_{max} 3400, 3220, 1712, 1655, 1605, 1545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.95 (6H, d, *J*=6.6 Hz), 1.50 (9H, s), 1.65 (2H, q, *J*=6.6 Hz), 1.71–1.87 (1H, m), 3.95 (2H, t, *J*=6.6 Hz), 5.01 (2H, s), 5.09 (2H, s), 6.51 (1H, t, *J*=2.2 Hz), 6.55–6.56 (1H, m), 6.59–6.60 (1H, m), 6.67 (1H, d, *J*=9.7 Hz), 6.95 (1H, s), 6.98 (1H, dd, *J*=7.8, 1.4 Hz), 7.05–7.10 (2H, m), 7.14 (1H, dd, *J*=7.8, 1.4 Hz), 7.24–7.29 (1H, m), 7.33–7.36 (1H, m), 7.47 (1H, s), 7.72 (1H, d, *J*=9.7 Hz), 9.30 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.62, 25.05, 28.38, 37.96, 66.66, 70.10, 71.11, 80.56, 101.74, 106.36, 106.86, 111.82, 117.55, 118.28, 120.07, 120.34, 121.99, 122.43, 122.77, 128.89, 129.45, 137.96, 138.11, 139.11, 140.69, 144.74, 153.11, 160.48, 160.93, 162.32; LRMS (EI): 458 (9%), 298 (22%), 161 (60%), 106 (100%).

3-Acetoxybenzyl alcohol. To a stirred solution of 3-hydroxybenzyl alcohol (3.72 g, 30 mmol) in 6.4N aqueous KOH (7 ml) at room temperature was added ice (15 g) followed by acetic anhydride (3.55 ml, 1.25 equiv.). After stirring for 45 min, water (250 ml) was added and the mixture was stirred for a further 30 min before extracting with dichloromethane (3×100 ml). The combined extracts were washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent gave a brown oil which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:6 to 1:4) to give 3-acetoxybenzyl alcohol[14] as a colourless oil (3.24 g, 65%).

3-Acetoxybenzyl bromide 8.[15] PBr_3 (1.53 ml, 0.5 equiv.)

was added dropwise to a solution of 3-acetoxybenzyl alcohol (5.4 g, 32.5 mmol) in dry toluene (75 ml) at 0°C under nitrogen. The mixture was stirred for a further 1.5 h then diluted with ethyl acetate (150 ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvents gave a crude oil which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:30) to give **8** as a colourless oil (5.07 g, 68%).

8-[3′-(*i*-Pentyloxy)-5′-(3″-*N*-BOC-aminobenzyloxy)benzyloxy]-2-[1-(3‴-acetoxybenzyl)]-quinolinone 9. To a stirred suspension of 8-[3′-(3-*i*-pentyloxy)-5′-(3″-*N*-BOC-aminobenzyloxy) benzyloxy]-2(1*H*)-quinolinone **7** (6.00 g, 10.74 mmol) and 3-acetoxybenzyl bromide (3.44 g, 1.4 equiv.) in dry toluene (80 ml) at room temperature under nitrogen was added TBAI (793 mg, 0.2 equiv.) and powdered KOH (844 mg, 1.4 equiv.). The mixture was heated at 50°C for 4 h. After cooling to room temperature the mixture was stirred over Na_2SO_4 for 10 min and then filtered through Celite. The filtrate was concentrated in vacuo to give a yellow oil which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:4 to 1:2.5) to give **9** as a white foam (2.90 g, 38%). CHN Calcd for $C_{42}H_{46}N_2O_8$. 0.27 EtOAc: C, 70.82; H, 6.64; N, 3.83. Found: C, 70.72; H, 6.68; N, 3.69; IR (nujol) ν_{max} 3240, 1760, 1717, 1650, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.95 (6H, d, J=6.6 Hz), 1.50 (9H, s), 1.65 (2H, q, J=6.6 Hz), 1.77–1.86 (1H, m), 2.19 (3H, s), 3.90 (2H, t, J=6.6 Hz), 4.79 (2H, s), 4.93 (2H, s), 5.88 (2H, s), 6.35–6.37 (2H, m), 6.46 (1H, t, J=2.2 Hz), 6.69–6.87 (5H, m), 6.96–7.24 (5H, m), 7.26–7.30 (2H, m), 7.49 (1H, s), 7.67 (1H, d, J=9.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.14, 22.63, 25.09, 28.39, 38.01, 49.40, 66.59, 69.97, 72.11, 80.65, 101.52, 105.86, 106.48, 115.51, 117.54, 118.24, 119.29, 119.51, 122.03, 122.31, 123.25, 123.44, 123.50, 129.25, 129.42, 130.76, 138.05, 138.70, 139.04, 140.27, 141.31, 147.52, 150.97, 153.01, 160.35, 160.78, 163.84, 169.59; HRMS (ES), Calcd for $C_{42}H_{47}N_2O_8$ (M^++H): 707.3332; Found: M^++H: 707.3347.

8-[3′-(3-*i*-Pentyloxy)-5′-(3″-aminobenzyloxy)benzyloxy]-2-[1-(3‴-acetoxybenzyl)]-quinolinone 10. To a stirred solution of **9** (2.84 g, 4.02 mmol) in dichloromethane (70 ml) was added, over 5 min, trifluoroacetic acid (12.06 ml, 39 equiv.). The mixture was stirred at room temperature for 2 h then concentrated in vacuo. The residue was treated with saturated aqueous $NaHCO_3$ (80 ml) and extracted with ethyl acetate (110 ml the 2×40 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated to give a pale yellow foam (2.41 g) which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:4 to 1:0.8) to give **10** as a white foam (2.20 g, 90%). CHN Calcd for $C_{37}H_{38}N_2O_6$. 0.12 EtOAc: C, 72.93; H, 6.36; N, 4.54. Found: C, 72.76; H, 6.35; N, 4.48; IR (film) ν_{max} 1757, 1650, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.95 (6H, d, J=6.6 Hz), 1.65 (2H, q, J=6.6 Hz), 1.75–1.89 (1H, m), 2.18 (3H, s), 3.71 (2H, br s), 3.90 (2H, t, J=6.6 Hz), 4.78 (2H, s), 4.89 (2H, s), 5.88 (2H, s), 6.35 (1H, m), 6.39 (1H, m), 6.47 (1H, t, J=2.2 Hz), 6.59–6.63 (1H, m), 6.68 (1H, m), 6.72–6.80 (4H, m), 6.84–6.87 (1H, m), 6.98 (1H, dd, J=8.0, 1.5 Hz), 7.05–7.16 (4H, m), 7.67 (1H, d, J=9.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.12, 22.63, 25.09, 38.01, 49.34, 66.57, 70.17, 72.12, 101.58, 105.92, 106.39, 114.03, 114.89, 115.48, 117.54, 119.29, 119.47, 122.02, 122.30, 123.22, 123.43, 123.45, 129.22, 129.73, 130.76, 138.25, 138.66, 140.26, 141.32, 147.11, 147.52, 150.96, 160.48, 160.78, 163.81, 169.54; LRMS (EI), 606 (1%, M^+), 530 (12%), 106 (100%); HRMS (ES), Calcd for $C_{37}H_{39}N_2O_6$ (M^++H): 607.2808; Found: M^++H: 607.2819.

Bis-BOC-guanidine 12. To a stirred solution of **10** (2.06 g, 3.40 mmol) and 1,3-bis-BOC-2-methyl-2-thiopseudourea **11** (1.04 g, 1.05 equiv.) in dry DMF (50 ml) at 0°C under nitrogen was added triethylamine (1.89 ml, 4 equiv.) and $HgCl_2$ (1.01 g, 1.1 equiv.). The resulting white suspension was stirred at 0°C for 3 h and then at room temperature for 2 h. The mixture was diluted with ethyl acetate (300 ml) and filtered through Celite. The filtrate was washed with water (400 ml) and the aqueous layer was extracted with ethyl acetate (2×80 ml). The combined organic extracts were filtered through Celite, washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave the crude product as a gum which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:4 to 1:2) to give **12** as a white foam (2.49 g, 86%). CHN Calcd for $C_{48}H_{56}N_4O_{10}$. 0.25 EtOAc: C, 67.57; H, 6.71; N, 6.43. Found: C, 67.22; H, 6.69; N, 6.31; IR (film) ν_{max} 1766, 1719, 1641, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.96 (6H, d, J=6.6 Hz), 1.50 (9H, s),1.54 (9H, s), 1.65 (2H, q, J=6.6 Hz), 1.78–1.87 (1H, m), 2.18 (3H, s), 3.91 (2H, t, J=6.6 Hz), 4.80 (2H, s), 4.94 (2H, s), 5.90 (2H, s), 6.36 (2H, d, J=2.2 Hz), 6.48 (1H, t, J=2.2 Hz), 6.71–6.72 (1H, m), 6.77 (1H, d, J=9.4 Hz), 6.81–6.83 (1H, m), 6.85–6.88 (1H, m), 6.98 (1H, dd, J=8.0, 1.6 Hz), 7.07 (1H, t, J=7.8 Hz), 7.14–7.19 (3H, m), 7.33 (1H, t, J=7.8 Hz), 7.59 (1H, m), 7.64–7.68 (1H, m), 7.67 (1H, d, J=9.4 Hz), 10.37 (1H, s), 11.67 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.13, 22.63, 25.08, 28.14, 28.23, 38.01, 49.43, 66.58, 69.84, 72.15, 79.82, 83.94, 101.61, 105.83, 106.44, 115.55, 119.28, 119.53, 121.12, 122.03, 122.12, 122.32, 123.22, 123.41, 123.48, 123.86, 129.26, 129.39, 130.80, 137.35, 137.93, 138.73, 140.24, 141.34, 147.52, 151.01, 153.60, 153.81, 160.34, 160.80, 163.78, 169.49; HRMS (ES), Calcd for $C_{48}H_{57}N_4O_{10}$ (M^++H): 849.4075; Found: M^++H: 849.4063.

Deacetylation of bis-BOC-guanidine 12 to give 13. Potassium carbonate (435 mg, 1.15 equiv.) was added to a solution of **12** (2.31 g, 2.72 mmol) in methanol (70 ml) at room temperature under nitrogen and stirred for a further 1 h. The mixture was concentrated in vacuo and the residue treated with water and extracted with ethyl acetate (110 ml and 2×30 ml). The combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation of the solvents gave a white foam (2.25 g) which was purified by column chromatography (silica, ethyl acetate/petroleum ether 1:3 to 1:2.5) to give **13** as white solid (1.66 g, 75%). mp 152.7–153.9°C; CHN Calcd for $C_{46}H_{54}N_4O_9$: C, 68.47; H, 6.75; N, 6.94. Found: C, 68.54; H, 6.81; N, 6.77; IR (nujol) ν_{max} 3253, 1728, 1646, 1630, 1611, 1598, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.95 (6H, d, J=6.6 Hz), 1.45 (9H, s), 1.54 (9H, s), 1.65 (2H, q, J=6.6 Hz), 1.75–1.86 (1H, m), 3.91 (2H, t, J=6.6 Hz), 4.79 (2H, s), 4.87 (2H, s), 5.87 (2H, s), 6.21 (1H, s), 6.37 (1H, m), 6.44–6.65 (5H, m), 6.94–7.15 (5H, m), 7.28 (1H, t, J=7.8 Hz), 7.45

(2H, t, J=9.3 Hz), 7.59 (1H, s), 10.34 (1H, s), 11.70 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.63, 25.08, 28.16, 38.00, 49.65, 66.64, 69.67, 71.88, 80.34, 84.06, 101.77, 105.08, 106.60, 113.27, 113.92, 115.41, 117.66, 121.59, 121.96, 122.29, 122.37, 123.14, 123.44, 124.29, 129.32, 129.43, 130.74, 136.87, 138.09, 138.71, 140.27, 140.96, 147.53, 153.61, 154.22, 157.07, 160.43, 160.68, 163.62, 163.96.

Dendroid I. A solution of **13** (200 mg) in dichloromethane (4.1 ml) was treated with trifluoroacetic acid (0.70 ml, 37 equiv.) at room temperature and the resulting pale yellow solution was stirred for a further 5 h. The solution was concentrated in vacuo and the residue purified by column chromatography (silica, dichloromethane/methanol 4–10%) to give dendroid **I** (142 mg, 76%). R_f 0.08 (CH_2Cl_2/MeOH 9:1). CHN Calcd for $C_{36}H_{38}N_4O_5$. 1.1 TFA· H_2O: C, 61.16; H, 5.52; N, 7.47; F, 8.36. Found: C, 60.99; H, 5.20; N, 7.26; F, 8.56; IR (film) ν_{max} 3362, 1683, 1650 1594 cm^{-1}; ^{1}H NMR (300 MHz, d_6-acetone) δ_H, 0.95 (6H, d, J=6.6 Hz), 1.63 (2H, q, J=6.6 Hz), 1.76–1.87 (1H, m), 3.08 (4H, br s), 3.96 (2H, t, J=6.6 Hz), 5.02 (2H, s), 5.03 (2H, s), 5.88 (2H, s), 6.48–6.53 (5H, m), 6.60–6.64 (1H, m), 6.66 (1H, d, J=9.5 Hz), 7.00 (1H, t, J=8.0 Hz), 7.10–7.20 (2H, m), 7.27–7.30 (2H, m), 7.39–7.47 (3H, m), 7.84 (1H, d, J=9.5 Hz), 7.94 (br s), 11.09 (1H, s); ^{13}C NMR (75 MHz, d_6-acetone) δ_C, 22.86, 25.75, 38.69, 49.40, 67.06, 69.76, 72.38, 102.21, 106.70, 107.31, 113.75, 114.00, 116.42, 118.02, 122.21, 123.05, 123.70, 124.02, 124.69, 125.10, 126.59, 129.92, 130.78, 131.44, 136.60, 139.84, 140.36, 140.95, 142.17, 147.96, 158.06, 158.29, 160.90, 161.47, 163.72; HRMS (ES), Calcd for $C_{36}H_{39}N_4O_5$ (M^++H): 607.2920; Found: M^++H: 607.2913.

2-(4-Acetoxyphenyl)ethanol 15. Synthesised following a similar procedure to that for 3-acetoxybenzyl alcohol to give **15** as a colourless oil (73%). CHN Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.61; H, 6.64; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H, 2.26 (3H, s), 2.34 (1H, brs), 2.78 (2H, t, J=6.6 Hz), 3.74 (2H, t, J=6.6 Hz), 6.97–7.01 (2H, m), 7.17–7.22 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.10, 38.55, 63.48, 121.72, 130.23, 136.68, 149.39, 170.14; LRMS 180 (M^+, 6%), 138 (40%), 107 (100%).

2-(4-Acetoxyphenyl)ethyl bromide 16. Colourless oil (78%). CHN Calcd for $C_{10}H_{11}O_2Br$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.46; H, 4.49; Br, 32.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H, 2.27 (3H, s), 3.14 (2H, t, J= 7.6 Hz), 3.53 (2H, t, J=7.6 Hz), 7.01–7.05 (2H, m), 7.18–7.23 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.13, 32.75, 38.78, 121.89, 129.86, 136.65, 149.82, 169.73; LRMS 244 (M^+, 6%), 242 (M^+, 6%), 202 (39%), 200 (42%), 107 (100%).

8-[3′-(3-*i*-Pentyloxy)-5′-(3″-*N*-BOC-aminobenzyloxy)-benzyloxy]-2-[1-(4‴-acetoxyphenyl)ethyl]quinolinone 17. Synthesised following a similar procedure to that for **9** to give **17** as a pale yellow foam (31%). IR (film) ν_{max} 1760, 1724, 1651, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H, 0.93 (6H, d, J=6.6 Hz), 1.50 (9H, s), 1.63 (2H, q, J= 6.6 Hz), 1.72–1.83 (1H, m), 2.28 (3H, s), 2.95–3.00 (2H, m), 3.91 (2H, t, J=6.6 Hz), 4.70–4.75 (2H, m), 4.93 (2H, s), 5.09 (2H, s), 6.55 (1H, t, J=2.2 Hz), 6.63–6.61 (2H, m), 6.71 (1H, d, J=9.5 Hz), 6.84–6.94 (5H, m), 7.00–7.03 (1H, m), 7.11–7.26 (4H, m), 7.36–7.38 (2H, m), 7.61 (1H, d, J=9.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.16, 22.59, 25.07, 28.39, 35.50, 37.90, 48.39, 66.70, 70.16, 72.40, 80.48, 102.05, 106.64, 107.53, 114.84, 117.62, 118.29, 121.40, 121.99, 122.20, 122.47, 122.86, 123.41, 129.40, 130.03, 130.74, 137.16, 137.72, 138.16, 139.19, 139.77, 147.43, 149.16, 153.07, 160.71, 161.06, 163.72, 170.02; HRMS (CI), Calcd for $C_{43}H_{48}N_2O_8$ (M^++H): 721.348; Found: M^++H: 721.3481.

8-[3′-(3-*i*-Pentyloxy)-5′-(3″-aminobenzyloxy)benzyloxy]-2-[1-(4‴-acetoxyphenyl)ethyl]-quinolinone 18. Synthesised following a similar procedure to that for **10** to give **18** as a pale yellow foam (84%). IR (film) ν_{max} 3456, 3356, 1757, 1654, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H, 0.92 (6H, d, J=6.6 Hz), 1.62 (2H, q, J=6.6 Hz), 1.72–1.83 (1H, m), 2.25 (3H, s), 2.95–3.00 (2H, m), 3.60 (2H, brs), 3.90 (2H, t, J=6.6 Hz), 4.70–4.75 (2H, m), 4.89 (2H, s), 5.07 (2H, s), 6.54–6.73 (7H, m), 6.83–6.95 (4H, m), 7.06–7.16 (4H, m), 7.59 (1H, d, J=9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.14, 22.57, 25.04, 35.47, 37.88, 48.33, 66.64, 70.27, 72.34, 101.96, 106.79, 107.27, 114.02, 114.80, 114.88, 117.42, 121.40, 122.15, 122.43, 122.82, 123.37, 129.67, 130.02, 130.71, 137.14, 138.01, 138.13, 139.75, 147.19, 147.39, 149.17, 160.77, 161.04, 163.66, 169.84; HRMS (CI), Calcd for $C_{38}H_{40}N_2O_6$ (M^++H): 621.2964; Found: M^++H: 621.2960.

Bis-BOC-guanidine 19. Synthesised following a similar procedure to that for **12** to give **19** as a white foam (83%). IR (film) ν_{max} 1762, 1720, 1642, 1596 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H, 0.93 (6H, d, J=6.6 Hz), 1.51 (9H, s), 1.53 (9H, s), 1.63 (2H, q, J=6.6 Hz), 1.75–1.82 (1H, m), 2.26 (3H, s), 2.99–3.04 (2H, m), 3.91 (2H, t, J=6.6 Hz), 4.75–4.80 (2H, m), 4.97 (2H, s), 5.11 (2H, s), 6.55 (1H, t, J=2.2 Hz), 6.60 (1H, m), 6.62–6.63 (1H, m), 6.71 (1H, d, J=9.5 Hz), 6.85–6.89 (2H, m), 6.96–6.99 (2H, m), 7.11–7.18 (4H, m), 7.31 (1H, t, J=8.0 Hz), 7.55 (1H, brs), 7.62 (1H, d, J=9.5 Hz), 7.64–7.67 (1H, m), 10.35 (1H, s), 11.66 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 21.15, 22.60, 25.06, 28.19, 35.45, 37.93, 48.30, 66.68, 69.94, 72.41, 101.95, 106.76, 107.12, 115.02, 121.05, 121.43, 122.16, 122.22, 122.49, 122.84, 123.43, 123.85, 129.42, 129.99, 130.80, 137.09, 137.34, 137.78, 138.27, 139.74, 147.43, 149.21, 153.59, 153.80, 160.62, 161.10, 163.70, 163.82, 169.77; HRMS (ES), Calcd for $C_{49}H_{58}N_4O_{10}$ (M^++H): 863.4231; Found: M^++H: 863.4226.

Deacetylation of bis-BOC-guanidine 19 to give 19a. The acetate protecting group was removed from **19** following an identical procedure to that for **12** to give **19a** as a white foam (84%). IR (film) ν_{max} 3263, 1721, 1646, 1612, 1596, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H, 0.93 (6H, d, J=6.6 Hz), 1.47 (9H, s), 1.54 (9H, s), 1.64 (2H, q, J=6.6 Hz), 1.74–1.85 (1H, m), 2.90–2.95 (2H, m), 3.94 (2H, t, J=6.6 Hz), 4.73 (2H, s), 4.81–4.87 (2H, m), 5.12 (2H, s), 6.55–6.56 (1H, m), 6.59–6.61 (2H, m), 6.65–6.68 (2H, m), 6.73 (1H, d, J=9.5 Hz), 6.81–6.84 (2H, m), 7.09–7.11 (1H, m), 7.15–7.22 (3H, m), 7.29 (1H, t, J=7.8 Hz), 7.44–7.47 (1H, m), 7.59–7.60 (1H, m), 7.62 (1H, d, J=9.5 Hz), 10.34 (1H, s), 11.71 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.61, 25.09, 28.17, 35.10, 37.96, 48.36, 66.69, 69.67, 72.66, 80.20, 84.07, 102.27, 106.34, 107.70, 115.19, 115.64, 122.06, 122.17, 122.53, 122.72,

122.97, 123.60, 124.45, 129.38, 129.78, 130.05, 130.75, 136.84, 138.00, 138.11, 139.88, 147.60, 153.57, 154.48, 155.48, 160.71, 160.92, 163.68, 163.91; HRMS (ES), Calcd for $C_{47}H_{57}N_4O_9$ (M^++H): 821.4125; Found: M^++H: 821.4133.

Dendroid II. Synthesised following a similar procedure to that for dendroid **I** to give dendroid **II** as a white foam (75%). **CHN** Calcd for $C_{37}H_{40}N_4O_5$ 1.1 TFA· 1.3 H_2O: C, 61.18; H, 5.72; N, 7.28; F, 8.15. Found: C, 60.89; H, 5.50; N, 6.98; F, 7.97 IR (film) ν_{max} 3346, 1685, 1649, 1595 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ_H, 0.92 (6H, d, J=6.6 Hz), 1.63 (2H, q, J=6.6 Hz), 1.73–1.87 (1H, m), 2.82–2.88 (2H, m), 3.10 (brs), 4.00 (2H, t, J=6.6 Hz), 4.67–4.73 (2H, m), 5.01 (2H, s), 5.26 (2H, s), 6.59–6.66 (4H, m), 6.74–6.82 (4H, m), 7.20 (1H, t, J=8.0 Hz), 7.27–7.44 (6H, m), 7.79 (1H, d, J=9.6 Hz), 7.95 (brs), 11.08 (1H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ_C, 22.84, 25.77, 35.88, 38.65, 48.89, 67.17, 69.94, 72.81, 102.60, 107.89, 108.52, 115.92, 122.41, 123.07, 123.48, 123.97, 124.83, 125.19, 126.70, 130.42, 130.73, 130.76, 131.34, 136.60, 139.46 140.23, 140.48, 147.98, 156.58, 158.07, 161.20, 161.67, 163.56; HRMS (ES), Calcd for $C_{37}H_{40}N_4O_5$ (M^++H): 621.3077; Found: M^++H: 621.3073.

8-[3′-(3-*i*-Pentyloxy)-5′-(3″-aminobenzyloxy)benzyloxy]-2-[1*H*]quinolinone 20. Synthesised following a similar procedure to that for **10** to give **20** as a white foam (87%). IR (film) ν_{max} 3353, 1660, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.94 (6H, d, J=6.6 Hz), 1.65 (2H, q, J=6.6 Hz), 1.75–1.87 (1H, m), 3.60 (2H, brs), 3.95 (2H, t, J=6.6 Hz), 4.94 (2H, s), 5.08 (2H, s), 6.52 (1H, t, J=2.2 Hz), 6.56–6.61 (3H, m), 6.65 (1H, d, J=9.6 Hz), 6.74–6.78 (2H, m), 6.96–6.99 (1H, m), 7.07 (1H, t, J=7.8 Hz), 7.11–7.15 (2H, m), 7.70 (1H, d, J=9.6 Hz), 9.34 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.63, 25.12, 38.02, 66.73, 70.38, 71.20, 101.90, 106.51, 106.87, 111.83, 114.15, 114.95, 117.63, 120.08, 120.37, 122.37, 122.83, 129.00, 129.74, 138.15, 138.26, 140.63, 144.81, 147.10, 160.70, 160.99, 162.28; HRMS (CI), Calcd for $C_{28}H_{30}N_2O_4$ (M^++H): 459.2284; Found: M^++H: 459.2273.

Bis-BOC-guanidine 21. Synthesised following a similar procedure to that for **12** to give **21** as a white foam (54%). IR (film) ν_{max} 1719, 1651, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H, 0.95 (6H, d, J=6.6 Hz), 1.52 (18H, s), 1.66 (2H, q, J=6.6 Hz), 1.78–1.86 (1H, m), 3.97 (2H, t, J=6.6 Hz), 5.04 (2H, s), 5.11 (2H, s), 6.53 (1H, t, J=2.2 Hz), 6.58–6.61 (2H, m), 6.66 (1H, d, J=9.6 Hz), 6.98–7.01 (1H, m), 7.08 (1H, t, J=7.7 Hz), 7.13–7.18 (2H, m), 7.33 (1H, t, J=7.7 Hz), 7.58 (1H, brs), 6.66–6.69 (1H, m), 7.72 (1H, d, J=9.6 Hz), 9.30 (1H, s), 10.36 (1H, s), 11.66 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, 22.59, 25.00, 28.12, 37.92, 66.54, 69.83, 71.03, 79.64, 83.75, 101.60, 106.29, 106.68, 111.52, 119.84, 120.11, 120.88, 121.94, 122.17, 122.57, 123.68, 128.66, 129.20, 137.10, 137.59, 137.86, 140.41, 144.51, 153.31, 153.53, 160.16, 160.68, 161.97, 163.45; HRMS (ES), Calcd for $C_{39}H_{48}N_4O_8$ (M^++H): 701.3550; Found: M^++H: 701.3557.

Dendroid III. Synthesised following a similar procedure to that for dendroid **I** to give dendroid **III** as a white foam (76%). CHN Calcd for $C_{29}H_{32}N_4O_4$. 1.3 TFA. 0.7 H_2O: C, 57.38; H, 5.29; N, 8.47. Found: C, 57.54; H, 4.98; N, 8.09; IR (film) ν_{max} 3356, 3183, 1657, 1604 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone) δ_H, 0.93 (6H, d, J=6.6 Hz), 1.62 (2H, q, J=6.6 Hz), 1.75–1.85 (1H, m), 3.16 (4H, s), 3.99 (2H, t, J=6.6 Hz), 5.13 (2H, s), 5.25 (2H, s), 6.54 (1H, t, J=2.2 Hz), 6.58 (1H, d, J=9.6 Hz), 6.72 (1H, m), 6.83 (1H, m), 7.12 (1H, t, J=7.8 Hz), 7.20–7.27 (3H, m), 7.32–7.43 (3H, m), 7.88 (1H, d, J=9.6 Hz), 7.98 (brs), 10.26 (1H, brs), 11.03 (1H, s); ^{13}C NMR (75 MHz, d_6-acetone) δ_C, 22.84, 25.75, 38.69, 67.08, 69.81, 71.32, 102.10, 107.19, 107.74, 113.26, 120.81, 121.13, 123.05, 124.58, 125.10, 126.45, 129.88, 130.73, 136.69, 139.80, 140.38, 141.58, 145.51, 158.07, 160.91, 161.42, 162.82; HRMS (CI), Calcd for $C_{29}H_{32}N_4O_4$ (M^++H): 501.2502; Found: M^++H: 501.2492.

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References

1. (a) Olivera, B. M.; Gray, W. R.; Zeikus, R.; McIntosh, J. M.; Varga, J.; Rivier, J.; de Santos, V.; Cruz, L. J. *Science* **1985**, *230*, 1338. (b) Olivera, B. M.; Rivier, J.; Scott, J. K.; Hillyard, D. R.; Cruz, L. J. *J. Biol. Chem.* **1991**, *266*, 22067.
2. Malmberg, A. B.; Yaksh, T. L. *Pain* **1995**, *60*, 83.
3. Olivera, B. M.; Cruz, U.; de Santos, V.; LeCheminant, G. W.; Griffin, D.; Zeikus, R.; McIntosh, J. M.; Galyean, R.; Varga, J.; Gray, W. R.; Rivier, J. *Biochemistry* **1987**, *26*, 2086.
4. (a) Miljanich, G. P.; Ramachandran, J. *Ann. Rev. Pharmacol. Toxicol.* **1995**, *35*, 704. (b) Olivera, B. M.; Miljanich, G. P.; Ramachandran, J.; Adam, M. E. *Ann. Rev. Biochem.* **1994**, *63*, 823. (c) Pringle, A. K.; Benham, C. D.; Sim, L.; Kennedy, S. J.; Iannotti, F.; Sundstrom, L. E. *Stroke* **1996**, *27*, 2124. (d) Bowersox, S. S.; Gadbois, T.; Singh, T.; Pettus, M.; Wang, Y.; Luther, R. R. *Pharmacol. Exp. Ther.* **1996**, *279*, 1243. (e) Bowersox, S. S.; Singh, T.; Luther, R. R. *Brain Res.* **1997**, *747*, 343.
5. Cox, B.; Denyer, J. C. *Exp. Opin. Ther. Patents* **1998**, *8*, 1237.
6. Allen, J. V.; Horwell, D. C.; Lainton, J. A. H.; O'Neill, J. A.; Ratcliffe, G. S. *Chem. Commun.* **1997**, 2121.
7. Menzler, S.; Bikker, J. A.; Horwell, D. C. *Tetrahedron Lett.* **1998**, *39*, 7619.
8. Kohno, T.; Kim, J. I.; Kobayashi, K.; Kodera, Y.; Maeda, T.; Sato, K. *Biochemistry* **1995**, *34*, 10256.
9. Brown, F. J.; Bernstein, P. R.; Cronk, L. A.; Dosset, D. L.; Hebbel, K. C.; Maduskuie, T. P.; Shapiro, H. S.; Vacek, E. P.; Yee, Y. K.; Willard, A. K.; Krell, R. D.; Snyder, D. W. *J. Med. Chem.* **1989**, *32*, 807.
10. Quick, J.; Crelling, J. K. *J. Org. Chem.* **1978**, *43*, 155.
11. Guo, Z. X.; Cammidge, A. N.; McKillop, A.; Horwell, D. C. *Tetrahedron Lett.* **1999**, *40*, 6999.
12. Miel, H.; Rault, S. *Tetrahedron Lett.* **1997**, *38*, 7865.
13. Lammin, S. G.; Pedgrift, B. L.; Radcliffe, A. J. *Tetrahedron Lett.* **1996**, *37*, 6815.
14. Borbaruah, M.; Barua, N. C.; Sharma, R. P. *Tetrahedron Lett.* **1987**, *28*, 5741.
15. Schmidt, U.; Lieberknecht, A.; Griesser, H.; Talbiersky, J. *J. Org. Chem.* **1982**, *47*, 3261.