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Research paper

Anti-HIV-1 activity of a tripodal receptor that recognizes mannose oligomers

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ABSTRACT

The glycoprotein gp120 of the HIV-1 viral envelope has a high content in mannose residues, particularly α-1,2-mannose oligomers. Compounds that interact with these high-mannose type glycans may disturb the interaction between gp120 and its (co)receptors and are considered potential anti-HIV agents. Previously, we demonstrated that a tripodal receptor (**1**), with a central scaffold of 1,3,5-triethylbenzene substituted with three 2,3,4-trihydroxybenzoyl groups, selectively recognizes α-1,2-mannose polysaccharides. Here we present additional studies to determine the anti-HIV-1 activity and the mechanism of antiviral activity of this compound. Our studies indicate that **1** shows anti-HIV-1 activity in the low micromolar range and has pronounced gp120 binding and HIV-1 integrase inhibitory capacity. However, gp120 binding rather than integrase inhibition seems to be the primary mechanism of antiviral activity of **1**.

1. Introduction

Highly active antiretroviral therapy (HAART) has significantly contributed to reduce the morbidity and mortality caused by human inmunodeficiency virus (HIV), the retrovirus responsible for the transmission and development of AIDS [1]. However, issues such as long-term toxicities, adverse drug–drug interactions, and the emergence and transmission of drug-resistant viral strains represent a serious problem to a successful long-term treatment [2]. There is, therefore, a need to develop novel therapeutic approaches and drugs for the efficient treatment of HIV-1 [3].

HIV is an enveloped virus that contains the glycoproteins gp120 and gp41 on its surface. These envelope glycoproteins interact with the CD4 receptor on the T cell surface. Glycoprotein gp120 is of particular importance during viral fusion and entry, as it serves as the first point of contact with the host cell. This glycoprotein is the main target for neutralizing antibodies that appear during natural infection [4]. The HIV gp120 glycoprotein is extensively glycosylated, so that approximately 50% of its molecular weight is due to a dense carbohydrate array. Interestingly gp120 carbohydrates contain an unusually high amount of mannose residues, in particular α-1,2-mannose, α-1,3-mannose and α-1,6-mannose oligomers [5].

A number of plant lectins, in particular those with specificity for mannose oligomers, display potent inhibitory activity against

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several viruses, including HIV [5]. These plant lectins exert their antiviral action by strongly binding to the carbohydrates of gp120, thereby compromising the required conformational changes in gp120/gp41 for optimal interaction with the (co)-receptors and fusion with the target cell membrane. However, the macromolecular and peptidic nature of these plant lectins precludes their use as anti-HIV agents due to the lack of the appropriate pharmacokinetic properties. Based on the anti HIV activity of these plant lectins a novel therapeutic concept to fight against HIV infection has been proposed [5]. According to this proposal agents that interact with the high-mannose type glycans of the HIV-1 gp120 may disturb the interaction between gp120 and its (co)receptors and, as consecuence, show anti-HIV activity.

Very recently [6] our group described the synthesis of two tripodal receptors, **1** and **2,** with a triethylbenzene central scaffold substituted respectively with three 2,3,4-trihydroxybenzoyl or its isomeric 3,4,5-trihydroxybenzoyl (galloyl) moieties (Fig. 1). Molecular Modeling and NMR studies showed that only compound **1** has a unique conformation that facilitates the recognition of $\alpha(1 \rightarrow 2)$-linked mannose polysaccharides that mimic the mannose composition of the glycans that are abundantly present on the HIV envelope glycoprotein gp120.

In this work compound **1** and similar structural analogues have been synthesized and tested against HIV in cell culture. Also the mechanism of antiviral activity of this class of agents have been investigated.

2. Results and discussion

2.1. Chemical results

To investigate the importance of the number and position of the phenolic OHs, compounds **5** and **7** with two contiguous and non-contiguous OHs respectively, were prepared (Scheme 1). These compounds were synthesized by reaction of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**3**) [7], with the respective OMe or OBn-protected dihydroxybenzoic acids. Reactions were performed in the presence of PyBOP/triethylamine or HATU/DIPEA as coupling reagents. These reactions allowed the synthesis of the OMe (**4**) or OBn (**6**) protected derivatives in good yields (57% and 80% respectively). Removal of the methyl groups in **4**, using boron tribromide gave **5** (70%) [8]. On the other hand, hydrogenolysis of **6** (H_2, 10% Pd/C) gave the corresponding phenol deprotected derivative **7** (45%)**.**

Compound **9**, bearing three dihydroxyphenylethyl moieties, as in hydroxytyrosol, a well-known polyphenol of natural origin [9], was also prepared (Scheme 1). For the synthesis of this compound the OBn protected derivative of caffeic acid [10] was used. Reaction of this compound with trisamine **3** in the presence of HATU/DIPEA afforded compound **8** in 93% yield that after simultaneous deprotection and reduction of the unsaturated double bond by catalytic hydrogenation afforded compound **9** in 48% in yield.

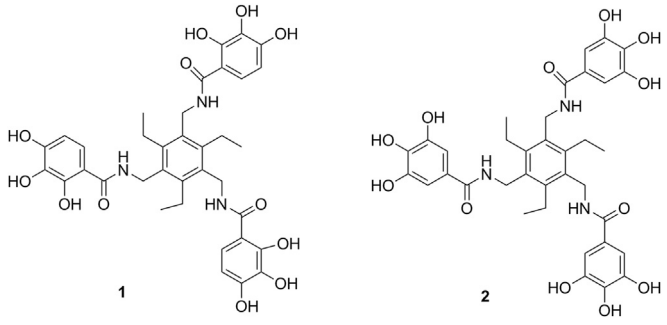


Fig. 1. Structure of **1** and **2.**

Next, compound **11,** with three non-contiguous OHs, was prepared by reaction of **3** [7] with the corresponding benzyl protected 2,4,6-trihydroxybenzoic acid [11] in the presence of HATU/DIPEA, followed by hydrogenolysis of the corresponding benzyl protected compound **10** (Scheme 2).

Shikimic acid and its corresponding fully saturated cyclohexyl derivative were also incorporated to the central scaffold (Scheme 3). The shikimic acid derivative **12** was prepared in 76% yield by treatment of the trisamine **3** [7] with the commercially available shikimic acid in the presence of HATU/DIPEA. Catalytic hydrogenation of **12** rendered the fully saturated derivative **13** in 45% yield.

Next, compounds **20, 22** and **24** with the three phenolic groups connected to the central scaffold by spacers of different lengths were prepared. With this purpose compounds **15**, **16** and **17** (Scheme 4) were firstly synthesized. These compounds were prepared in excellent yields (94%, 89% and 99% respectively) by reaction of 2,3,4-tribenzyloxybenzoic acid (**14**) [12] with excess of ethylenediamine, tetramethylene diamine or piperazine in the presence of PyBOP and trietylamine.

Treatment of **15**–**17** with the 1,3,5-tris(bromomethyl)-2,4,6-trietylbenzene intermediate **18** [7] in the presence of triethylamine afforded **19** (57%), **21** (46%) and **23** (75%) (Scheme 5). Hydrogenolysis of **19**, **21** and **23** in the presence of 10% Pd/C gave the corresponding phenol-deprotected derivatives **20** (96%)**, 22** (27%) and **24** (50%).

Next, aminopyridine, as carbohydrate recognition moiety [13], aniline and pyrrole, were incorporated as substituents of the triethylbenzene scaffold. The corresponding compounds **25** (82%), **26** (21%) and **27** (54%) [14] were prepared in good to moderate yields by coupling of **3** [7], with the corresponding carboxylic acid in the presence of PyBOP/Et_3N (Scheme 6).

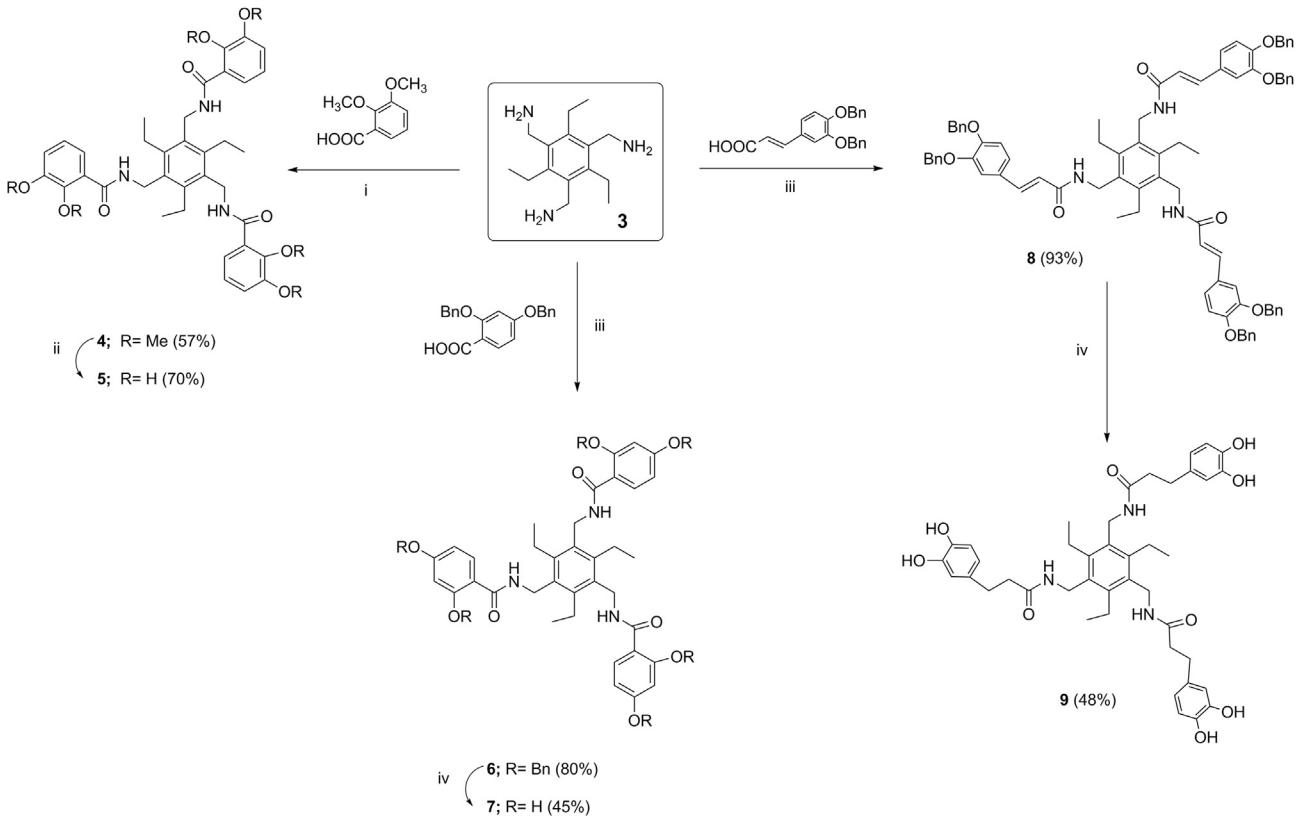
Next, we prepared compound **31** with six phenolic entities around the central scaffold (Scheme 7). In this case the disubstituted amine **28** was used as starting compound and *cis,cis*-1,3,5-ciclohexane carboxylic acid (**29**) as central core. The disubstituted amine **28** was prepared by reaction of **3** [7] with two equivalents of **14** [12]. Starting from **28** and following the coupling/deprotection procedure, compound **30** (92%) and its corresponding deprotected derivative **31** (57%) were obtained.

Finally, and in order to perform SPR experiments, compound **35,** an analogue of **1** containing a linker (**32**) with a terminal amino (NH_2) group suitable for its covalent attachment to the SPR sensorchip, was synthesized (Scheme 8). Linker **32** was prepared, from commercially available 4,7,10-trioxa-1,13-tridecanediamine by reaction with succinic anhydride and subsequent amine protection with Fmoc *N*-hydroxysuccinimide ester (Fmoc-OSu) [15]. Reaction of the disubstituted derivative **28** with linker **32** [15], in the presence of PyBOP and trimethylamine, gave compound **33** (95%). Subsequent removal of the Fmoc protecting group using 20% of piperidine in DMF at room temperature gave compound **34** in 77% yield that after removal of OBn afforded **35** in 89% yield.

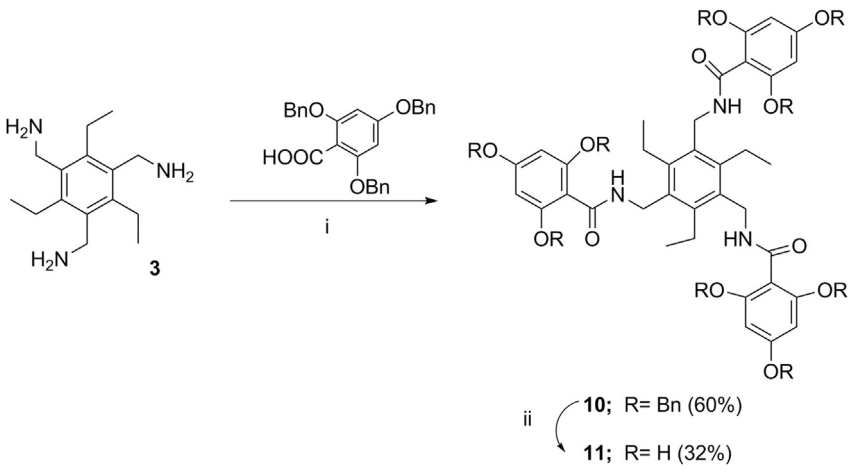
2.2. Antiviral activity

The compounds synthesized were evaluated as potential inhibitors of the replication of human immunodeficiency virus (HIV-1 and HIV-2) in human CD_4^+ T-lymphocyte CEM cell cultures and the results are given in Table 1.

As reference, Pradimicin-A (PRM-A), a non-peptidic antibiotic of natural origin that shows anti-HIV activity by binding to the high-mannose type glycans of the HIV-1 gp120, was included.



Scheme 1. Synthesis of compounds **5, 7** and **9**. *Reagents and conditions:* (i) pyBOP, Et_3N (ii) BBr_3, CH_2Cl_2 (iii) HATU, DIPEA (iv) H_2, Pd/C.



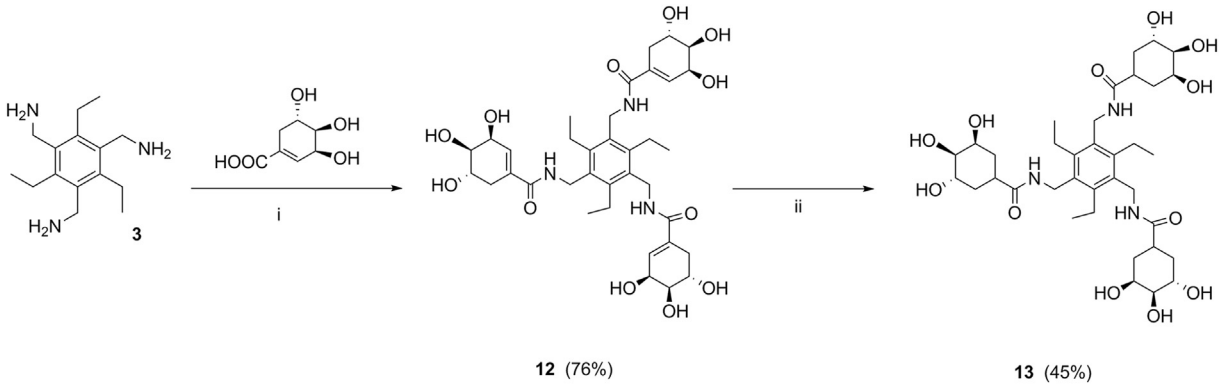
Scheme 2. Synthesis of compound **11**. *Reagents and conditions:* (i) HATU, DIPEA (ii) H_2, Pd/C.

As shown in Table 1, the conformationally-constrained tripodal receptor **1**, is the only compound able to inhibit the replication of HIV-1 with a clear safety profile. This result highlights the importance of the unique structural features present in **1** (three 2,3,4-trihydroxybenzoyl groups directly attached to a trietylbenzene scaffold through amide linkers) for anti-HIV activity.

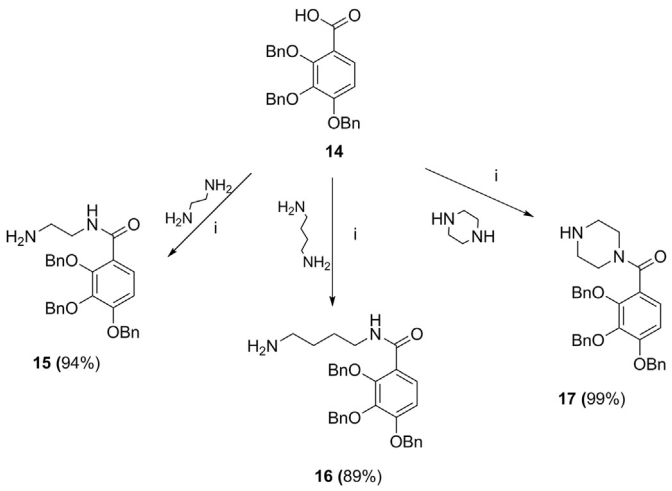
It should be emphasized that the activity showed by **1** (6.3 ± 1.0 μM), in the low micromolar range, is very similar to that of Pradimicin A (3.4 ± 1.3 μM). However, Pradimicin A is a structurally complex molecule difficult to synthesize and obtained by fermentation. By contrast, **1** is a molecule that is easy to prepare by conventional synthetic procedures.

2.3. SPR experiments

Surface Plasmon Resonance (SPR) was used to study in real time the interactions of **1** with the mannose oligomers of the glycoprotein gp120. First, the glycoprotein gp120 was attached to the sensorchip surface ("direct experiment"). As shown in Fig. 2, a remarkable binding signal was observed for **1**. The binding amplitude was comparable or even somewhat stronger than that of the reference compound, Pradimicin-S (PRM-S), a soluble derivative of PRM-A (Fig. 2). The remarkable binding signal suggests that there are pronounced interactions between **1** and the gp120 glycoprotein. Moreover, whereas the on-rate (association of **1** to gp120) is in



Scheme 3. Synthesis of compounds **12** and **13**. *Reagents and conditions:* (i) HATU, DIPEA (ii) H_2, Pd/C.



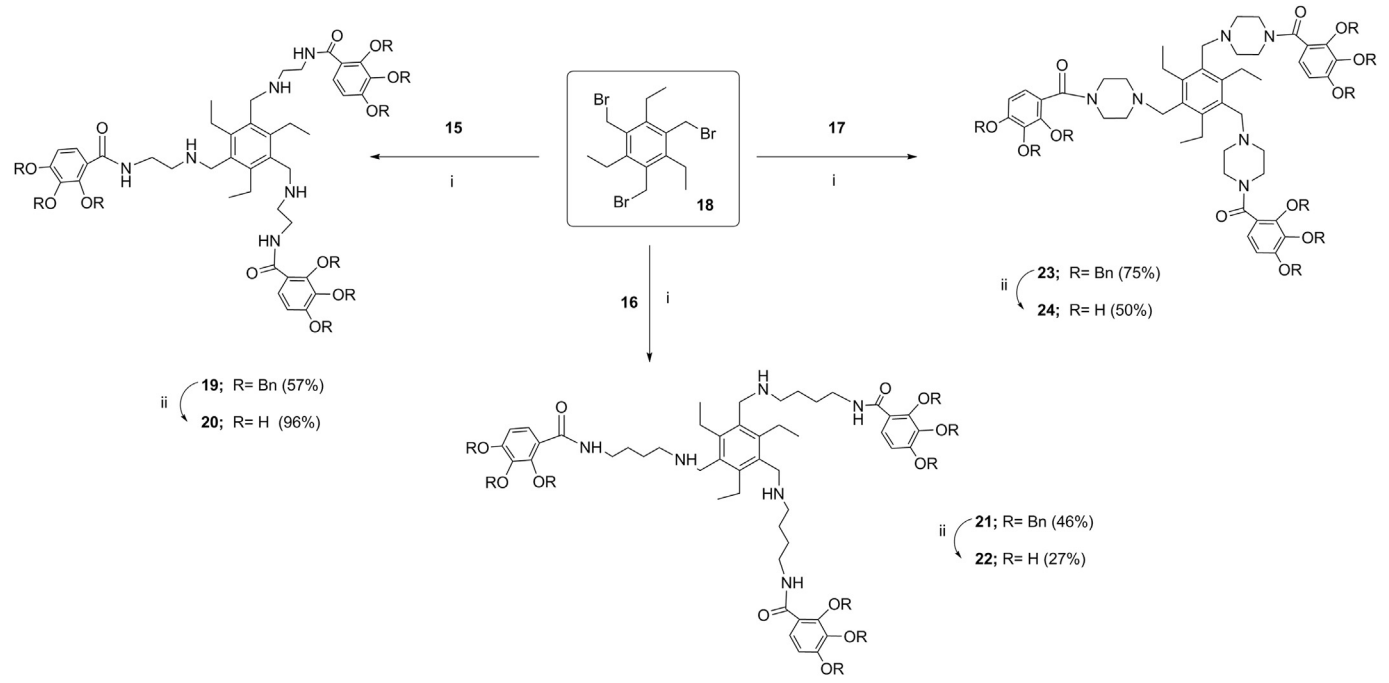
Scheme 4. Synthesis of compounds **15**–**17**. *Reagents and conditions:* (i) pyBOP, Et_3N.

the same order of magnitude as Pradimicin-S, the off-rate (dissociation of **1** from gp120) proved much slower.

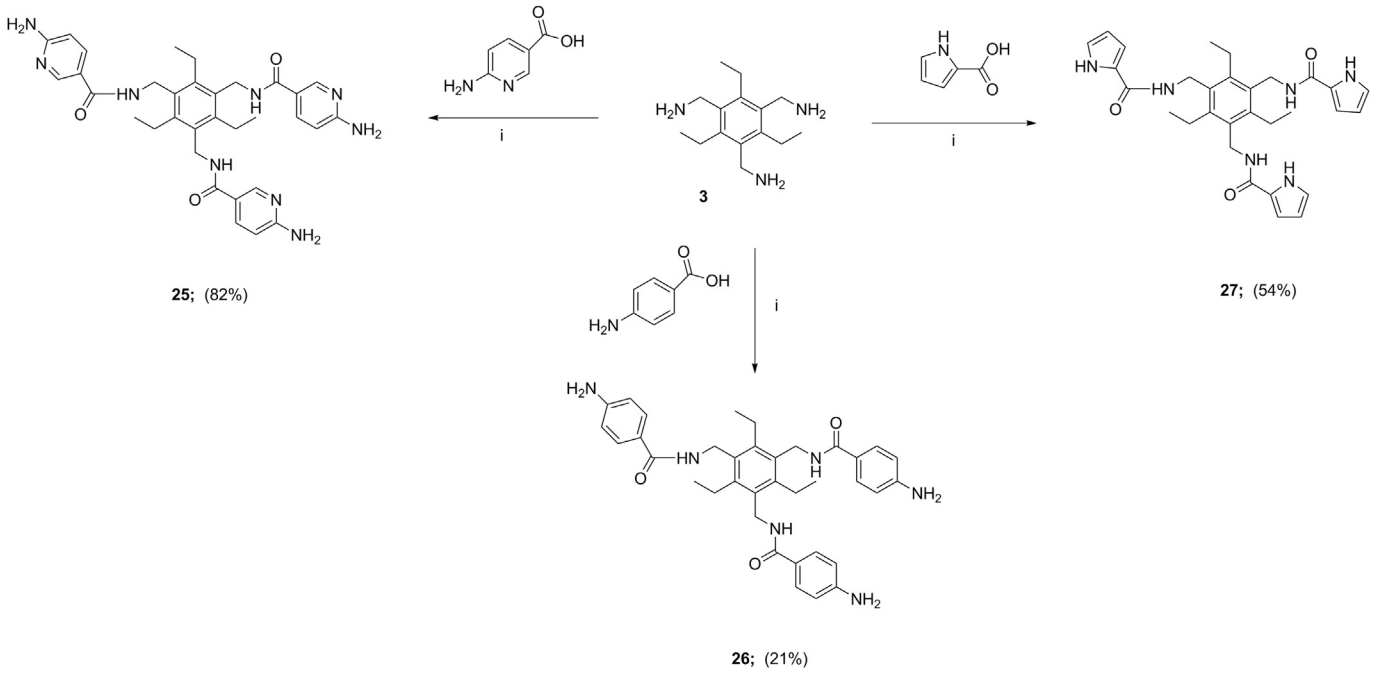
In a reverse experiment, compound **35,** the analogue of **1** containing a linker with a terminal amino (NH_2) group suitable for its covalent attachment to the SPR sensorchip, was attached to the SPR sensorchip surface through the terminal amino group of its flexible linker and glycoprotein gp120 was then injected (Fig. 3).

As in the direct binding experiment, where gp120 was bound to the sensorchip, it was observed that the off-rate (dissociation) was quite slow compared with the on-rate.

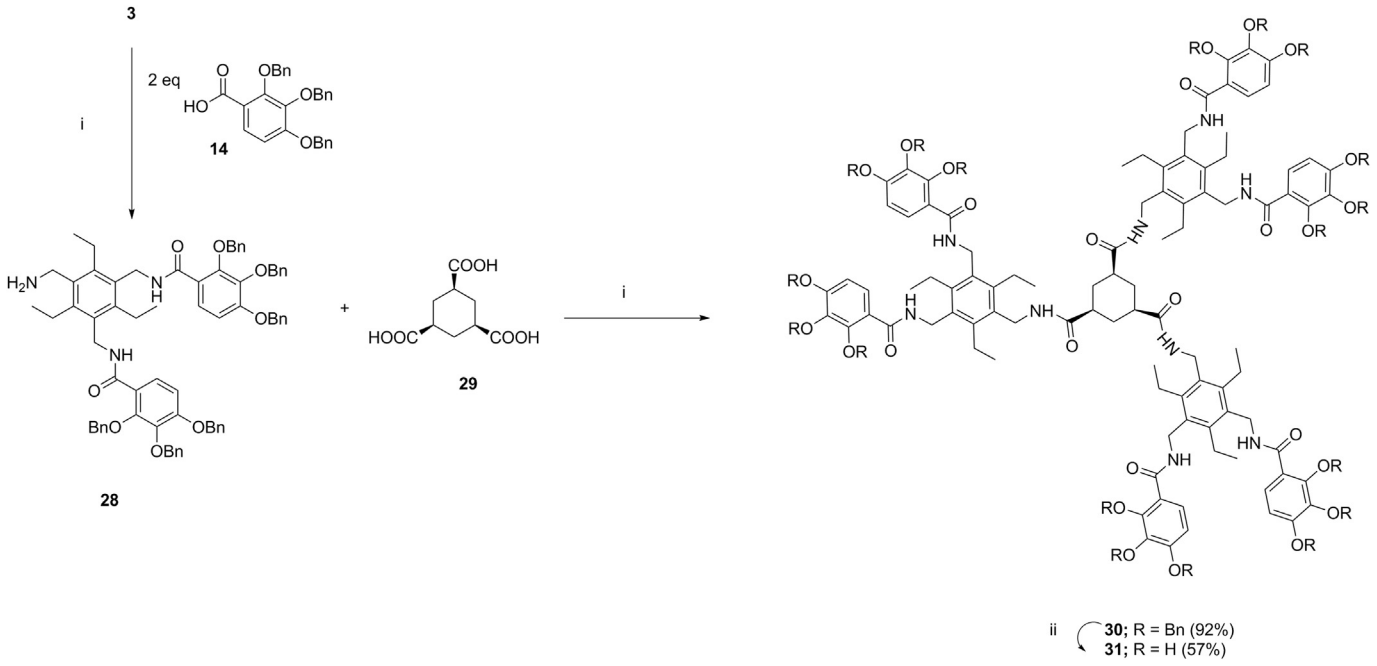
In addition bovine serum albumin (BSA), (as negative non-glycosylated protein control) was injected across the sensorchip surface (green curve) but no binding of BSA to compound **35** was detected (Fig. 3). These results add further evidence to the fact that **35,** and by extension **1,** is able to interact in a rather specific manner with the HIV glycoprotein gp120. Moreover, it was observed that **35** also binds to itself (red curve) (self-aggregation). This result supports the markedly pronounced accumulation of molecules on the chip surface observed in the direct binding experiment, where gp120 was bound to the sensorchip.



Scheme 5. Synthesis of compounds **20, 22** and **24**. *Reagents and conditions:* (i) Et_3N (ii) H_2, Pd/C.



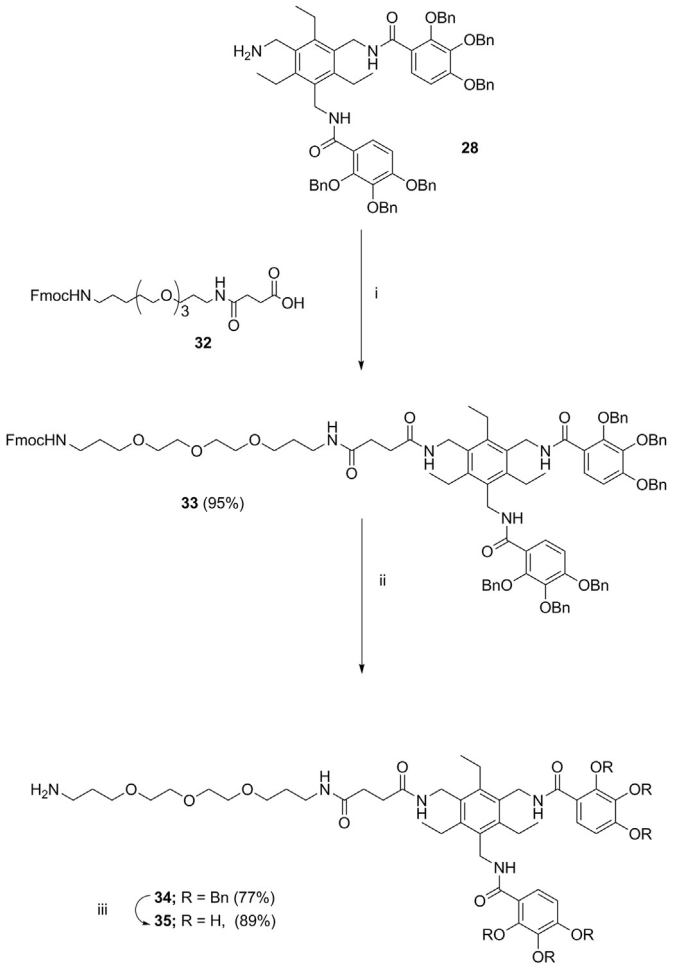
Scheme 6. Synthesis of compounds **25**–**27**. *Reagents and conditions:* (i) pyBOP, Et_3N.



Scheme 7. Synthesis of compound **31**. *Reagents and conditions:* (i) pyBOP, Et_3N (ii) H_2, Pd/C.

The association and dissociation of compound **1** to the gp120-bound sensorchip was also studied in the presence of two different mannose trimers mann $(\alpha\text{-}1,2)_3$ and mann $(\alpha\text{-}1,3\text{–}1,6)_3$ at two different concentrations, 100 μM and 400 μM (Fig. 4). Interestingly, both mannose trimers were able to decrease the interaction of compound **1** with gp120, being mann $(\alpha\text{-}1,3/1,6)_3$ more efficient than mann $(\alpha\text{-}1,2)_3$ in the preventive binding of compound **1** to gp120. These findings suggest an interaction of compound **1** with these mannose glycans and by extension to those that are present on gp120.

Although compound **1** clearly shows mannose-specific gp120 binding (demonstrated in our SPR experiments) it cannot be excluded that other targets of the HIV life cycle could also be targeted by this compound. It has been indeed reported that several polyphenols, such as caffeic acid phenyl ester (CAPE), dicaffeoyl quinic acid (DCQA) and dicaffeoyl tartaric acid inhibit the virus-encoded integrase (IN) enzyme and show antiviral activity [16]. Therefore, IN inhibition may also play a certain role in the eventual antiviral activity of the polyphenolic compounds here described. In order to exclude (or confirm) IN as a potential target of this class of



Scheme 8. Synthesis of compound **35**. *Reagents and conditions:* (i) pyBOP, Et_3N (ii) piperidine, CH_2Cl_2 (iii) H_2, Pd/C.

Table 1
Inhibitory effects of test compounds on HIV-1 and HIV-2 replication in CEM cell culture.

Compound	EC_{50} (μM)[a]		CC_{50} (μM)[b]
	HIV-1	HIV-2	
1	6.3 ± 1.0	41 ± 14	144 ± 15
2	>10	>10	49 ± 2.6
5	>2	>2	5.0 ± 0.14
7	>4	>4	28 ± 1.4
9	>10	>10	22 ± 0.71
11	>50	>50	112 ± 4.2
12	>250	>250	>250
13	>250	>250	>250
20	>10	>10	117 ± 3.5
22	>10	>10	25 ± 9.9
24	>10	>10	36 ± 25
25	>250	>250	>250
26	>250	>250	>250
27	>10[c]	>10[c]	>10[c]
31	>10	>10	25 ± 2.1
PRM-A	3.4 ± 1.3		>50

Data are the mean ± S.D. of at least 2 to 4 independent experiments.
[a] 50% Effective concentration, or the compound concentration required to inhibit HIV-induced cytopathicity by 50%.
[b] 50% Cytostatic concentration, or the compound concentration required to inhibit CEM cell proliferation by 50%.
[c] Compound precipitation (due to insolubility) was detected at higher compound concentration.

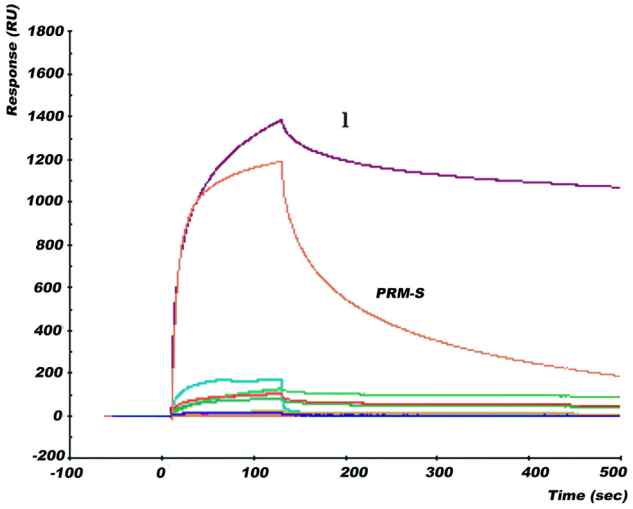


Fig. 2. "Direct" SPR experiment.

anti HIV agents, the potent antiviral compound **1** as well as its structurally closely related, but antivirally inactive, analogue **24** were evaluated for their potential HIV-1 IN inhibitory capacity in cell-free enzyme assays [17]. Inhibition of both the IN 3′-processing and strand transfer enzymatic activities, were assessed by using the 5′-[γ-32P]-labeled full length 21T or precleaved 19T duplex oligonucleotide, respectively (Table 2). The tested compounds, **1** and **24,** were found to inhibit the 3′-processing activity with IC_{50} values of 31 and 42 μM respectively, and strand transfer at concentrations of 10.9 μM and 5.6 μM respectively. Despite the HIV-1 IN inhibitory potency of the tested compounds in the cell-free IN assays only **1** demonstrated strong antiviral properties. Hence, HIV-1 IN is unlikely the cellular target of this class of agents, most probably due to the inability of the compounds to be efficiently taken-up by the virus-infected cells. However, this assumption has still to be confirmed by experimental data.

3. Conclusions

Our previous studies showed that the tripodal receptor **1,** with a central scaffold of 1,3,5-triethylbenzene substituted with three 2,3,4-trihydroxybenzoyl groups, is able to recognize α-1,2-mannose polysaccharides similar to those that are present in the envelope glycoprotein of HIV. Based on this result we determined the anti-HIV activity of **1** and several analogues and the results are described in this work. Only compound **1** markedly inhibits the replication of HIV-1.

"Direct" or "reverse" SPR binding experiments showed the specific interaction of **1** with the HIV glycoprotein gp120. The interaction of compound **1** with the glycoprotein gp120 was also studied in the presence of two different mannose trimers similar to those present on gp120. Our results suggest a preferential interaction of compound **1** with these mannose trimers and by extension to those present on gp120.

Although **1** is also endowed with anti-integrase activity in cell-free enzyme assays, our investigations revealed that virus entry (gp120 binding), but not IN is the presumed molecular target for the eventual antiviral activity of compound **1**.

It can be concluded that the particular structural features of **1**, containing three 2,3,4-trihydroxybenzoyl residues directly attached to a central triethylbenzene scaffold through amide linkers, are important for their anti-HIV activity and ability to specifically interact with the HIV glycoprotein gp120.

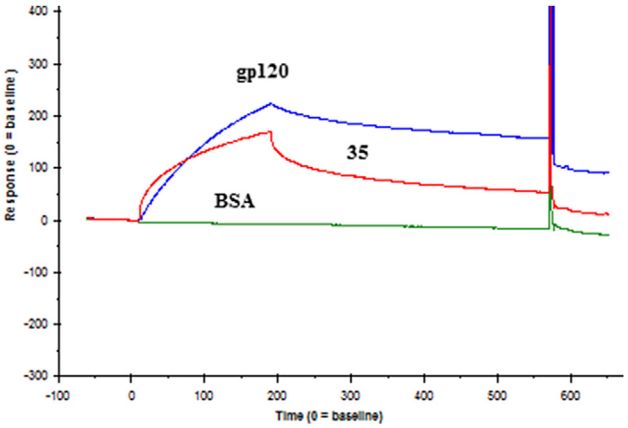


Fig. 3. "Reverse" SPR experiment.

4. Materials and methods

4.1. Synthesis

4.1.1. General method for OBn deprotection

A solution of the corresponding OBn protected derivative in THF/methanol (1:1) (20 mL) containing 30 wt% of Pd/C (10%) was hydrogenated at 30 °C overnight under atmospheric pressure using a balloon filled with hydrogen gas and a glass flask as the reaction vessel. The Pd/C was filtered through Whatman® filter paper 42, washed with methanol and the solvent was removed under reduced pressure to give the crude product which was then purified as mentioned for each case.

Table 2
IN inhibitory activity of **1** and **24** in a cell-free enzyme assay.

Compound number	IC_{50} (μM)[a]	
	3′-Processing	Strand transfer
1	31 ± 1	10.9 ± 1.5
24	42 ± 1	5.6 ± 1.5
DTG	0.4 ± 0.04	<0.05[b]

[a] Inhibitory concentration 50% (IC_{50}, μM) determined from dose response curves.
[b] Inhibition of strand transfer by dolutegravir (DTG, positive control) at the lowest tested concentration (50 nM) was greater than 50%.

4.1.2. 1,3,5-Tris(2,4-dibenzyloxybenzamidomethyl)-2,4,6-triethylbenzene (**6**)

To a solution of trisamine **3** [7] (100 mg, 0.4 mmol) in DMF (20 mL), 2,4-dibenzyloxybenzoic acid (550 mg, 1.6 mmol) [18], HATU (608 mg, 1.6 mmol) and DIPEA (279 μL, 1.6 mmol) were added. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was dissolved in dichloromethane (50 mL) and washed successively with aqueous solutions of citric acid (10%) (3 × 20 mL), saturated $NaHCO_3$ (3 × 20 mL) and brine (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified on a Biotage HPFC system (High Performance Flash Chromatography) using hexane:ethyl acetate (1:1) as eluent to afford 381 mg (80%) of **6** as an amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ:* 1.00 (t, *J* = 7.3 Hz, 9H, CH_3CH_2), 2.44 (m, 6H, CH_2CH_3), 4.53 (s, 6H, CH_2NH), 4.84 (s, 6H, CH_2Ar), 5.13 (s, 6H, CH_2Ar), 6.60 (d, *J* = 2.3 Hz, 3H, Ar), 6.75 (dd, *J* = 2.3 Hz, 6.5 Hz, 3H, Ar), 7.02 (m, 15H, Ar), 7.45 (m, 18H, Ar), 8.29 (s, 3H, NH).

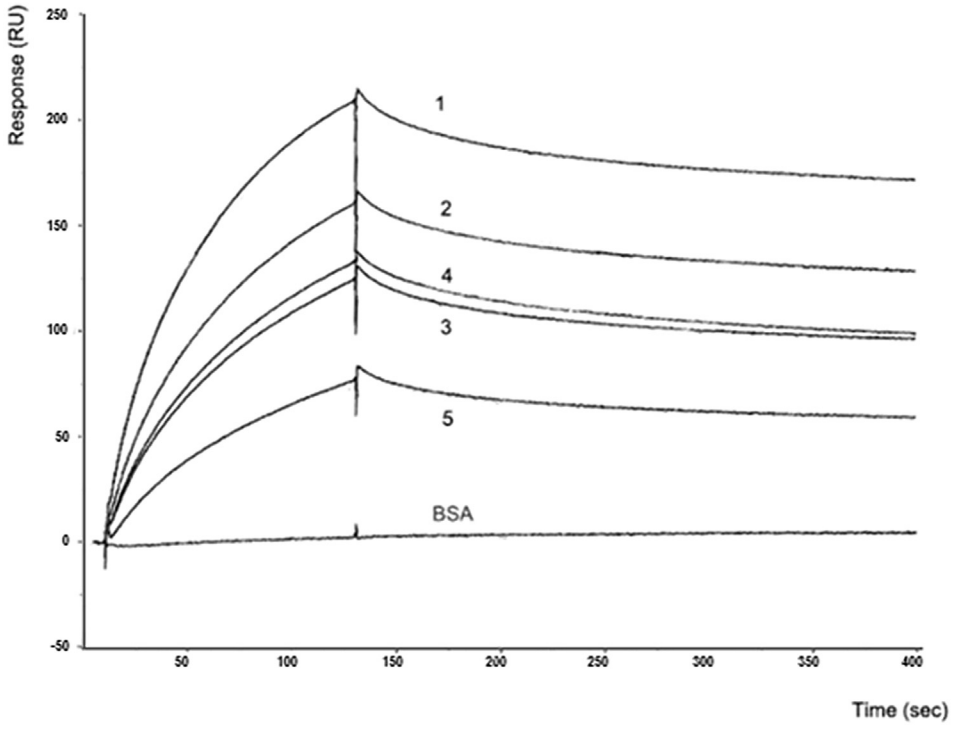


Fig. 4. "Direct" SPR experiment in the presence of mannose trimers. 1) Compound **1** (5 μM). 2) Compound **1** (5 μM) + $(\alpha\text{-}1,2)_3$Mann (100 μM). 3) Compound **1** (5 μM) + $(\alpha\text{-}1,3\text{-}1,6)_3$Mann (100 μM). 4) Compound **1** (5 μM) + $(\alpha\text{-}1,2)_3$Mann (400 μM). 5) Compound **1** (5 μM) + $(\alpha\text{-}1,3\text{-}1,6)_3$Mann (400 μM).

4.1.3. 1,3,5-Tris(2,4-dihydroxybenzamidomethyl)-2,4,6-triethylbenzene (**7**)

Following the general deprotection procedure, the OBn derivative **6** (381 mg, 0.32 mmol) gave a crude product which was then purified on a Biotage HPFC system (High Performance Flash Chromatography) on reverse phase using water:acetonitrile (1:1) as eluent to afford 119 mg (45%) of **7** as a white solid m.p. 301–303 °C. MS (ES+): *m/z* 680.3 $(M + Na)^+$, *m/z* 658.3 $(M + H)^+$. ^{1}H-RMN (500 MHz, DMSO-d_6) *δ:* 1.11 (t, $J = 7.3$ Hz, 9H, CH_3CH_2), 2.78 (m, 6H, CH_2CH_3), 4.54 (s, 6H, CH_2NH), 6.23 (m, 3H, Ar), 7.76 (d, $J = 8.7$ Hz, 3H, Ar), 8.40 (s, 3H, NHCO), 9.96 (br s, 3H, *p*-OH), 12.43 (br s, 3H, *o*-OH).^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 21.31 (CH_3), 27.86 (CH_2), 42.51 (CH_2), 107.82 (CH), 112.16 (C), 112.67 (C), 135.39 (CH), 137.12 (CH), 148.99 (CH), 166.55 (C), 167.18 (C), 173.17 (C=O). HPLC [gradient: A:B, 10–100% of A in 10 min]: 7.80 min. Anal. $C_{36}H_{39}N_3O_9$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65, 68; H, 6.08; N, 6.14.

4.1.4. 1,3,5-Tris-(N-3,4-dibenzyloxyphenylpropionylaminomethyl)-2,4,6-triethylbenzene (**8**)

To a solution of the OBn protected caffeic acid [10] (721 mg, 2 mmol), in DMF (20 mL), trisamine **3** [7] (100 mg, 0.4 mmol), HATU (760 mg, 2 mmol) and DIPEA (348 μL, 2 mmol) was added. The mixture was treated as described for **6** to afford a residue that was triturated with acetone/ether to yield 476 mg (93%) of **8** as a yellow solid; m.p. 208–210 °C. ^{1}H NMR (300 MHz, DMSO) *δ:* 1.11 (m, 9H, CH_3CH_2), 2.73 (m, 6H, CH_2CH_3), 4.43 (s, 6H, CH_2NH), 5.11 (s, 6H, CH_2Ar), 5.14 (s, 6H, CH_2Ar), 6.57 (d, $J = 15.7$ Hz, 3H, CH=CH), 7.05 (s, 3H, Ar), 7.21–7.43 (m, 45H, CH=CH, Ar), 7.94 (s, 3H, NH). Anal. Calcd for: $C_{84}H_{81}N_3O_9$: C, 79.03; H, 6.40; N, 3.29. Found: C, 78, 91; H, 6.51; N, 3.53.

4.1.5. 1,3,5-Tris-(N-3,4-dihydroxyphenylpropionylaminomethyl)-2,4,6-triethylbenzene (**9**)

Following the general deprotection procedure, the OBn caffeoyl derivative **8** (476 mg, 0.37 mmol) gave a crude product which was then triturated with hexane to afford 143 mg (48%) of **9** as a white solid; m.p. 180–182 °C. HRMS (ES+): *m/z* calculated for $C_{42}H_{25}N_3O_9^+$ $(M + H)^+$ 742.3704; found 742.3657. ^{1}H NMR (300 MHz, CD_3OD) *δ*: 1.05 (m, 9H, CH_3CH_2), 2.41 (m, 6H, CH_2), 2.52 (m, 6H, CH_2CH_3), 2.76 (t, $J = 7.2$ Hz, 6H, CH_2), 4.31 (s, 6H, CH_2NH), 6.51 (m, 3H, Ar), 6.62 (m, 6H, Ar). ^{13}C NMR (75 MHz, CD_3OD) *δ*: 16.85 (CH_3), 24.13 (CH_2), 32.78 (CH_2), 39.36 (CH_2), 39.42 (CH_2), 116.76 (CH), 117.05 (CH), 121.06 (C), 133.02 (C), 134.02 (C), 145.03 (C), 145.66 (C), 146.60 (C), 175.49 (C=O). HPLC [gradient: A:B, 10–100% of A in 10 min]: 5.64 min. Anal. Calcd for $C_{42}H_{51}N_3O_9$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68,39; H, 6.39; N, 5.61.

4.1.6. 1,3,5-Tris(2,4,6-tribenzyloxybenzamidomethyl)-2,4,6-triethylbenzene (**10**)

To a solution of trisamine **3** [7] (50 mg, 0.2 mmol) in DMF (20 mL), 2,4,6-tribenzyloxybenzoic acid [11] (440 mg, 1 mmol), HATU (274 mg, 1 mmol) and DIPEA (126 μL, 1 mmol) were added. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was dissolved in dichloromethane (50 mL) and washed successively with aqueous solutions of citric acid (10%) (3 × 20 mL), saturated $NaHCO_3$ (3 × 20 mL), and brine (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified on a Biotage HPFC system (High Performance Flash Chromatography) using hexane:ethyl acetate (1:1) as eluent to afford 184 mg (60%) of **10** as an amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) *δ:* 0.94 (t, $J = 7.3$ Hz, 9H, CH_3CH_2), 2.46 (q, $J = 7.5$ Hz, 6H, CH_2CH_3), 4.49 (s, 6H, CH_2NH), 4.91 (m, 12H, CH_2Ar), 4.95 (m, 6H, CH_2Ar), 6.13 (s, 6H, Ar), 7.23 (m, 30H, Ar), 7.34 (m, 15H, Ar).

4.1.7. 1,3,5-Tris(2,4,6-trihydroxybenzamidomethyl)-2,4,6-triethylbenzene (**11**)

Following the general deprotection procedure, the OBn derivative **10** (184 mg, 0.12 mmol) gave a crude product which was then triturated with ether to afford 24 mg (32%) of **11** as a white solid; m.p. 301–303 °C. MS (ES+): *m/z* 706.82 $(M + H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) *δ*: 1.26 (m, 9H, CH_3CH_2), 2.88 (m, 6H, CH_2CH_3), 4.68 (m, 6H, CH_2NH), 5.49 (m, 3H, Ar), 5.80 (m, 3H, Ar), 8.55 (s, 3H, NHCO), 9.95 (s, 3H, *p*-OH), 12.55 (s, 3H, *o*-OH). ^{13}C-NMR (75 MHz, CD_3OD) *δ*: 17.07 (CH_3), 24.25 (CH_2), 38.78 (CH_2), 97.23 (CH), 134.05 (C), 145.90 (C), 163.40 (C), 163.84 (C), 171.86 (C=O). HPLC [gradient: A:B, 10–100% of A in 10 min]: 6.66 min. Anal. Calcd for $C_{36}H_{39}N_3O_{12}$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61,11; H, 5.80; N, 5.86.

4.1.8. 1,3,5-Tris-((3S,4R,5S)-3,4,5-trihydroxycyclohex-1-en-1-yl-carbonylaminomethyl)-2,4,6-triethylbenzene (**12**)

To a solution of trisamine **3** [7] (50 mg, 0.2 mmol) in DMF (20 mL), shikimic acid (122 mg, 0.7 mmol), HATU (266 mg, 0.7 mmol) and DIPEA (105 μL, 0.6 mmol) were added. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was dissolved in isobutanol (50 mL) and washed with brine (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was triturated with ether to yield 109 mg (76%) of **12** as a white solid; m.p. 242–244 °C. MS (ES+): *m/z* 740.36 $(M + Na)^+$; *m/z* 718.43 $(M + H)^+$. ^{1}H-NMR (300 MHz, CD_3OD) *δ:* 1.17 (t, 9H, $J = 7.4$ Hz, CH_3CH_2), 2.15 (dd, 3H, $J = 18.0$ Hz, 6.0 Hz, CH_{2A}), 2.75 (m, 9H, CH_{2B} and CH_2CH_3), 3.62 (dd, 3H, $J = 7.5$ Hz, 4.2 Hz, *C*HOH), 3.96 (m, 3H, *C*HOH), 4,30 (m, 3H, *C*HOH) 4.51 (s, 6H, CH_2NH), 6.28 (m, 3H, CH=CH).^{13}C-NMR (75 MHz, CD_3OD) *δ:* 16.09 (CH_3), 23.38 (CH_2), 32.01 (CH_2), 39.10 (CH_2), 66.97 (CH), 68.19 (CH), 72.80 (CH),133.00 (CH), 133,19 (C), 134.68 (C), 146.07 (C), 170.96 (C=O). HPLC [gradient: A:B, 2–30% of A in 5 min]: 4.93 min. Anal Calcd for $C_{36}H_{51}N_3O_{12}$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60, 37; H, 6.87; N, 5.45.

4.1.9. 1,3,5-Tris-((3S,4R,5S)-3,4,5-trihydroxycyclohexylcarbonylaminomethyl)-2,4,6-triethylbenzene (**13**)

To a solution of the unsaturated derivative **12** (69 mg, 0.1 mmol) in THF/methanol (1:1) was added 30 wt% of Pd/C (10%) and the mixture was hydrogenated at 30 °C and 2.9 atm (42 psi) during 1 h. The Pd/C was filtered through Whatman® filter paper 42, washed with methanol and the solvent was removed under reduced pressure. The residue was triturated with methanol/ether (1:1) to give 31 mg (45%) of **13** as a white solid; m.p. 285–287 °C. HRMS (ES+): *m/z* calculated for $C_{36}H_{58}N_3O_{12}^+$ $(M + H)^+$ 724.4020; found 724.4002; *m/z* calculated for $C_{36}H_{57}N_3NaO_{12}^+$ $(M + Na)^+$ 746.3840; found 746.3805; *m/z* calculated for $C_{36}H_{57}KN_3O_{12}^+$ $(M + K)^+$ 762.3579; found 762.3511. ^{1}H-NMR (300 MHz, CD_3OD) *δ:* 1.20 (m, 9H, CH_3CH_2), 1.85–2.10 (m, 12H, CH_A, $CH_{B'}$, CH_B), 2.72–2.78 (m, 9H, CH_2CH_3, $CHCH_2$), 3.97 (m, 3H, *C*HOH), 4.16 (m, 3H, *C*HOH), 4.24 (m, 3H, *C*HOH), 4.50 (s, 6H, CH_2NH), 7.52 (s, 3H, NH). HPLC [gradient: A:B, 10–100% of A in 10 min]: 4.04 min. Anal. $C_{36}H_{57}N_3O_{12}$: C, 59.73; H, 7.94; N, 5.81. Hallado: C, 59,99; H, 7.88; N, 5.51.

4.1.10. N-(2-aminoethyl)-2,3,4-tris(benzyloxy)benzamide (**15**)

To a solution of **14** [12] (750 mg, 1.70 mmol) in dichloromethane (8.5 mL), PyBOP (1.15 g, 2.21 mmol) and triethylamine were added (307 μl, 2.21 mmol). The reaction mixture was stirred at room temperature for 2 h and then a solution of ethylenediamine (433 μl, 6.38 mmol) in dichloromethane (5 mL) was added. The reaction mixture was stirred at room temperature for 3 h, diluted with dichloromethane (25 mL) and washed with brine (2 × 20 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and

evaporated to dryness. The residue was purified by CCTLC using a gradient of dichloromethane:methanol (10:1) to dichloromethane:methanol:ammonia (10:1:0.2) as eluent to yield 482 mg (94%) of **15** as a yellow oil. MS (ES+): *m/z* 483 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 2.85 (br s, 2H, CH_2NH_2), 3.35 (m, 2H, CH_2NH), 5.06 (s, 2H, CH_2Ar), 5.15 (s, 2H, CH_2Ar), 5.16 (s, 2H, CH_2Ar), 6.87 (d, $J = 9.0$ Hz, 1H, Ar), 7.28–7.46 (m, 15H, Ar), 7.84 (d, $J = 8.9$ Hz, 1H, Ar), 8.22 (t, $J = 5.4$ Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 41.2 (CH_2), 42.2 (CH_2), 70.6 (CH_2), 75.4 (CH_2), 76.8 (CH_2), 108.8 (CH), 119.4 (C), 126.6 (CH), 127.3–126.6 (CH), 135.9 (C), 136.1 (C), 136.9 (C), 140.8 (C), 151.5 (C), 155.4 (C), 165.0 (C=O).

4.1.11. N-(4-aminobutyl)-2,3,4-tris(benzyloxy)benzamide (**16**)

In a procedure analogous to that described for compound **15**, a solution of **14** (198 mg, 0.45 mmol) in dichloromethane (6.7 mL) was treated with a solution of butane-1,4-diamine (270 μl, 2.67 mmol) in dichloromethane (2.2 mL) to yield 205 mg (89%) of **16** as a colorless oil. MS (ES+): *m/z* 512 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) *δ:* 1.29 (m, 4H, CH_2), 1.92 (br s, 2H, NH_2), 2.63 (t, $J = 6.4$ Hz, 2H, CH_2NH_2), 3.25 (m, 2H, CH_2NH), 5.07 (s, 2H, CH_2Ar), 5.14 (s, 2H, CH_2Ar), 5.16 (s, 2H, CH_2Ar), 6.88 (d, $J = 9.0$ Hz, 1H, Ar), 7.31–7.45 (m, 15H, Ar), 7.90–7.94 (m, 2H, Ar, NH). ^{13}C NMR (75 MHz, $CDCl_3$) *δ:* 26.6 (CH_2), 30.4 (CH_2), 39.3 (CH_2), 41.5 (CH_2), 70.8 (CH_2), 75.7 (CH_2), 77.2 (CH_2), 109.1 (CH), 119.5 (C), 126.8 (CH), 127.5 (CH), 128.2 (CH), 128.4 (CH), 128.6–128.7 (CH), 136.2 (C), 136.4 (C), 137.1 (C), 141.0 (C), 151.7 (C), 155.6 (C), 164.8 (C=O).

4.1.12. Piperazin-1-yl-(2,3,4-tris(benzyloxy)phenyl)methanone (**17**)

In a procedure analogous to that described for compound **15**, a solution of **14** (198 mg, 0.45 mmol) in dichloromethane (6.7 mL) was treated with a solution of piperazine (235 mg, 2.67 mmol) in dichloromethane (2.2 mL) to yield a residue that was purified by CCTLC using dichloromethane:methanol (20:1) as eluent to afford 225 mg (99%) of **17** as a yellow oil. MS (ES+): *m/z* 509 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) *δ:* 2.67 (m, 3H, CH_2), 2.86 (m, 1H, CH_2), 3.12 (m, 2H, CH_2), 3.72 (m, 2H, CH_2), 4.88 (d, $J = 10.6$ Hz, 1H, CH_2Ar), 5.04–5.20 (m, 5H, CH_2Ar), 6.81 (d, $J = 8.5$ Hz, 1H, Ar), 6.97 (d, $J = 8.6$ Hz, 1H, Ar), 7.24–7.48 (m, 15H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) *δ:* 42.6 (CH_2), 45.4 (CH_2), 45.9 (CH_2), 47.9 (CH_2), 71.0 (CH_2), 75.2 (CH_2), 76.3 (CH_2), 109.8 (CH), 122.7 (C), 124.3 (CH), 127.4 (CH), 128.0–128.8 (CH), 136.5 (C), 137.1 (C), 137.3 (C), 141.2 (C), 149.5 (C), 154.0 (C), 167.4 (C=O).

4.1.13. 1,3,5-Tris(2,3,4-tribenzyloxybenzamidoethylaminomethyl)-2,4,6-triethylbenzene (**19**)

To a solution of the tris bromo derivative **18** [7] (50 mg, 0.11 mmol) in dichloromethane (1 mL) the aminoethyl derivative **15** (231 mg, 0.47 mmol) and Et_3N (65 μl, 0.47 mmol) were added. The reaction mixture was stirred at 30 °C overnight, diluted with dichloromethane (15 mL) and washed with brine (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by CCTLC using dichloromethane:methanol:ammonia (15:1:0.4) as eluent to yield 106 mg (57%) of **19** as a colorless oil. MS (ES+): *m/z* 1647 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.14 (t, $J = 7.2$ Hz, 9H, CH_3CH_2), 2.63–2.69 (m, 12H, CH_2CH_3, CH_2), 3.36 (m, 6H, CH_2), 3.61 (s, 6H, CH_2NH), 5.04 (s, 6H, CH_2Ar), 5.09 (s, 6H, CH_2Ar), 5.14 (s, 6H, CH_2Ar), 6.86 (dd, $J = 9.2$, 0.5 Hz, 3H, Ar), 7.22–7.41 (m, 45H, Ar), 7.88 (dd, $J = 8.9$, 0.7 Hz, 3H, Ar), 8.01 (t, $J = 5.2$ Hz, 3H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 17.0 (CH_3), 22.6 (CH_2), 39.5 (CH_2), 47.5 (CH_2), 49.4 (CH_2), 70.8 (CH_2), 75.6 (CH_2), 109.1 (CH), 119.9 (C), 126.7 (CH), 127.5 (CH), 128.1–128.8 (CH), 134.0 (C), 136.2 (C), 137.1 (C), 141.1 (C), 142.1 (C), 151.7 (C), 155.6 (C), 164.9 (C=O).

4.1.14. 1,3,5-Tris(2,3,4-trihydroxybenzamidoethylaminomethyl)-2,4,6-triethylbenzene (**20**)

Following the general deprotection procedure, the OBn derivative **19** (119 mg, 0.23 mmol) gave 45 mg (96%) of **20** as a white solid; m.p. 164–166 °C. MS (ES+): *m/z* 835 $(M + 1)^+$. ^{1}H NMR (400 MHz, CD_3OD) *δ*: 1.19 (t, $J = 7.3$ Hz, 9H, CH_3CH_2), 2.91 (q, $J = 7.3$ Hz, 6H, CH_2CH_3), 3.50 (m, 6H, CH_2), 3.81 (m, 6H, CH_2), 4.22 (s, 6H, CH_2NH), 6.39 (d, $J = 8.8$ Hz, 3H, Ar), 7.22 (d, $J = 8.8$ Hz, 3H, Ar). ^{13}C NMR (100 MHz, CD_3OD) *δ*: 16.6 (CH_3), 25.7 (CH_2), 37.5 (CH_2), 43.3 (CH_2), 50.2 (CH_2), 108.2 (C), 108.4 (CH), 120.0 (CH), 128.9 (C), 134.1 (C), 149.4 (C), 151.4 (C), 150.7 (C), 173.2 (C=O). Anal. Calcd for $C_{42}H_{54}N_6O_{12}$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.21; H, 6.75; N, 9.94.

4.1.15. 1,3,5-Tris(2,3,4-tribenzyloxybenzamidobutylaminomethyl)-2,4,6-triethylbenzene (**21**)

To a solution of the tris bromo derivative **18** [7] (29 mg, 0.07 mmol) in dichloromethane (0.5 mL), the aminobutyl derivative **16** (133 mg, 0.26 mmol) and triethylamine were added (36 μl, 0.47 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane (15 mL) and washed with brine (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by CCTLC using dichloromethane:methanol (10:1) as eluent to yield 51 mg (46%) of **21** as a yellow oil. MS (ES+): *m/z* 866 $(1/2M + 1)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.15 (t, $J = 6.2$ Hz, 9H, CH_3CH_2), 1.37 (m, 6H, CH_2), 1.64 (m, 6H, CH_2), 2.88 (m, CH_2CH_3, CH_2NH), 3.20 (m, 6H, CH_2NH), 3.93 (br s, 6H, CH_2NH), 5.05 (s, 6H, CH_2Ar), 5.12 (s, 6H, CH_2Ar), 5.14 (s, 6H, CH_2Ar), 6.86 (d, $J = 7.8$ Hz, 3H, Ar), 7.26–7.42 (m, 45H, Ar), 7.86 (d, $J = 7.8$ Hz, 3H, Ar), 7.94 (m, 3H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 17.1 (CH_3), 24.2 (CH_2), 25.0 (CH_2), 27.2 (CH_2), 39.1 (CH_2), 46.63 (CH_2), 49.5 (CH_2), 71.09 (CH_2), 75.91 (CH_2), 77.59 (CH_2), 109.1 (CH), 119.7 (CH), 127.8 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 136.4 (C), 137.3 (C), 141.3 (C), 152.0 (C), 156.0 (C), 165.3 (C=O).

4.1.16. 1,3,5-Tris(2,3,4-trihydroxybenzamidobutylaminomethyl)-2,4,6-triethylbenzene (**22**)

Following the general deprotection procedure, the OBn derivative **21** (50 mg, 0.023 mmol) gave a crude product which was then purified on a Biotage HPFC system (High Performance Flash Chromatography) on reverse phase using water:acetonitrile (100:0 to 70:30) as eluent to afford 7 mg (27%) of **22** as a white amorphous solid. MS (ES+): *m/z* 920 $(M + H)^+$. ^{1}H NMR (300 MH, CD_3OD) *δ:* 1.18 (t, $J = 7.5$ Hz, 9H, CH_3CH_2), 1.72 (m, 6H, CH_2), 1.85 (m, 6H, CH_2), 2.87 (q, $J = 7.3$ Hz, 6H, CH_2CH_3), 3.32 (m, 6H, CH_2NH), 3.40 (m, 6H, CH_2NH), 3.48 (m, 6H, $NHCH_2CH_2$), 4.32 (s, 6H, CH_2NH), 6.35 (d, $J = 8.8$ Hz, 3H, Ar), 7.09 (d, $J = 8.8$ Hz, 3H, Ar). ^{13}C NMR (100 MHz, CD_3OD) *δ:* 16.3 (CH_3), 24.1 (CH_2), 25.3 (CH_2), 27.7 (CH_2), 38.9 (CH_2), 45.9 (CH_2), 108.0 (C), 108.6 (CH), 119.1 (CH), 128.8 (C), 134.0 (C), 149.3 (C), 150.9 (C), 151.4 (C), 172.2 (C=O). Anal. Calcd for $C_{48}H_{66}N_6O_{12}$: C, 66.73; H, 7.24; N, 9.14. Found: C, 66.97; H, 7.16; N, 9.08.

4.1.17. 1,3,5-Tris[(4-(2,3,4-tribenzyloxyphenylcarbonyl)piperazin-1-yl)methyl]-2,4,6-triethylbenzene (**23**)

To a solution of the tris bromo derivative **18** [7] (43 mg, 0.10 mmol) in dichloromethane (1 mL), the piperazinyl derivative **17** (198 mg, 0.39 mmol) and Et_3N were added (54 μl, 0.39 mmol). The reaction mixture was stirred at room temperature overnight, diluted with dichloromethane (15 mL) and washed with brine (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by CCTLC using dichloromethane:methanol (30:1) to yield 127 mg (75%) of **23** as a yellow oil. MS (ES+): *m/z* 1725 $(M + 1)^+$, 863 $(1/2M + 1)^+$. ^{1}H-RMN

(400 MHz, Acetone-d_6) *δ:* 1.09 (t, J = 6.9 Hz, 9H, CH_3CH_2), 2.27 (m, 6H, CH_2CH_3), 2.33 (m, 3H, CH_2), 2.46 (m, 3H, CH_2), 2.90 (m, 6H, CH_2), 3.01 (m, 6H, CH_2), 3.47 (m, 9H, CH_2, CH_2NH), 3.70 (m, 3H, CH_2), 4.90 (m, 3H, CH_2Ar), 5.08–5.19 (m 15H, CH_2Ar), 6.88–6.93 (m, 6H, Ar), 7.20–7.24 (m, 9H, H–Ar), 7.35–7.41 (m, 30H, Ar), 7.53–7.55 (m, 6H, Ar). ^{13}C NMR (100 MHz, Acetone-d_6) *δ:* 17.0 (CH_3), 22.3 (CH_2), 42.4 (CH_2), 47.8 (CH_2), 52.9 (CH_2), 53.2 (CH_2), 55.7 (CH_2), 71.5 (CH_2), 75.5 (CH_2), 76.5 (CH_2), 110.5 (CH), 123.2 (C), 125.9 (CH), 128.6–129.6 (CH), 131.9 (C), 138.0 (C), 138.4 (C), 138.6 (C), 141.9 (C), 145.4 (C), 150.3 (C), 154.6 (C), 167.2 (C=O).

4.1.18. 1,3,5-Tris[(4-(2,3,4-trihydroxyphenylcarbonyl)piperazin-1-yl)methyl]-2,4,6-triethylbenzene (**24**)

Following the deprotection procedure, the OBn derivative **23** (122 mg, 0.07 mmol) gave a crude product which was then purified on a Biotage HPFC system (High Performance Flash Chromatography) on reverse phase using water:acetonitrile (100:0 to 80:20) as eluent to afford 32 mg (50%) of **24** as a white solid; m.p > 350 °C. MS (ES+): *m/z* 914 $(M + 1)^+$. ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.10 (t, J = 7.2 Hz, 9H, CH_3CH_2), 3.17 (m, 6H, CH_2CH_3), 3.45 (br s, 12H, CH_2), 3.88 (br s, 12H, CH_2), 4.57 (s, 6H, CH_2NH), 6.41 (d, J = 8.5 Hz, 3H, Ar), 6.70 (d, J = 8.5 Hz, 3H, Ar). ^{13}C NMR (100 MHz, Acetone-d_6) *δ:* 16.4 (CH_3), 24.7 (CH_2), 52.7 (CH_2), 54.9 (CH_2), 99.87 (CH), 107.5 (C), 112.5 (C), 120.2 (CH), 133.5 (C), 146.2 (C), 148.7 (C), 170.3 (C=O). Anal. Calcd for $C_{48}H_{60}N_6O_{12}$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.37; H, 6.60; N, 9.48.

4.1.19. 1,3,5-Tris(6-aminopyridinyl-3-carbonylaminomethyl)-2,4,6-triethylbenzene (**25**)

To a solution of 6-aminoniconitic acid (111 mg, 0.8 mmol) in DMF (20 mL), PyBOP (424 mg, 0.8 mmol) was added. After 5 min **3** [7] (50 mg, 0.2 mmol) and triethylamine (102 μL, 0.8 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, and volatiles were removed. The residue was dissolved in isobutanol (20 mL) and washed with brine (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was triturated with ether and methanol to afford 99.94 mg (82%) of **25** as a white solid; m.p. 267–269 °C. HRMS (ES+): *m/z* calculated for $C_{33}H_{39}N_9O_3$ 609.3176; found 609.3176. ^{1}H NMR (300 MHz, DMSO) *δ:* 1.09 (m, 9H, CH_3CH_2), 2.81 (m, 6H, CH_2CH_3), 4.50 (s, 6H, CH_2NH), 6.41 (m, 3H, Ar), 7.84 (m, 3H, Ar), 8.07 (br s, 6H, NH_2-Ar), 8.40 (s, 3H, Ar).^{13}C NMR (75 MHz, DMSO) *δ*: 15.90 (CH_3), 22.36 (CH_2), 38.35 (CH_2), 106.21 (CH), 117.52 (C), 131.81 (C), 136.01 (C), 143.22 (CH), 148.32 (CH), 161.00 (C), 164.71 (C=O). HPLC [gradient: A:B, 10–100% of A in 10 min]: 4.39 min.

4.1.20. 1,3,5-Tris(4-aminobenzamidomethyl)-2,4,6-triethylbenzene (**26**)

In a procedure analogous to that described for compound **25**, a solution of **3** [7], (50 mg, 0.2 mmol), 4-aminobenzoic acid (110 mg, 0.8 mmol), PyBOP (424 mg, 0.8 mmol) and Et_3N (102 μL, 0.8 mmol) in DMF (20 mL), gave a residue that was dissolved in isobutanol (20 mL) and washed with brine (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by trituration with ether and methanol to afford 25 mg (21%) of **26** as a white solid; m.p. >350 °C. HRMS (ES+): *m/z* calculated for $C_{36}H_{42}N_6O_3$ 606.3318; found 606.3330. ^{1}H-RMN (300 MHz, DMSO-d_6) *δ:* 1.10 (t, J = 7.4 Hz, 9H, CH_3CH_2), 2.77 (m, 6H, CH_2CH_3), 4.49 (s, 6H, CH_2NH), 5.23 (br s, 6H, NH_2), 6.48 (d, J = 8.7 Hz, 6H, Ar), 7.38 (br s, 3H, NH), 7.53 (d, J = 8.7 Hz, 6H, Ar). ^{13}C-RMN (75 MHz, DMSO-d_6) *δ*: 16.91 (CH_3), 23.34 (CH_2), 38.45 (CH_2), 113.18 (CH), 121.80 (CH), 129.49 (C), 132.75 (C), 144.11 (C), 151.99 (C), 166.97 (C=O). HPLC [gradient: A:B, 10–100% of A in 10 min]: 5.51 min.

4.1.21. 1-Aminomethyl-3,5-bis(2,3,4-tribenzyloxybenzamidomethyl)-2,4,6-triethylbenzene (**28**)

To a solution of 2,3,4-tribenzyloxybenzoic acid **14** (200 mg, 0.45 mmol) [12] in dichloromethane (3 mL), PyBOP (263 mg, 0.50 mmol) and Et_3N (70 μL, 0.50 mmol) were added. The mixture was stirred at room temperature for 1 h, and then added dropwise to a suspension of trisamine **3** (63 mg, 0.25 mmol) [7] in dichloromethane (1 mL). The mixture was stirred at room temperature for 2 h. Dichloromethane (50 mL) was added and the reaction mixture was washed with brine (20 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by CCTLC using dichloromethane:methanol (20:1) as eluent to afford 114 mg (41%) of **28** as a pale yellow oil. MS (ES+): *m/z:* 1094 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) *δ:* 0.96–1.28 (m, 9H, CH_3CH_2), 2.44 (m, 2H, CH_3CH_2), 2.66 (m, 4H, CH_3CH_2), 3.93 (m, 2H, CH_2NH_2), 4.52–4.60 (m, 4H, CH_2NH), 4.83–4.94 (m, 8H, CH_2Ar), 5.14 (m, 4H, CH_2Ar), 6.78–7.40 (m, 32, Ar), 7.85 (m, 2H, NH), 7.94 (m, 2H, Ar).

4.1.22. Cis-N^1,N^3,N^5-tris[3,5-bis(2,3,4-tribenzyloxybenzamido methyl)-1-methyl-2,4,6-triethylphenyl]-1,3,5-cyclohexanetricarboxamide (**30**)

To a solution of *cis*-1,3,5-cyclohexanetricarboxylic acid **29** (10.1 mg, 0.05 mmol) in dichloromethane (0,5 mL), PyBOP (78 mg, 0.15 mmol) was added. After 5 min **28** (137 mg, 0.15 mmol), and triethylamine (33 μL, 0.24 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. Dichloromethane (50 mL) was added and the reaction mixture was washed with brine (20 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by CCTLC using dichloromethane:methanol (20:1) as eluent to afford 69 mg (92%) of **30** as a colorless oil. ^{1}H-RMN (400 MHz, $CDCl_3$) *δ:* 1.08 (m, 27H, CH_3CH_2), 1.34 (m, 3H, CH_2CH), 1.72 (m, 3H, CH_2CH), 2.49–2.58 (m, 18H, CH_3CH_2), 3.15 (m, 3H, $CHCH_2$), 4.30 (br s, 6H, CH_2NH), 4.62 (br s, 12H, CH_2NH), 4.89–4.92 (m, 24H, CH_2Ar), 5.15 (s, 12H, CH_2Ar), 6.81–7.52 (m, 96H, Ar), 7.89 (m, 6H, NH), 7.97 (m, 6H, Ar). ^{13}C-RMN (100 MHz, $CDCl_3$) *δ:* 16.3 (CH_3), 16.4 (CH_3), 22.9 (CH_2), 37.8 (CH_2), 38.3 (CH_2), 43.5 (CH_2), 69.7 (CH), 70.8 (CH_2), 75.5 (CH_2), 76.4 (CH_2), 109.3 (CH), 119.4 (C), 126.8 (CH), 127.5 (CH), 128.0–128.5 (CH), 131.3 (C), 132.6 (C), 135.9 (C), 136.0 (C), 136.8 (C), 141.0 (C), 143.8 (C), 144.3 (C), 151.4 (C), 155.8 (C), 164.4 (C=O), 173.0 (C=O).

4.1.23. Cis-N^1,N^3,N^5-tris[3,5-bis(2,3,4-trihydroxybenzamido methyl)-1-methyl-2,4,6-triethylphenyl]-1,3,5-cyclohexanetricarboxamide (**31**)

Following the deprotection procedure, the OBn derivative **30** (147 mg, 0.042 mmol) gave a residue that was triturated with dichloromethanemethanol to give 43.4 mg (57%) of **31** as a brownish amorphous solid. HRMS (ES+): *m/z* calculated for $C_{96}H_{111}N_9O_{27}$ 1821.7589; found 1821.7681. ^{1}H NMR (400 MHz, CD_3OD) *δ:* 1.14 (t, 18H, J = 7.5 Hz, CH_3CH_2), 1.19 (t, 9H, J = 7.5 Hz, CH_3CH_2), 1.59–1.73 (m, 3H, CH_2CH), 1.76–1.85 (m, 3H, CH_2CH), 2.21–2.30 (m, 3H, $CHCH_2$), 2.76 (q, 12H, J = 7.5 Hz, CH_2CH_3), 2.88 (q, 6H, J = 7.5 Hz, CH_2CH_3), 4.40 (s, 6H, CH_2NH), 4.64 (s, 12H, CH_2NH), 6.34 (d, 6H, J = 9.8 Hz, Ar), 7.19 (d, 6H, J = 9.8 Hz, Ar). ^{13}C NMR (100 MHz, CD_3OD) *δ:* 15.44 (CH_3), 15.53 (CH_3), 22.67 (CH_2), 22.89 (CH_2), 31.42 (CH_2), 37.87 (CH_2), 43.36 (CH), 107.95 (CH), 109.52 (C), 120.22 (CH), 133.08 (C), 133.94 (C), 145.63 (C), 150.63 (C), 150.78 (C), 170.73 (C=O), 177.04 (C=O). HPLC [gradient: A:B, 10–100% of A in 10 min]: 7.29 min.

4.1.24. 1-N-(Fmoc-18-amino-4-oxo-9,12,15-trioxa-5-aminooctadecanoil)aminomethyl-3,5-bis(2,3,4-tribenzyloxybenzamidomethyl)-2,4,6-triethylbenzene (**33**)

To a solution of Fmoc-18-amino-4-oxo-9,12,15-trioxa-5-

aminooctadecanoic acid (**32**) (232 mg, 0.43 mmol) [12] in dichloromethane (2 mL), PyBOP (222 mg, 0.43 mmol) was added. After 5 min **28** (233 mg, 0.21 mmol) and triethylamine Et_3N (60 μL, 0.43 mmol) were added. The reaction mixture was stirred at room temperature for 1 h, diluted with dichloromethane (15 mL) and washed with brine (3 x 15 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by CCTLC using dichloromethane:methanol, (20:1) as eluent to afford 326 mg (95%) of **33** as a pale yellow amorphous solid. HRMS (ES+): *m/z:* 1620 $(M + H)^+$. ^{1}H-RMN (400 MHz, $CDCl_3$) *δ:* 1.05 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 1.13 (t, *J* = 7.2 Hz, 6H, CH_3CH_2), 1.67–1.78 (m, 4H, CH_2), 2.23 (m, 2H, CH_2), 2.38–2.50 (m, 4H, CH_3CH_2, CH_2), 2.66 (m, 4H, CH_3CH_2), 3.35 (m, 4H, CH_2), 3.48–3.63 (m, 12H, CH_2), 4.21 (m, 2H, CH_2NH), 4.32–4.41 (m, 3H, CH_2CH, $CHCH_2$), 4.60 (m, 4H, CH_2NH), 4.88 (s, 4H, CH_2Ar), 4.91 (s, 4H, CH_2Ar), 5.14 (s, 4H, CH_2Ar), 6.89 (m, 6H, Ar), 7.05 (m, 4H, Ar), 7.14–7.41 (m, 34H, Ar), 7.59 (m, 2H, Ar), 7.75 (m, 2H, Ar), 7.89 (m, 2H, NH), 7.96 (d, *J* = 9 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 16.6 (CH_3), 23.1 (CH_2), 24.6 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 29.0 (CH_2), 29.6 (CH_2), 31.5 (CH_2), 38.1 (CH_2), 46.7 (CH_2), 46.8 (CH_2), 47.5 (CH_2), 66.6 (CH_2), 7034 (CH_2), 70.7 (CH_2), 71.0 (CH_2), 75.8 (CH_2), 76.1 (CH_2), 109.5 (CH), 120.2 (CH), 125.3 (CH), 127.1 (CH), 127.2 (CH), 127.8 (CH), 127.9 (CH), 128.5 (CH), 128.8 (C), 136.1 (C), 144.2 (C), 151.7 (C), 156.1 (C=O), 164.7 (C=O), 190.7 (C=O).

*4.1.25. 1-N-(18-Amino-4-oxo-9,12,15-trioxa-5-aminooctadecanoyl) aminomethyl-3,5-bis(2,3,4-tribenzyloxybenzamidomethyl)-2,4,6-triethylbenzene (**34**)*

A solution of **33** (325 mg, 0.20 mmol) in dichloromethane (2 mL) was treated with piperidine (0.5 mL). The reaction mixture was stirred at room temperature for 1 h, and the volatiles were removed. The residue was purified by CCTLC using dichloromethane:methanol, (10:1) as eluent to afford 217 mg (77%) of **34** as a pale yellow amorphous solid. MS (ES+): *m/z:* 1397 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) *δ:* 0.92–1.03 (m, 9H, CH_3CH_2), 1.57 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 2.25 (m, 4H, CH_2), 2.50–2.59 (m, 2H, CH_2NH_2), 2.81 (m, 2H, CH_3CH_2), 3.03 (m, 4H, CH_3CH_2), 3.37–3.52 (m, 14H, CH_2), 4.21 (m, 2H, CH_2NH), 4.45 (m, 4H, CH_2NH), 4.89 (s, 4H, CH_2Ar), 4.91 (s, 4H, CH_2Ar), 5.19 (s, 4H, CH_2Ar), 7.03–7.57 (m, 34H, Ar), 7.89 (m, 4H, NH).

*4.1.26. 1-N-(18-Amino-4-oxo-9,12,15-trioxa-5-aminooctadecanoyl) aminomethyl-3,5-bis(2,3,4-trihydroxybenzamidomethyl)-2,4,6-triethylbenzene (**35**)*

Following the deprotection procedure, the OBn derivative **34** afforded a residue that was triturated with methanol/ether to give 70 mg (89%) of **35** as a pale yellow amorphous solid. MS (ES+): *m/z* 856 $(M + H)^+$. ^{1}H NMR (400 MHz, CD_3OD) *δ:* 1.18–1.23 (m, 9H, CH_3CH_2), 1.71 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.47 (s, 4H, CH_2), 2.81 (q, *J* = 7.6 Hz, 4H, CH_2CH_3), 2.90 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 3.08 (t, *J* = 6.4 Hz, 2H, CH_2), 3.20 (m, *J* = 7.0 Hz, 2H, CH_2), 3.46 (t, *J* = 6.1 Hz, 2H, CH_2), 3.55 (m, 2H, CH_2), 3.60–3.65 (m, 8H, CH_2), 4.45 (m, 2H, CH_2NH), 4.66 (s, 4H, CH_2NH), 6.34 (d, *J* = 8.8 Hz, 2H, Ar), 7.21 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, CD_3OD) *δ:* 16.6 (CH_3), 16.7 (CH_3), 23.9 (CH_2), 24.1 (CH_2), 28.0 (CH_2), 30.4 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 37.8 (CH_2), 38.9 (CH_2), 39.0 (CH_2), 40.2 (CH_2), 69.7 (CH_2), 70.4 (CH_2), 71.0 (CH_2), 71.3 (CH_2), 108.0 (C), 109.5 (CH), 120.2 (CH), 133.0 (C), 133.9 (C), 145.6 (C), 145.7 (C), 150.6 (C), 150.8 (C), 170.7 (C=O), 174.2 (C=O), 174.6 (C=O).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.10.027.

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