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# Higher Order Iminodiacetic Acid Libraries for Probing Protein–Protein Interactions

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**Abstract**—Full details of the preparation of iminodiacetic acid diamide dimer (2040 compounds), trimer (560 compounds), and tetramer (1596 compounds) libraries by multistep convergent solution-phase synthesis for studying protein–protein interactions are provided. The libraries were assembled in a format providing small 8–10 compound mixtures and the deconvolution of many of the small mixtures to identify screening leads by resynthesis of the individual components have been conducted for 320 of the individual compounds to date. A representative example of the subsequent exploration of the structure–activity relationships for an identified receptor binding antagonist (200 additional individual compounds) and steps taken for potential elaboration to a receptor dimerization agonist are defined with preparation of representative linked dimers (70 compounds). © 1998 Elsevier Science Ltd. All rights reserved.

# Introduction

Ligand-induced receptor and protein dimerization or oligomerization has emerged as a general mechanism for signal transduction<sup>1,2</sup> and important members of many receptor superfamilies are activated by such a process. These include protein tyrosine kinase receptors (homoor heterodimerization),<sup>3</sup> class I cytokine receptors (homo- or heterodimerization),<sup>4</sup> serine/threonine kinase receptors (hetero-oligomerization),<sup>5</sup> and members of the TNF-receptor family (trimerization), Table 1.6 Within the cytokine receptor superfamily, the most extensively studied examples are the human growth hormone (hGHr),<sup>7</sup> prolactin (PRLr)<sup>8</sup> and erythropoietin receptors (EPOr),9 which form homodimers upon binding their endogenous protein ligands. Similarly, intracellular signal transduction often proceeds by protein-protein homo- or heterodimerization and important examples include activators of transcription (e.g. Myc-Max dimerization, JAK homo- and heterodimerization, STAT homo- and heterodimerization).<sup>10–12</sup>

Important therapeutic applications may emerge from either the development of agonists or antagonists of

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such receptor or protein dimerization and representative examples are provided in Table 2 for the cytokine receptor superfamily. That many of these receptors and proteins appear to bind their ligands using small clusters of residues for the majority of their binding interaction<sup>7–9</sup> has led to the expectation that small molecules may be capable of inducing dimerization and triggering a receptor response. Although the generation of detailed knowledge concerning the dimerization modes and ligand binding domains of single transmembrane domain receptors will provide a basis for the design of functional agonists as well as ligand antagonists, the noncontiguous and multiple binding domains involved in the protein-protein and ligand-protein interactions make it difficult to assess the dimerization mode or ligand binding domains in the absence of three-dimensional structural information. This is especially true considering the size of the typical endogenous protein ligands which themselves contain noncontiguous binding domains which interact with both subunits of the dimerized receptor.9 Our interest in combinatorial chemistry rested on its potential to provide candidate leads for promoting receptor activation by dimerization. This interest in studying receptor dimerization and activation coupled with the potential of utilizing a single approach for the discovery of antagonists and their

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Family	Examples	Activation characteristics
GH receptor IL-3 receptor IL-6 receptor IL-2 receptor	GHR, EPOR, PRLR, G-CSFR IL-3R, GM-CSFR, IL-5R IL-6R, LIFR, CNTFR, IL-11R IL-2Rα, IL-2Rβ, IL-4R, IL-7R	homodimers heterodimeration with $\beta_{\rm C}$ heterodimerization with gp130 heterodimerization with IL-2R $\gamma$
Protein–tyrosine kina Family	se receptors activated by dimerization or oligomerization Examples	
PDGF receptor EGF receptor FGF receptor IGF receptor HGF receptor VEGF receptor Neutrophin Eph receptor	PDGFR-α, PDGFR-β, SCFR, CSF-R, Fik-2 EGFR (erbB), erbB-2 (Neu), erbB-3, erbB-4 FGFR-1, FGFR-2, FGFR-3. FGFR-4 Insulin R, IGF-1R HGFR (Met), MSPR (Ron) Flt-1, Flt-2 (KDR) Trk, TrkB, TrkC Eph, Elk, Eck, Cck5, Sek, Eck, Erk	

#### Table 1. Class I cytokine receptors

Abbreviations: R, receptor; GH, growth hormone; EPO, erythropoietin; PRL, prolactin; IL, interleukin; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; PDGF, platelet-derived growth factor; SCF, stem cell factor; CSF, colony-stimulating factor; EGF, epidermal growth factor; FGF, fibroblast growth factor, IGF, insulin-like growth factor; HGF, hepatocyte growth factor; MSP, microphage-stimulating protein; VEGF, vascular endothelial growth factor; FN, fibronectin.

Table 2. Approved or potential therapeutic applications of cytokine agonists and antagonists

Cytokine	Agonist	Antagonist
EPO	anemias, selective blood donation	cancer, leukemia
ТРО	thrombocytopenia	
IL-2	cancer	histoincompatibility
IL-3	leukopenia, myeloid reconstitution	leukemia
IL-4	inflammation, cancer	allergy
IL-6	thrombocytopenia	cancer, osteoporosis, inflammation
IL-11	thrombocytopenia	
IL-12	cancer, infections	histoincompatibility, autoimmunity
G-CSF	neutropenia, myeloid reconstitution	leukemia
GM-CSF	leukopenia, myeloid reconstitution	leukemia
IFN α/β	cancer, viral infections, autoimmunity	inflammation
IFN γ	chronic granulonatous disease, infections	inflammation, autoimmunity

conversion to agonists<sup>13</sup> was one important element underlying our pursuit of solution-phase combinatorial chemistry at a time when solid-phase techniques were considered most useful.

Combinatorial chemistry, initially pursued with peptide and oligonucleotide libraries, has undergone rapid development providing a new paradigm for drug discovery.<sup>14</sup> Perhaps as a consequence of the extension from linear peptide and oligonucleotide synthesis, the majority of applications have relied on linear solidphase synthesis and methodological advances continue to extend common synthetic transformations to polymersupported versions.<sup>15</sup> A less commonly employed approach is the development of protocols for solutionphase combinatorial synthesis.<sup>16</sup> Preceding the disclosure of our own efforts on the development of a multistep solution-phase parallel synthesis of chemical libraries,<sup>17</sup> the single step solution-phase synthesis of mixture libraries was detailed by at least three groups.<sup>18-20</sup> In addition to continued advances in this work, progress in using solution-phase multicomponent reactions for generating combinatorial mixtures,<sup>21,22</sup> the use of resin capture as well as resin scavenger techniques<sup>23</sup> including ion-exchange resins for solid-phase acid-base extractions,<sup>17,23</sup> fluorous phase extractions,<sup>24</sup> and liquid-phase polymers<sup>25</sup> have been described.<sup>26</sup> Our efforts focused on the development of a technically non-demanding multistep, solution-phase strategy for the preparation of chemical libraries which relied on the removal of excess reactants and reagents by liquid-liquid or liquid-solid extractions.<sup>17</sup> The approach was shown to dependably

deliver pure individual compounds in large quantities (50-150 mg), and libraries of >1000 individual members were assembled in initial efforts.<sup>17</sup> It has been since implemented on scales producing 50-150 mg of the final materials in formats for the parallel synthesis of individual pure compounds,17 for modest sized libraries composed of small mixtures<sup>27-29</sup> (1000-10,000 member libraries, 10-100 compounds/mixture), or combinatorially assembled to provide larger compound libraries<sup>30,31</sup> (25,000-450,000 member libraries, 25,000-450,000 compounds/mixture) allowing its compatibility with any screening objective or protocol. Since the libraries are produced on a relatively large scale, they may be repeatedly dispensed for screening without depletion of the growing collection. These features along with its technically non-demanding implementation are among its greatest attributes.

Herein, we summarize its extension to the preparation of modest sized libraries suitable for probing proteinprotein interactions. This entailed the dimerization, trimerization, or tetramerization via sequential dimerization of iminodiacetic acid diamides using symmetrical carboxylic acids.<sup>27,28</sup> These complement a related approach we detailed that utilizes the olefin metathesis reaction to join iminodiacetic acid diamides and randomize the length of the linking tether.<sup>29-31</sup> In this latter case, we have also disclosed the twofold dimerization linkage of iminodiacetic acid diamides to provide higher order libraries containing up to eight variable groups and the accompanying technique of deletion synthesis deconvolution<sup>31</sup> to identify lead compounds derived from unsymmetrical dimerizations. Unlike the linear divergent synthesis of libraries derived from solid-phase synthesis, the convergent dimerizations are especially suited for solution-phase synthesis and would be precluded by typical solid-phase techniques where the combining components are on mutually exclusive solid phases (Fig. 1).

Dimerization of iminodiacetic acid diamides. In a design that minimizes the number of chemical reactions, that maximizes the diversity impact and that provides a convenient screening/deconvolution format, a library of 600 compounds was constructed in a  $6 \times 10 \times 10$  matrix with the final diversification being accomplished in one reaction to provide a mixture of 10 compounds containing variations in only the dicarboxylic acid linking domain (Fig. 2). For the three-step synthesis, this required six amines ( $R^1NH_2$ , A1–A6), 10 amines ( $R^2NH_2$ , B1-B10), and 10 dicarboxylic acids (HO<sub>2</sub>C-X-CO<sub>2</sub>H, C1-C10), and the conduct of 126 reactions to produce 60 sublibraries each containing 10 compounds containing variations only in the dicarboxylic acid linking domain. Deconvolution of such a mixture by resynthesis of the individual components from archived samples of the



Figure 1.

immediate precursor 3 is straightforward and the screening assays are applied to a modest mixture of 10 compounds. In addition to the advantages associated with the testing of a modest mixture of 10 compounds, the variability within each sublibrary was only in the nature of the linker. This might potentially minimize the false positive or negative screening results that accompany the testing of mixtures of compounds and permit the simultaneous examination of a range of linkers.

Reaction of *N*-BOC-iminodiacetic acid with the water soluble coupling reagent EDCI (1–1.05 equiv, DMF,  $25 \,^{\circ}$ C, 1 h),<sup>32</sup> and subsequent in situ anhydride ringopening with the six primary amines A1–A6 (R<sup>1</sup>NH<sub>2</sub>, 1 equiv, DMF, 25  $^{\circ}$ C, 12 h, 64–99%) was conducted on 20 mmol scales and provided approximately 7g of the monoamides **3** in superb yields (avg=90%, Table 3). Simply washing the crude product diluted in EtOAc with aqueous acid (10% aqueous HCl) served to remove unreacted R<sup>1</sup>NH<sub>2</sub>, EDCI and its reaction byproducts and provided the pure monoamides ( $\geq$ 95% pure).

Each of the six monoamides 3 was partitioned into 10 portions with an additional larger portion retained for archival and resynthesis purposes. Each portion was treated with the 10 amines (B1-B10, 1.1 equiv) and PyBOP (1.1 equiv, 2–2.2 equiv *i*-Pr<sub>2</sub>NEt, DMF, 25°C, 16 h, 7-99%) to afford 60 individual diamides 4 which were purified by sequential acid (10% aqueous HCl), base (saturated aqueous NaHCO<sub>3</sub>), and saturated aqueous NaCl extractions from EtOAc to remove reagent-derived reaction byproducts, unreacted starting material, and PyBOP. Each reaction was conducted on a 1.75 mmol scale corresponding to approximately 600 mg of **3** and provided **4** in yields that ranged from 7-100% (Table 3, avg = 53%). The lower yielding reactions were compromised by the water solubility of the products. Irrespective of the reaction efficiency or product recovery and without deliberate reaction optimization,



Figure 2.

the purities of the resulting diamides were uniformly satisfactory ( $\geq$ 90–95%) and the identities of products were confirmed by matrix characterization (HRMS, <sup>1</sup>H NMR and IR).

We briefly examined alternatives to PyBOP for the second coupling and found that EDCI and BOPCl were less effective than PyBOP (Scheme 1). In addition, although polymersupported EDCI<sup>33</sup> was ineffective at promoting the second coupling to provide the diamides **4**, it was found to constitute a convenient alternative for the in situ conversion of *N*-BOC-iminodiacetic acid (**2**) to the anhydride **1** for the first functionalization reaction with the generation of **3** (A**3**, 68%; DMF, 25°C, 20 h).

The assembly of the library of 600 compounds entailed 60 coupling reactions each composed of one iminodiacetic acid diamide 4 and an equimolar mixture of 10 dicarboxylic acids (C1-C10) producing 60 sublibraries of 10 compounds each containing variations only in the linking dicarboxylic acid. This was accomplished by acid-catalyzed deprotection of 4 (4 N HCl-dioxane, 25°C, 2h) conducted on each of the individual 60 iminodiacetic acid diamides (A1B1-A6B10, 0.15 mmol) followed by coupling (0.15 mmol PyBrOP, 0.45 mmol *i*-Pr<sub>2</sub>NEt, DMF, 25 °C, 12 h, 9–99%) of the crude amine hydrochloride salt with an equimolar mixture of the dicarboxylic acids C1-C10 (0.005 mmol each, 0.05 mmol total, 0.67 equiv). The use of the secondary amine in excess for an extended reaction time insured the complete consumption of the limiting diacid linkers and the near equimolar generation of each compound. Purification by sequential aqueous acid and aqueous base extractions served to remove the unreacted excess secondary amines derived from AXBX, any unreacted dicarboxylic acids C1-C10 as well as any monocarboxylic acid contaminant derived from partial reactions of C1-C10, the excess reagents (PyBrOP, i-Pr2NEt) and their reaction



Scheme 1.

Table 3. Yields (%) of 3 and 4 and isolated amounts (mg) and yields (%) of the 60 final sublibraries 5 (AXBXC1-10)

3	A1,	, 98	A2,	99	A3	, 64	A4, 99	A5, 99	A6, 80				
4	A1	A2	A3	A4	A5	A6	5	Al	A2	A3	A4	A5	A6
B1	90	95	а	75	81	100	B1	49 mg, 99%	49 mg, 99%	48 mg, 99%	49 mg, 99%	50 mg, 99%	36 mg, 74%
B2	12	17	9	18	27	18	B2	10 mg, 24%	13 mg, 29%	37 mg, 84%	10 mg, 21%	14 mg, 32%	6 mg, 13%
B3	81	81	84	67	50	97	B3	36 mg, 79%	46 mg, 93%	20 mg, 41%	4 mg, 9%	26 mg, 56%	38 mg, 59%
B4	89	68	40	56	64	89	B4	36 mg, 74%	39 mg, 76%	22 mg, 46%	37 mg, 73%	28 mg, 57%	36 mg, 73%
<b>B</b> 5	97	96	а	68	92	100	B5	47 mg, 99%	50 mg, 99%	49 mg, 99%	50 mg, 99%	31 mg, 59%	42 mg, 82%
<b>B</b> 6	57	85	50	43	46	86	<b>B</b> 6	18 mg, 44%	58 mg, 66%	9 mg, 21%	22 mg, 50%	12 mg, 27%	29 mg, 66%
<b>B</b> 7	13	15	19	13	7	36	<b>B</b> 7	11 mg, 29%	28 mg, 66%	18 mg, 46%	21 mg, 50%	11 mg, 26%	14 mg, 34%
<b>B</b> 8	43	32	18	26	33	50	<b>B</b> 8	7 mg, 13%	26 mg, 47%	21 mg, 40%	22 mg, 39%	18 mg, 33%	20 mg, 37%
B9	20	27	12	16	12	42	B9	20 mg, 42%	10 mg, 20%	10 mg, 20%	19 mg, 38%	18 mg, 37%	52 mg, 88%
B10	99	97	100	72	91	100	B10	52 mg, 91%	48 mg, 78%	27 mg, 45%	33 mg, 53%	40 mg, 68%	21 mg, 41%

<sup>a</sup>hygroscopic.

byproducts. Using this protocol, each of the 60 sublibraries of 10 compounds was produced in yields ranging from 9-99% (avg = 57%) in amounts ranging from 4-52 mg (Table 3). Irrespective of the conversion, the extractive purification coupled with the scale provided the libraries in high purity ( $\geq 90\%$ ) and in sufficient quantity suitable for direct broad screening in a variety of assays. Matrix characterization of the 60 sublibraries by MS and <sup>1</sup>H NMR confirmed the constitution of the mixtures and the detailed evaluation of the sublibrary A2B6C1-10 established its integrity as described below. Although <sup>1</sup>H NMR was not especially useful at quantitating the mixture components and only marginally useful at establishing the mixture identity, it was effective at identifying and quantitating contaminate secondary amine (AXBX), reagents (PyBrOP, *i*-Pr<sub>2</sub>NEt), and reagent-derived reaction byproducts ensuring the integrity of the extraction purification.

That this protocol would produce the sublibraries satisfactorily was first demonstrated by examining the individual and mixture couplings of 6 and 7, and with the individual and mixture construction of the sublibrary A2B6C1–C10. Although PyBOP and EDCI proved less satisfactory for promoting the individual and mixture couplings of 6 and 7 with C1-C10, PyBrOP<sup>34</sup> smoothly provided the linked dimers (Scheme 2). Excess i-Pr<sub>2</sub>NEt was employed to neutralize any residual acid remaining after BOC deprotection, and conducting the reaction with excess AXBX (0.3 mmol) versus dicarboxylic acid (0.1 mmol, 0.67 equiv) for 8-24 h in the presence of PyBrOP (0.3 mmol) and *i*-Pr<sub>2</sub>NEt (0.9 mmol) led to satisfactory conversions with the complete consumption of the C1-C10 dicarboxylic acid linker. Conventional extractive workup with aqueous 10% HCl to remove unreacted AXBX and i-Pr2NEt led to occasional loss of product due to its water solubility especially with the more hydrophilic sublibraries. The use of either an acidic ion exchange resin (liquid-solid extraction, DOWEX 50WX8-400)<sup>35</sup> or aqueous 20% HCl saturated

with NaCl improved the mass balance recovery and effectively removed the excess amine reactants and



Scheme 2.

reagents. Using either of these protocols, the extractive purification provided the individual compounds and the mixture sublibraries at an exceptional level of purity with satisfactory recoveries.

Prior to implementing the full library synthesis, the A2B6C1-C10 sublibrary was prepared by running each of the 10 individual coupling reactions and the mixture coupling reaction (Scheme 3). The conversions and recovery (70–100%, 90% avg) as well as the purity (>90–95%) of the individual reactions were uniformly high and correspond nicely to the mixture coupling reaction (95% yield, >90% purity by <sup>1</sup>H NMR/ HPLC). This is illustrated with the preparation of A2B6C2 (Fig. 3) where the <sup>1</sup>H NMR spectra of each of the two intermediates and the final reaction product are presented as they were obtained directly from the reaction sequence and extraction purification. Following characterization (<sup>1</sup>H NMR, IR, HRMS) of the separate products (A2B6C1-A2B6C10), these were subjected to reverse-phase HPLC separation, both separately and after pooling in equimolar proportions. The MS established the presence of each mixture component and both <sup>1</sup>H NMR and HPLC revealed no significant differences in the reconstituted and combinatorial mixtures. Thus, the mixture coupling and the subsequent extraction purification were established to provide a near equimolar mixture of the reaction products and each of the 10 components was found to be present in the final sublibrary. In part, this may be attributed to the choice of coupling reaction conditions that ensure

MeC 1) HCl-dioxane 2) C1 C2 C10 and A2B6 C1+C2+....C10 PyBrOP, i-Pr2NEt DMF, 25 °C, 16 h OMe MeC OMe Individual and Mixture Coupling Yields A2B6C1 81% A2B6C5 98% A2B6C2 89% A2B6C6 100% A2B6C3 70% A2B6C7.8 81% A2B6C4 A2B6C9,10 97% 100% A2B6C1-C10 95%



Figure 3. Comparison <sup>1</sup>H NMR spectra (DMSO- $d_6$ , 400 MHz) of A2, A2B6, and A2B6C2 as isolated.

near complete consumption of the limiting diacids and to the choice of the diacid linkers which have little differential impact on the relative solubility of the final products.

In the course of screening the library against various targets, the A1B10C1–C10, A2B10C1–C10, A4B10C1–C10, A5B10C1–C10, A6B10C1–C10, A2B1C1–C10, A4B1C1–C10, A5B4C1–C10, and A3B3C1–C10 sublibraries have been deconvoluted to provide the 90 individual compounds. In addition, this initial library of 600 compounds was subsequently extended to the additional 1440 compound library illustrated in Fig. 4 enlisting a slightly modified and expanded set of 80 individual diamides 4 (*cf.* Fig. 5) and their coupling with two different mixture sets of dicarboxylic acids C11–C20



Figure 4.

and **C21–C28**. The former produced 80 mixtures of 10 compounds each (800 compounds) and the latter provided 80 mixtures of eight compounds each (640 compounds) in average final coupling yields of 65% and 63%, respectively.

**Trimerization of iminodiacetic acid diamides.** Complementary to the approach of assembling iminodiacetic acid diamides dimers through a final *N*-acylation

with symmetrical dicarboxylic acids, a library of 560 symmetrical trimers was assembled in a  $8 \times 10 \times 7$  matrix with the final reaction being conducted with the tricarboxylic acid mixture C31-C37 to provide mixtures of seven compounds containing variations only in the linking tricarboxylic acid domain (Fig. 5). For the three-step synthesis, this utilized eight amines (A1-A8), 10 amines (B1–B10), and seven tricarboxylic acids (C31–C37) in 168 reactions to produce 80 sublibraries each containing seven compounds. The library screening is conducted with small mixtures of seven compounds, and deconvolution by resynthesis of the seven individual components of the final mixtures from archived samples of the 80 immediate precursors 4 is straightforward. The preceding or simultaneous examination of the intermediate N-BOC iminodiacetic acid diamides 4 permits, in principle, the identification of competitive binders (antagonists) that upon trimerization might function as agonists of ligandinduced protein homodimerization or trimerization.

Reaction of N-BOC-iminodiacetic acid (2) with EDCI (1.0 equiv, DMF, 25°C, 1 h) and subsequent treatment with A1-A8 (1 equiv, DMF, 25°C, 70-99%) was conducted on 20 mmol scales to provide 6-10 g of each of the eight monoamides 3 in superb yields (Table 4, avg = 89%). Simply washing the crude product diluted with EtOAc with 10% aqueous HCl and saturated aqueous NaCl served to remove unreacted amine, EDCI and its byproducts to provide the pure monoamides  $(\geq 95\%$  pure). Each monoamide was divided into 10 portions and treated with the 10 amines B1-B10 (1.5 equiv) and PyBOP (1-1.1 equiv, 3 equiv i-Pr<sub>2</sub>NEt, DMF, 25 °C, 16 h, 44-100%) to afford the 80 diamides 4 which were purified by sequential 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub> and saturated aqueous NaCl extractions. Each reaction was conducted on a 1.5 mmol scale (ca. 0.5 g of monoamide) providing 1.6–0.35 g of 4 (Table 4, avg = 92%) in  $\geq 95\%$  purity independent of the reaction efficiency. The final step in the preparation of the library of 560 compounds entailed 80 coupling reactions of each diamide 4 with an equimolar mixture of the seven tricarboxylic acids (C31-C37) producing 80 sublibraries of seven compounds. This was accomplished by acid-catalyzed deprotection of 4 (0.15 mmol, 4 N HCl-dioxane, 25 °C, 3 h) followed by coupling (0.15 mmol PyBrOP, 1.5 mmol *i*-Pr<sub>2</sub>NEt, DMF, 25°C, 16h, 19-100%) of the crude amine hydrochloride with an equimolar mixture of the tricarboxylic acids C31-C37 (0.005 mmol each, 0.035 mmol total, 0.7 equiv). The secondary amine was used in excess and the reactions were run for an extended time period to drive the couplings to completion ensuring a near equimolar generation of each compound. Purification by sequential extractions with 10% aqueous HCl  $(3\times)$ , saturated aqueous NaHCO<sub>3</sub>  $(2\times)$ , and saturated aqueous NaCl provided the final mixtures (Table 5,



Figure 5.

avg = 86%, 10–34 mg) free of contaminant starting materials, reagents and their byproducts, and any partially coupled free carboxylic acid ( $\geq$ 95% pure). Matrix characterization of the 80 sublibraries by MS and <sup>1</sup>H NMR confirmed the constitution of the mixtures and a comparison of the sublibrary **A1B3C31–C37** with a reconstituted mixture prepared by combining an equimolar mixture of the individual components established its integrity.

Of these mixtures, the A1B2C31–37, A1B3C31–37, A1B9C31–37, A1B9C31–37, A1B10C31–37, and A2B6C31–37 sublibraries have been prepared as 35 individual compounds (deconvoluted) in the course of screening efforts to date.

Sequential dimerizations of iminodiacetic acid diamides. An additional approach that complements our disclosure of a twofold dimerization of iminodiacetic acid diamides via the olefin metathesis reaction that ultimately incorporates eight variable groups and randomizes the length of the linking tether adding a ninth degree of diversification,<sup>31</sup> entails their twofold dimerization by sequential coupling with appropriately functionalized dicarboxylic acids. This is illustrated with the preparation of the tetramers 17 derived first from dimerization of 4 with N-BOC-iminodiacetic acid (2) to provide 16 which, following N-BOC deprotection, sets up the second dimerization conducted with a range of dicarboxylic acids (Scheme 4, Fig. 6). In addition to the eight variable groups incorporated into the iminodiacetic acid diamides, a ninth diversification is incorporated with the second set of linking dicarboxylic acids. A library of 1596 compounds was prepared in a format of 168 mixtures of 10 or 8 compounds each. Thus, 42 individual iminodiacetic acid diamides 4 were prepared in a  $3 \times 14^{36}$  format on a scale analogous to that described previously. Deprotection of 4 (4 N HCldioxane, 25°C, 4h) followed by the individual dimerization coupling of each amine hydrochloride with N-BOC-iminodiacetic acid (1.0 equiv 2, 3 equiv PyBrOP, 9 equiv *i*-Pr<sub>2</sub>NEt, DMF, 25 °C, 16 h, 31–100%) provided 16. Conducting the reaction with excess amine hydrochloride (3 molar equiv) and stoichiometry limiting dicarboxylic acid insured complete dimerization coupling and the excess starting amine, residual carboxylic acid, reagents, and reagent byproducts were removed by acid/base extraction providing the 42 individual dimers 16 ( $\geq$ 95% pure, avg yield = 81%). These individual 42 diamide dimers (1.5 equiv/3 molar equiv), which themselves constitute an important dimer sublibrary for antagonist screening, were deprotected (4 N HCl-dioxane, 25°C, 4h) and subsequently coupled (3 equiv PyBrOP, 9 equiv i-Pr<sub>2</sub>NEt, DMF, 25 °C, 16 h, 10-97%, avg = 80%) with 38 dicarboxylic acids in mixture groupings of 10 or 8 (C1-C10, C11-C20, C21-C28, and C41–C50) producing 168 mixtures each containing 10 or 8 compounds with mixture variations only in the last

Table 4. Yields (%) of 3 and 4

3	A1, 97	A2, 99	A3, 83	A4, 90	A5, 89	A6, 92	A7, 91	A8, 70
4	Al	A2	A3	A4	A5	A6	A7	A8
B1	89	100	85	100	76	100	76	100
B2	70	85	100	87	100	100	91	100
B3	86	89	78	100	76	78	79	90
B4	100	99	93	79	100	100	75	85
B5	90	100	100	87	94	92	78	100
<b>B</b> 6	90	100	98	96	89	100	90	44
<b>B</b> 7	75	93	88	100	100	89	100	100
<b>B</b> 8	100	100	100	89	100	100	94	95
B9	93	100	100	100	96	100	97	86
B10	78	94	95	100	100	83	100	100

Table 5. Yields (%) and isolated amounts (mg) of the 60 final sublibraries 15 (AXBXC31-37)

5	A1	A2	A3	A4	A5	A6	A7	A8
<b>B</b> 1	61 mg, 100%	58 mg, 100%	45 mg, 91%	68 mg, 100%	51 mg, 92%	65 mg, 100%	51 mg, 100%	42 mg, 75%
B2	62 mg, 100%	64 mg, 100%	48 mg, 100%	74 mg, 100%	62 mg, 100%	67 mg, 100%	60 mg, 100%	50 mg, 98%
<b>B</b> 3	44 mg, 81%	49 mg, 86%	31 mg, 62%	51 mg, 89%	47 mg, 85%	55 mg, 97%	56 mg, 78%	20 mg, 36%
B4	48 mg, 85%	55 mg, 94%	30 mg, 59%	52 mg, 88%	43 mg, 75%	56 mg, 80%	59 mg, 80%	22 mg, 38%
B5	90 mg, 100%	78 mg, 100%	85 mg, 100%	80 mg, 100%	83 mg, 100%	43 mg, 100%	68 mg, 100%	57 mg, 99%
<b>B</b> 6	36 mg, 74%	30 mg, 63%	17 mg, 33%	39 mg, 75%	32 mg, 64%	60 mg, 84%	50 mg, 74%	10 mg, 18%
<b>B</b> 7	51 mg, 100%	63 mg, 100%	43 mg, 85%	61 mg, 100%	54 mg, 100%	51 mg, 100%	62 mg, 100%	43 mg, 84%
<b>B</b> 8	41 mg, 85%	54 mg, 100%	40 mg, 79%	53 mg, 100%	45 mg, 89%	33 mg, 100%	60 mg, 100%	32 mg, 64%
B9	44 mg, 80%	48 mg, 91%	35 mg, 61%	54 mg, 92%	49 mg, 86%	54 mg, 93%	68 mg, 92%	18 mg, 30%
B10	70 mg, 100%	65 mg, 100%	56 mg, 82%	77 mg, 100%	71 mg, 100%	82 mg, 100%	84 mg, 100%	57 mg, 84%

linking dicarboxylic acid domain. Thus, the library preparation and screening are conducted with small mixtures of 8 or 10 compounds, and deconvolution by resynthesis of the individual components of a final mixture is straightforward from archived samples of the 42 precursors 16. Matrix full characterization of the 42 dimers 16, full characterization of representative individual tetramers 17, and the resynthesis of the 176 individual members of A2B4C1-10, A2B4C21-28, A2B4C41-50. A2B6C21-28, A2B6C41-50, A6B6C21-28, A6B6C41-50, A7B3C11-20, A7B4C11-20, A7B4C21-28, A7B4C41-50, A7B6C11-20, A7B6C21-28, A7B6C41-50, A7B10C11-20, A7B14C21-28, A7B14C41-50, A7B15C21-28, and A7B15C41-50 have been conducted in deconvolution studies to identify screening leads. The comparison of the reconstituted authentic equimolar mixture with the sublibraries established the integrity of the mixtures (A2B4C1-10, A2B4C41-50), and MS characterization of the A2B4C1-10, A2B2"C11-20, and A2B4C41-50 sublibraries confirmed the presence of all 10 components in the final mixtures.

**Elaboration of lead antagonists.** Follow up libraries based upon the results of screening assays can be conducted with the preparation of individual compounds

for a more complete definition of the structure-activity relationships. One of the more extensive series we have examined was based on the identification of 5, A6B10C4 as a weak antagonist of endogenous ligand binding to a target receptor in which the B10 subunit was critical to observation of activity while that of A6 simply modulated it (cf. Fig. 2). Based on these results, an extensive series of A substitutions were examined and a more classical detailed examination of the critical **B10** subunit was conducted simultaneously. The synthesis of 114 additional compounds containing the A substitutions was carried out by sequential couplings to iminodiacetic acid (Scheme 5, Fig. 7), whereas 77 compounds containing B10 analogues were synthesized in one step from diacid 20 which already contained the 4-fluorophenethylamine (A6) and isophthalic acid (C4) components (Scheme 5, Fig. 8).

Subsequent to these studies which identified 5: A2B10C4, A5B10C4, A6B10C4, A7B10C4, A8B10C4, A12B10C4, and A6B23C4 as viable ligand binding antagonists, their potential conversion into agonists of receptor dimerization and activation through chemical dimerization was explored. This entailed adding a protected C5-aminoethoxy appendage to the isophthalic core which allows a second dimerization of the iminodiacetic acid diamides providing the target tetramers (Scheme 6). The seven individual iminodiacetic acid diamides were coupled to **22** using conditions analogous to those previously described. Deprotection of the primary amine (4 N HCl–dioxane, 25 °C, 2 h) was followed by dimerization coupling (2.2 equiv of amine hydrochloride, 3 equiv PyBrOP, 6 equiv *i*-Pr<sub>2</sub>NEt, DMF, 25 °C, 12 h) with 10 individual dicarboxylic acids of varied shape, length, and hydrophilicity (Fig. 9). Purification using acid/base extractions or solid/liquid extractions cleanly provided the 70 individual compounds in good to excellent yield (70–99%). One set of 10 products was fully characterized, and MS analysis confirmed the identity of the desired tetramers.

**Conclusions.** Complementary to our use of the olefin metathesis reaction to assemble higher order iminodiacetic acid diamide libraries,<sup>29–31</sup> their dimerization, trimerization, or sequential dimerizations with symmetrical carboxylic acids provide a powerful approach to the convergent synthesis of combinatorial libraries







Figure 6.



## Scheme 5.

applicable to the discovery of antagonists of ligand induced protein-protein dimerization/oligomerization and their conversion to potential agonists. Such applications are in progress and will be disclosed in due course.

# Experimental

*N*-((*tert*-Butyloxy)carbonyl)iminodiacetic acid (2). A 1 L flask was charged with iminodiacetic acid (13.3 g, 100 mmol), dioxane (200 mL) and NaOH (8 g,

200 mmol) dissolved in 200 mL of water. When a homogeneous solution had formed, di-*tert*-butyl dicarbonate (25 mL, 110 mmol) was added in portions. After stirring at  $25 \degree \text{C}$  for 72 h, the reaction mixture was washed with Et<sub>2</sub>O (2 ×100 mL) and the aqueous layer was then acidified with the addition of 10% aqueous HCl (100 mL). This was extracted with EtOAc ( $3 \times 150 \text{ mL}$ ) and the combined organic layers were washed with saturated aqueous NaCl ( $2 \times 150 \text{ mL}$ ), and dried (Na<sub>2</sub>SO<sub>4</sub>). Concentration provided 30 g of a colorless oil, which upon addition of 30 mL of EtOAc followed by 60 mL of hexane afforded **2** (17.2 g, 74%) as colorless crystals: mp 135–137 °C.

General procedure for 3: N-((tert-butyloxy)carbonyl)-N'-(2-(4-methoxyphenyl)ethyl)iminodiacetic acid monoamide (3, A2). Method A: A mixture of 2 (4.66 g, 20 mmol) and EDCI (3.8 g, 20 mmol) in 60 mL of anhydrous DMF was stirred for 1 h at 25 °C. 4-Methoxyphenethyl amine (A2, 3.0 g, 20 mmol) was added to the resulting solution in four portions (slightly exothermic). The reaction mixture was stirred for 20h at 25 °C before it was poured into 250 mL of 10% aqueous HCl in a separatory funnel. The product was extracted into EtOAc  $(3 \times 200 \text{ mL})$  and the combined organic phases were washed with 10% aqueous HCl (2×200 mL), saturated aqueous NaCl (2×200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed in vacuo to afford 7.3 g (99%) of the title compound as a white solid: <sup>1</sup>H NMR (DMSO $d_6$ , 500 MHz)  $\delta$  8.27 (m, 1H), 7.12 (m, 2H), 6.84 (m, 2H), 3.91, 3.87, 3.83 and 3.80 (four s, 4H), 3.70 (s, 3H), 3.25 (m, 2H), 2.64 (m, 2H), 1.35 and 1.32 (two s, 9H); IR (film) V<sub>max</sub> 2976, 2931, 1705, 1635, 1513, 1456, 1393, 1368, 1248, 1164, 1032, 824, 600 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 367.1862 (M+H<sup>+</sup>, C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub> requires 367.1869).

Method B: A solution of 2 (0.058 g, 0.25 mmol) dissolved in DMF (5 mL) was added to polymer-bound EDCI<sup>33</sup> (0.5 g, 0.5 mmol/g, 0.25 mmol). This mixture was allowed to stand for 1 h at 25 °C. Tyramine (A3, 0.041 g, 0.30 mmol) was added and the mixture was allowed to stand for 20 h. After filtration, the resin was washed with DMF (5 mL) and EtOAc (50 mL). The combined organic phases were washed with 10% aqueous HCl (2×25 mL) and saturated aqueous NaCl (2×50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 0.060 g (68%) of A3 identical to that prepared with solution-phase EDCI.

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(phenyl)ethyl)iminodiacetic acid monoamide (3, A1): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.29 (m, 1H), 7.27 (m, 5H), 3.90, 3.86, 3.83 and 3.80 (four s, 4H), 3.33 (m, 2H), 2.73 (m, 2H), 1.35 and 1.33 (two s, 9H); IR (film)  $V_{\text{max}}$  3291, 2977, 2931, 1700, 1653, 1635, 1559, 1509, 1497, 1456, 1394, 1368, 1251,



Figure 7. Synthesis of a series of analogues for optimization of the A component of 5, AXB10C4 (A-scan).



Figure 8. Synthesis of a series of analogues for optimization of the B component of 5, A6BXC4 (B-scan).

1163, 1141, 857, 750, 700 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 337.1769 (M + H<sup>+</sup>, C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub> requires 337.1763).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-hydroxyphenyl)ethyl)iminodiacetic acid monoamide (3, A3): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  9.19 (d, 1H, *J*=3.8 Hz), 8.26 (m, 1H), 6.99 (d, 2H, *J*=6.0 Hz), 6.66 (d, 2H, *J*=6.0 Hz), 3.91, 3.87, 3.83 and 3.80 (four s, 4H), 3.22 (m, 2H), 2.60 (m, 2H), 1.35 and 1.33 (two s 9H); IR (film) *V*<sub>max</sub> 3406, 1653, 1559, 1540, 1517, 1457, 1250, 1049, 1025, 1001, 826, 765 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m/z* 353.1719 (M+H<sup>+</sup>, C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub> requires 353.1713).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(3-methoxyphenyl)ethyl)iminodiacetic acid monoamide (3, A4): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.26 (m, 1H), 7.19 (m, 1H), 6.76 (m, 3H), 3.90, 3.87, 3.84 and 3.81 (four s, 4H), 3.73 (s, 3H), 3.32 (m, 2H), 2.69 (q, 2H, *J*=10 Hz), 1.35 and 1.32 (two s, 9H); IR (film)  $V_{\text{max}}$  3853, 3744, 3675, 3648, 3294, 2976, 1700, 1653, 1635, 1584, 1559, 1506, 1490, 1457, 1394, 1368, 1259, 1165, 1038, 963, 877, 781, 697 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 367.1860 (M+H<sup>+</sup>, C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub> requires 367.1869).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(4-methoxybenzyl)iminodiacetic acid monoamide (3, A5): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.64 (m, 1H), 7.19 (m, 2H), 6.87 (m, 2H), 4.23 (d, 2H, *J* = 5.8 Hz), 3.94, 3.92, 3.89 and 3.86 (four s, 4H), 3.72 (s, 3H), 1.35 and 1.29 (two s, 9H); IR (film)  $V_{\text{max}}$  3406, 2978, 2530, 1700, 1653, 1559, 1514, 1457, 1394, 1368, 1302, 1250, 1165, 1142, 1048, 1026, 998, 908, 827, 766 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m/z* 353.1720 (M + H<sup>+</sup>, C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub> requires 353.1713).



Scheme 6.

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2(4-fluorophenyl)ethyl)iminodiacetic acid monoamide (3, A6): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.23 (m, 1H), 7.24 (m, 2H), 7.09 (m, 2H), 3.89, 3.86, 3.82 and 3.80 (four s, 4H), 3.30 (m, 2H), 2.71 (m, 2H), 1.35 and 1.32 (two s, 9H); IR (film)  $V_{\text{max}}$  3852, 3744, 3675, 3648, 3295, 2978, 1700, 1684, 1653, 1635, 1559, 1540, 1510, 1457, 1394, 1368, 1222, 1161, 896, 772 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 355.1661 (M+H<sup>+</sup>, C<sub>17</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub> requires 355.1669).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(5-((benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid monoamide (3, A7): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.30 (m, 5H), 5.10 (m, 2H), 4.00 (m, 4H), 3.70 (m, 4H), 3.30 (m, 2H), 1.80 (m, 2H), 1.50 (m, 13H); IR (film) *V*<sub>max</sub> 3328,



Figure 9.

2949, 1706, 1634, 1537, 1455, 1393, 1252, 1165, 1027 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 642.1446 (M + Cs<sup>+</sup>, C<sub>24</sub>H<sub>35</sub>N<sub>3</sub>O<sub>9</sub> requires 642.1428).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(4-(1',4'-dioxolano)piperidino)iminodiacetic acid monoamide (3, A8): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  4.21 (s, 2H), 3.97 (m, 4H), 3.88 (s, 2H), 3.75 (t, 2H, *J*=6 Hz), 3.50 (t, 2H, *J*=6 Hz), 1.74 (m, 4H), 1.42 and 1.418 (two s, 9H); IR (film) *V*<sub>max</sub> 3462, 2973, 1702, 1609, 1452, 1396, 1241, 1140, 1103, 944, 908 cm<sup>-1</sup>; FABHRMS (NBA) *m/z* 359.1830 (M+H<sup>+</sup>, C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub> requires 359.1818).

General procedure for 4: N-((tert-butyloxy)carbonyl)-N'-(4-methoxybenzyl)-N''-(3-fluoro-5-(trifluoromethyl)benzyl)iminodiacetic acid diamide (4, A5B5). The acid 3, A5 (0.616 g, 1.75 mmol) was dissolved in DMF (18 mL)and added to a flask containing  $i-Pr_2NEt$  (0.45g, 3.5 mmol) and 3-fluoro-5-(trifluoromethyl)benzylamine (B5, 0.37 g, 1.9 mmol). PyBOP (1.00 g, 1.9 mmol) was added in portions and the resulting mixture was stirred overnight (16h). The reaction mixture was poured into a separatory funnel containing 100 mL of 10% aqueous HCl. Extraction into EtOAc  $(2 \times 40 \text{ mL})$  followed by washing of the combined organic phases with 10% aqueous HCl (2×40 mL), saturated aqueous NaCl (1×40 mL), saturated aqueous NaHCO<sub>3</sub> (2×40 mL) and saturated aqueous NaCl  $(1 \times 40 \text{ mL})$ , drying  $(Na_2SO_4)$ and evaporation provided 0.79 g (90%) of 4, A5B5 as an oil: <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  9.50 (m, 0.5H), 9.30 (m, 0.5H), 8.96 (m, 1H), 7.49 (m, 3H), 7.18 (d, 2H, J = 6.4 Hz), 6.84 (d, 2H, J = 8.8 Hz), 4.40 (m, 2H), 4.24 (m, 2H), 4.04 (s, 4H), 3.71 (s, 3H), 1.28 and 1.27 (two s, 9H); IR (film) V<sub>max</sub> 3246, 3071, 2978, 2935, 2839, 1656, 1610, 1563, 1514, 1456, 1394, 1366, 1343, 1302, 1251, 1230, 1170, 1131, 1030, 976, 959, 874, 847, 759, 718, 699 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 550.1291  $(M + Na^+, C_{25}H_{29}F_4N_3O_5$  requires 550.1941).

The remaining **AXBX** were characterized in a matrix format which allowed for an assessment of the integrity of each of the coupling reactions.

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2-(phenyl)ethyl)-*N*''-(2-(2,5-dimethoxyphenyl)ethyl)iminodiacetic acid diamide (4, A1B1): <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  8.68 (m, 2H), 7.25 (m, 5H), 6.87 (d, 1H, J= 8.5 Hz), 6.73 (s, 2H), 3.79 and 3.75 (two s, 2H), 3.72 (s, 3H), 3.72 and 3.68 (two s, 2H), 3.67 (s, 3H), 3.33 (m, 4H), 2.70 (m, 4H), 1.33 and 1.31 (two s, 9H); IR (film)  $V_{\text{max}}$  3423, 3074, 2975, 2934, 2833, 1970, 1651, 1567, 1500, 1454, 1393, 1367, 1337, 1305, 1250, 1225, 1165, 1141, 1043, 960, 895, 850, 802, 752, 701, 666 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 632.1745 (M+Cs<sup>+</sup>, C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>6</sub> requires 632.1737).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(2,5-dimethoxyphenyl)ethyl)-*N''*-((5-(benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A7B1): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.27 (m, 5H), 6.74 (m, 3H), 5.70 (m, 1H), 5.08 (s, 2H), 4.35 (m, 1H), 3.71 (m, 13H), 3.50 (m, 2H), 3.25 (m, 2H), 2.75 (m, 2H), 1.80 (m, 2H), 1.55 (m, 2H), 1.38 (m, 11H); IR (film) *V*<sub>max</sub> 3247, 3064, 2938, 1702, 1654, 1560, 1500, 1458, 1395, 1361, 1225, 1163, 1042, 847 cm<sup>-1</sup>; FABHRMS (NBA– CsI) *m/z* 805.2459 (M+Cs<sup>+</sup>, C<sub>34</sub>H<sub>48</sub>N<sub>4</sub>O<sub>10</sub> requires 805.2425).

*N*-((*tert*-Butyloxy)carbonyl)-*N*<sup>*t*</sup>-(2-(4-fluorophenyl)ethyl)-*N*<sup>*t*</sup>-(3-(*N*-pyrrolidin-2-onyl)propyl)iminodiacetic acid diamide (4, A6B2): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$ 8.65 (m, 2H), 7.25 (m, 2H), 7.09 (m, 2H), 3.79 (d, 2H, *J*=6 Hz), 3.77 and 3.75 (two s, 2H), 3.30 (m, 4H), 3.17 (m, 2H), 3.08 (m, 2H), 2.77 (m, 2H), 2.19 (m, 2H), 1.96 (m, 2H), 1.58 (m, 2H), 1.33 and 1.31 (two s, 9H); IR (film)  $V_{\text{max}}$  3415, 3082, 2977, 2936, 1654, 1560, 1510, 1458, 1395, 1369, 1253, 1221, 1163, 1144, 1100, 1016, 961, 847, 761 cm<sup>-1</sup>; FABHRMS (NBA– CsI) *m*/*z* 611.1659 (M+Cs<sup>+</sup>, C<sub>24</sub>H<sub>35</sub>FN<sub>4</sub>O<sub>5</sub> requires 611.1646).

*N*-((*tert*-Butyloxy)carbonyl)-*N*"-(2-(phenyl)ethyl)-*N*"-(1,2, 3,4-tetrahydro-1-(naphthyl)iminodiacetic acid diamide (4, A1B2'): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.20 (m, 9H), 5.20 (m, 1H), 3.85 (m, 4H), 3.48 (m, 2H), 2.80 (m, 4H), 1.90 (m, 4H), 1.41 and 1.39 (two s, 9H); IR (film) *V*<sub>max</sub> 3251, 2932, 1702, 1648, 1560, 1453, 1392, 1250, 1167 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 488.2508 (M + Na<sup>+</sup>, C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub> requires 488.2525).

*N*-((*tert*-Butyloxy)carbonyl)-*N*''-(2-(4-methoxyphenyl)ethyl)-*N*'''-(2-(3,4-dimethoxyphenyl)ethyl)iminodiacetic acid diamide (4, A2B3): <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  8.67 (m, 2H), 7.13 (m, 2H), 6.84 (m, 4H), 6.72 (d, 1H, *J*=8.0 Hz), 3.79 and 3.76 (two s, 2H), 3.73 (s, 3H), 3.72 and 3.70 (two s, 2H), 3.70 (s, 6H), 3.33 (m, 4H), 2.65 (m, 4H), 1.31 (s, 9H); IR (film) *V*<sub>max</sub> 3250, 3074, 2935, 2835, 2056, 1650, 1212, 1571, 1514, 1454, 1417, 1393, 1367, 1301, 1247, 1159, 1141, 1029, 960, 895, 848, 809, 762, 665 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 662.1850 (M+Cs<sup>+</sup>, C<sub>28</sub>H<sub>39</sub>N<sub>3</sub>O<sub>7</sub> requires 662.1842).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-hydroxyphenyl)ethyl)-*N''*-(3,4,5-trimethoxybenzyl)iminodiacetic acid diamide (4, A3B4): <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  9.20 (m, 1H), 8.70 (m, 1H), 7.01 (m, 2H), 6.68 (m, 2H), 6.65 (s, 1H), 6.62 (s, 1H), 4.30 (m, 2H), 3.85 (m, 4H), 3.78 and 3.76 (two s, 6H), 3.62 (s, 3H), 3.26 (m, 2H), 3.60 (m, 2H), 1.37 and 1.26 (two s, 9H); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  6.59 (d, 2H, *J*=8 Hz), 6.32 (d, 2H, *J*=8 Hz), 6.20 (d, 2H, *J*=9 Hz),4.00 (m, 2H), 3.45 (m, 13H), 3.00 (m, 2H), 2.21 (m, 2H), 0.98 and 0.92 (two s, 9H); IR (film)  $V_{\text{max}}$  3426, 2359, 1650, 1515, 1456, 1238, 1126 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 664.1656 (M + Cs<sup>+</sup>, C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>8</sub> requires 664.1635).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2-(4-fluorophenyl)ethyl)-*N*''-(3,4,5-trimethoxybenzyl)iminodiacetic acid diamide (4, A6B4): <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  9.15 (m, 0.5H), 9.01 (m, 0.5H), 8.72 (m, 1H), 7.24 (m, 2H), 7.07 (m, 2H), 6.61 (d, 2H, *J* = 11.4 Hz), 4.25 (m, 2H), 3.88 (s, 2H), 3.83 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 3.30 (m, 2H), 2.71 (m, 2H), 1.30 and 1.25 (two s, 9H); IR (film) *V*<sub>max</sub> 3348, 3073, 2997, 2839, 1700, 1653, 1593, 1559, 1509, 1457, 1424, 1394, 1367, 1329, 1237, 1162, 1128, 1005, 959, 898, 826, 755, 667 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 666.1574 (M+Cs<sup>+</sup>, C<sub>27</sub>H<sub>36</sub>FN<sub>3</sub>O<sub>7</sub> requires 666.1592).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(5-((benzyloxycarbonyl)amino)-5-methoxylcarbonyl)pentyl)-*N'*-(3,4,5-trimethoxybenzyl)iminodiacetic acid diamide (4, A7B4): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.59 and 8.20 (two s, 1H, NH), 7.25 (m, 5H), 6.60 and 6.52 (two s, 2H), 5.54 (apparent d, 1H), 5.08 (apparent d, 2H), 4.38 (m, 3H), 3.88 (m, 13H), 3.32 (s, 3H), 3.25 (m, 2H), 1.80 (m, 2H), 1.74 (m, 2H), 1.68 (m, 2H), 1.38 and 1.29 (two s, 9H); IR (film) *V*<sub>max</sub> 3426, 2995, 1641, 1508 cm<sup>-1</sup>; FABHRMS (NBA– CsI) *m*/*z* 821.2398 (M+Cs<sup>+</sup>, C<sub>34</sub>H<sub>48</sub>N<sub>4</sub>O<sub>11</sub> requires 821.2374).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2-(4-fluorophenyl)ethyl)-*N*''-(3-fluoro-5-(trifluoromethyl)benzyl)iminodiacetic acid diamide (4, A6B5): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.40 (d, 1H), 7.10 (m, 4H), 6.94 (m, 2H), 4.48 (m, 2H), 3.82 (m, 4H), 3.46 (m, 2H), 2.77 (m, 2H), 1.36 and 1.32 (two s, 9H); IR (film) *V*<sub>max</sub> 3248, 3072, 2978, 2931, 1649, 1561, 1508, 1455, 1390, 1343, 1249, 1226, 1167, 1132, 1020, 972, 955, 867, 826, 773, 714, 697, 550 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 530.2063 (M+H<sup>+</sup>, C<sub>25</sub>H<sub>28</sub>F<sub>5</sub>N<sub>3</sub>O<sub>4</sub> requires 530.2078).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-methoxyphenyl)ethyl)-*N''*-di(2-methoxyethyl)iminodiacetic acid diamide (4, A2B6): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.70 (m, 1H), 7.12 (m, 2H), 6.82 (m, 2H), 4.15 (s, 1H), 4.10 (s, 1H), 3.74 (s, 1H), 3.71 (s, 3H), 3.68 (s, 1H), 3.43 (m, 10H), 3.26 (s, 3H), 3.23 (s, 3H), 2.64 (m, 2H), 1.34 and 1.32 (two s, 9H); IR (film)  $V_{max}$  3852, 3749, 3674, 3647, 3446, 2932, 1700, 1684, 1653, 1635, 1559, 1540, 1513, 1457, 1394, 1367, 1247, 1176, 1116, 1033, 844 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 614.1820 (M+Cs<sup>+</sup>, C<sub>24</sub>H<sub>39</sub>N<sub>3</sub>O<sub>7</sub> requires 614.1842).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2-(4-hydroxyphenyl)ethyl)-*N*"-di(2-methoxyethyl)iminoacetic acid diamide (4, A3B6): <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  9.11 (br s, 1H), 8.67 (m, 1H), 6.98 (m, 2H), 6.67 (m, 2H), 4.15 and 4.10 (two s, 2H), 3.74 and 3.68 (two s, 2H), 3.44 (m, 8H), 3.26 (s, 3H), 2.24 (s, 3H), 3.22 (m, 2H), 2.57 (m, 2H), 1.34 and 1.33 (two s, 9H); IR (film)  $V_{\text{max}}$  3234, 3078, 2978, 2931, 1698, 1643, 1515, 1453, 1393, 1367, 1252, 1169, 1118, 1015, 962, 893, 832, 754, 665 cm<sup>-1</sup>; FABHRMS (NBA) m/z 468.4724 (M+H<sup>+</sup>, C<sub>23</sub>H<sub>37</sub> N<sub>3</sub>O<sub>7</sub> requires 468.2710).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2-(3-methoxyphenyl)ethyl)-*N*"-di(2-methoxyethyl)iminodiacetic acid diamide (4, A4B6): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.15 (m, 1H), 6.75 (m, 3H), 4.16 (s, 1H), 4.04 (s, 1H), 3.91 (s, 1H), 3.55 (s, 1H), 3.54 (s, 4H), 3.50 (m, 10H), 3.30 (m, 5H), 2.80 (m, 2H), 1.39 (s, 9H); IR (film) *V*<sub>max</sub> 3490, 3241, 2932, 1703, 1643, 1583, 1454, 1254, 1167, 1118 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 614.1860 (M+Cs<sup>+</sup>, C<sub>24</sub>H<sub>39</sub>N<sub>3</sub>O<sub>7</sub> requires 614.1842).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-fluorophenyl)ethyl)-*N''*-di(2-methoxyethyl)iminodiacetic acid diamide (4, A6B6): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  9.20 and 9.96 (two t, 1H, NH), 7.05 (m, 2H), 6.80 (m, 2H), 4.05, 3.92, 3.76, and 3.66 (four s, 4H), 3.38 (m, 8H), 3.17 (m, 6H), 2.68 (m, 2H), 1.27 (s, 9H); IR (film) *V*<sub>max</sub> 3508, 3241, 3077, 2974, 2923, 1702, 1641, 1564, 1508, 1441, 1390, 1364 1251, 1221, 1164, 1010, 964, 928, 892, 826 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 602.1634 (M+Cs<sup>+</sup>, C<sub>23</sub>H<sub>36</sub>FN<sub>3</sub>O<sub>6</sub> requires 602.1642).

*N*-((*tert*-Butyloxy)carbonyl)-*N*''-(2-(4-fluorophenyl)ethyl)-*N*''-(5-hydroxy-3-oxapentyl)iminodiacetic acid diamide (4, A6B7): <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  8.64 (m, 2H), 7.26 (m, 2H), 7.08 (m, 2H), 3.79 (m, 4H), 3.37 (m, 10H), 2.71 (m, 2H), 1.33 and 1.30 (two s, 9H); IR (film) *V*<sub>max</sub> 3450, 2977, 2937, 2118, 1650, 1459, 1609, 1456, 1392, 1368, 1340, 1253, 1220, 1161, 1140, 1065, 960, 823 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 574.1317 (M + Cs<sup>+</sup>, C<sub>21</sub>H<sub>32</sub>FN<sub>3</sub>O<sub>6</sub> requires 574.1329).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(4-methoxybenzyl)-*N''*-(*trans*-2-phenylcyclopropyl)iminodiacetic acid diamide (4, A5B7'): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.20 (m, 7H), 6.79 (m, 2H), 4.35 (m, 2H), 3.75 (m, 7H), 2.95 (m, 1H), 2.06 (m, 1H), 1.39 and 1.30 (two s, 9H), 1.20 (m, 2H); IR (film) *V*<sub>max</sub> 3414, 2068, 1650, 1513, 1455, 1393, 1249, 1166 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 600.1490 (M+Cs<sup>+</sup>, C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub> requires 600.1475).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(4-methoxybenzyl)-*N''*-(2-(4-methoxyphenyl)ethyl)iminodiacetic acid diamide (4, A2B7''): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.20–7.00 (m, 4H), 6.79 (m, 4H), 4.36 (m, 2H), 3.74 (m, 10H), 3.40 (m, 2H), 2.75 (m, 2H), 1.36 and 1.32 (two s, 9H); IR (film) *V*<sub>max</sub> 3225, 3072, 2931, 2837, 1696, 1655, 1567, 1514, 1455, 1390, 1243, 1173, 1138, 1032, 820 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 486.2615 (M + H <sup>+</sup>, C<sub>26</sub>H<sub>35</sub> N<sub>3</sub>O<sub>6</sub> requires 486.2604).

*N*-((*tert*-Butyloxy)carbonyl)-*N*<sup>*i*</sup>-(2-(4-methoxyphenyl)ethyl)-*N*<sup>*i*</sup>-(3-(2,6-dimethoxybenzoyl)aminopropyl)iminodiacetic acid diamide (4, A2B8): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.66 (m, 2H), 8.00 (m, 1H), 7.27 (m, 1H), 7.12 (m, 2H), 6.83 (m, 2H), 6.64 (d, 2H, *J* = 10 Hz), 3.80 (m, 4H), 3.71 (s, 9H), 3.22 (m, 6H), 2.64 (m, 2H), 1.60 (m, 2H), 1.34 and 1.31 (two s, 9H); IR (film) *V*<sub>max</sub> 3260, 2936, 2838, 1651, 1598, 1514, 1474, 1393, 1388, 1302, 1252, 1158, 1141, 1113, 1034, 959, 897, 847, 757, 666 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 719.2079 (M+Cs<sup>+</sup>, C<sub>30</sub>H<sub>42</sub>N<sub>4</sub>O<sub>8</sub> requires 719.2057).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(2-(4-fluorophenyl)ethyl)-*N*''-(2-(2'-thienyl)ethyl)iminodiacetic acid diamide (4, A6B8'): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.15 (m, 3H), 6.91 (m, 3H), 6.81 (m, 1H), 3.74 (d, 4H), 3.42 (m, 4H), 3.00 (m, 2H), 2.70 (m, 2H), 1.34 (s, 9H); IR (film) *V*<sub>max</sub> 3238, 2974, 1655, 1570, 1509, 1454, 1394, 1165, 849 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 596.0975 (M + Cs<sup>+</sup>, C<sub>23</sub>H<sub>30</sub>N<sub>3</sub>O<sub>4</sub>FS requires 596.0995).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(phenyl)ethyl)-*N''*-(5-acetamido-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A1B9): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  8.73 (m, 2H), 8.57 (m, 1H), 7.27 (m, 5H), 4.17 (m, 1H), 3.78 (m, 4H), 3.60 (s, 3H), 3.32 (m, 2H), 3.12 (m, 2H), 2.71 (m, 2H), 1.43 (m, 4H), 1.39 (m, 2H), 1.32 and 1.30 (two s, 9H); IR (film)  $V_{\text{max}}$  3751, 3277, 3079, 2937, 1738, 1652, 1557, 1514, 1456, 1394, 1369, 1301, 1248, 1177, 1143, 1033, 961, 894, 847, 767, 665 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 653.1983 (M+Cs<sup>+</sup>, C<sub>26</sub>H<sub>40</sub>N<sub>4</sub>O<sub>7</sub> requires 653.1951).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(5-((benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)-*N*''-methyl-*N*''-(2-(3,4dimethoxyphenyl)ethyl)iminodiacetic acid diamide (4, A7B9'): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.30 (m, 5H), 6.70 (m, 3H), 5.07 (d, 2H), 4.30 (m, 1H), 3.85 (m, 8H), 3.70 and 3.68 (two s, 3H), 3.55 (m, 4H), 3.13 (m, 2H), 2.90 (m, 2H), 2.70 (s, 3H), 1.55 (m, 6H), 1.39 and 1.36 (two s, 9H); IR (film) *V*<sub>max</sub> 3248, 2936, 1704, 1642, 1516, 1454, 1392, 1263, 1160 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 819.2606 (M+Cs<sup>+</sup>, C<sub>35</sub>H<sub>50</sub>N<sub>4</sub>O<sub>10</sub> requires 819.2581).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-benzyl-*N*''-((5-benzyloxy-carbonylamino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A7B9''): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.28 (m, 10H), 5.60 (m, 1H), 5.10 (s, 2H), 4.35 (m, 3H), 3.80 (m, 4H), 3.69 (s, 3H), 3.25 (m, 2H), 1.80 (m, 2H), 1.38 (m, 13H); IR (film) *V*<sub>max</sub> 3260, 3072, 2943, 1690, 1549, 1455, 1390, 1367, 1249, 1161, 844, 732, 697 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 621.2914 (M+Na<sup>+</sup>, C<sub>31</sub>H<sub>42</sub>N<sub>4</sub>O<sub>8</sub> requires 621.2900).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-methoxyphenyl)ethyl)-*N''*-((5-(benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A7B12 and A2B10): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.31 (m, 5H), 7.10 (m, 2H), 6.80 (m, 2H), 5.60 (m, 1H), 5.07 (s, 2H), 4.30 (m, 1H), 3.75 (m, 10H), 3.50 (m, 2H), 3.25 (m, 2H), 2.75 (m, 2H), 1.75 (m, 2H), 1.38 (m, 13H); IR (film) *V*<sub>max</sub> 3248, 3072, 2943, 1713, 1661, 1514, 1455, 1390, 1367, 1249, 1214, 1173, 1138, 1038, 903, 844, 732, 697, 597, 562 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 775.2290 (M + Cs<sup>+</sup>, C<sub>33</sub>H<sub>46</sub>N<sub>4</sub>O<sub>9</sub> requires 775.2319).

*N*-((*tert*-Butyloxy)carbonyl)-*N*"-((3-methoxyphenyl)ethyl)-*N*"-(5-(benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A7B2" and A4B10): <sup>1</sup>H NMR (DMSO- $d_6$ , 500 MHz) δ 8.68 (m, 3H), 7.73 (m, 1H), 7.34 (m, 5H), 7.17 (m, 1H), 7.76 (m, 2H), 5.03 (s, 2H), 3.99 (m, 2H), 3.76 (m, 7H), 3.61 (s, 3H), 3.30 (m, 2H), 3.05 (m, 2H), 2.68 (m, 2H), 1.36 (m, 14H); IR (film)  $V_{max}$  3384, 3268, 3074, 2936, 1707, 1656, 1583, 1562, 1546, 1492, 1454, 1393, 1367, 1266, 1210, 1166, 1039, 848, 780, 752, 697 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 775.2328 (M+Cs<sup>+</sup>, C<sub>33</sub>H<sub>46</sub>N<sub>4</sub>O<sub>9</sub> requires 775.2319).

*N*-((*tert*-Butyloxy)carbonyl)-*N*'-(4-(1',4'-dioxolano)piperidino)-*N*''-((5-(benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A7B14 and A8B10): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.33 (m, 5H), 5.10 (s, 2H), 4.30 (m, 1H), 4.00 (m, 6H), 3.75 (m, 7H), 3.43 (m, 2H), 3.20 (m, 3H), 1.80 (m, 2H), 1.68 (m, 5H), 1.55 (m, 3H), 1.50 (m, 9H); IR (film) *V*<sub>max</sub> 3425, 2955, 1698, 1643, 1537, 1453, 1394, 1253, 1167, 1102 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 767.2293 (M+Cs<sup>+</sup>, C<sub>31</sub>H<sub>47</sub>N<sub>4</sub>O<sub>10</sub> requires 767.2268).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-methoxyphenyl)ethyl)-*N''*-(2-(phenyl)ethyl)iminodiacetic acid diamide (4, A2B11): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.16 (m, 9H), 3.71 (m, 7H), 3.45 (m, 2H), 3.30 (m, 2H), 2.90–2.60 (m, 4H), 1.36 (s, 9H); IR (film) *V*<sub>max</sub> 3237, 3072, 2931, 1567, 1555, 1508, 1455, 1390, 1296, 1243, 1173, 1138, 1032, 820 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m/z* 470.2642 (M+H<sup>+</sup>, C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub> requires 470.2655).

*N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-fluorophenyl)ethyl)-*N''*-((5-(benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)iminodiacetic acid diamide (4, A7B13): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.31 (m, 5H), 7.10 (m, 2H), 6.92 (m, 2H), 5.60 (m, 1H), 5.05 (s, 2H), 4.35 (m, 1H), 3.75 (m, 7H), 3.50 (m, 2H), 3.25 (m, 2H), 2.75 (m, 2H), 1.80 (m, 2H), 1.55 (m, 2H), 1.38 (m, 11H); IR (film) *V*<sub>max</sub> 3260, 3060, 2931, 2861, 1708, 1655, 1549, 1508, 1455, 1390, 1367, 1249, 1220, 1161, 1138, 1044, 891, 832, 738, 697 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z*763.2102 (M + Cs<sup>+</sup>, C<sub>32</sub>H<sub>43</sub>FN<sub>4</sub>O<sub>8</sub> requires 763.2119). *N*-((*tert*-Butyloxy)carbonyl)-*N*''-(2-(4-fluorophenyl)ethyl)-*N*''-(furan-2-ylmethyl)iminodiacetic acid diamide (4, A6B15): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.59–8.34 (m, NH, 2H), 7.21 (m, 1H), 7.07 (m, 2H), 6.85 (m, 2H), 6.17 (m, 2H), 4.33 (m, 2H), 3.74 (m, 4H), 3.37 (m, 2H), 2.72 (m, 2H), 1.29 and 1.25 (two s, 9H); IR (film) *V*<sub>max</sub> 3237, 3060, 2966, 2919, 1655, 1555, 1502, 1455, 1390, 1361, 1249, 1220, 1161, 1138, 1014, 961, 897, 826, 732, 662, 597, 556 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m/z* 434.0208 (M+H<sup>+</sup>, C<sub>22</sub>H<sub>28</sub>FN<sub>3</sub>O<sub>5</sub> requires 434.2091).

General procedure for 5: sublibrary A1B3C1-C10. A sample of **4**, **A1B3** (0.075 g, 0.15 mmol) in CHCl<sub>3</sub> (1 mL) was treated with 4 N HCl-dioxane (1 mL) in a 4 mL vial and this mixture was allowed to stand for 2h. TLC (10% CH<sub>3</sub>OH-CHCl<sub>3</sub> eluent) then indicated that conversion to the amine was complete. The solvent and excess acid were removed by evaporation. A stock solution was prepared by diluting a mixture of 0.5 mmol of each diacid C1-C10 and 45 mmol of *i*-Pr<sub>2</sub>NEt to 100 mL in anhydrous DMF. This stock solution (1mL, 0.005 mmol of each diacid, 0.45 mmol of *i*-Pr<sub>2</sub>NEt) was added to the diamide and the mixture was shaken to effect dissolution. PyBrOP (0.070 g, 0.15 mmol) was added and the mixture was capped, shaken, and allowed to stand for 8 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with 20% aqueous HCl saturated with NaCl  $(3 \times 25 \text{ mL})$ , saturated aqueous NaHCO<sub>3</sub>  $(1 \times 25 \text{ mL})$  and saturated aqueous NaCl  $(1 \times 25 \text{ mL})$ , dried  $(Na_2SO_4)$  and concentrated to afford 0.036 g (79%) of the sublibrary.

MS data confirming the integrity of the mixtures with the inclusion of each expected member was collected for the following **5** mixtures: A1B1C1–10, A2B1C1–10, A3B1C1–10, A2B2C1–10, A2B6C1–10, A3B3C1–10, A4B4C1–10, A5B5C1–10, A6B6C1–10, A5B7C1–10, A4B8C1–10, A3B9C1–10 and A2B10C1–10.

General procedure for the synthesis of individual sublibrary entries for 5, (A2B6C1-10): preparation of (E)-(N, N'-bis(N-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-N, N'-bis(N, N-di(2-methoxyethyl)carboxamidomethyl)ethene-1,2-dicarboxamide (5, A2B6C2). The BOC-derivative 4, A2B6 (0.84 g) was stirred in 4 N HCldioxane (8.5 mL) for 2 h. Removal of the solvent under a stream of N<sub>2</sub> and in vacuo gave the deprotected material (0.78 g), which was dissolved in anhydrous DMF to provide a 0.15 M solution (12.5 mL). An aliquot of this solution (2 mL, 0.3 mmol) was syringed into a two dram vial equipped with a stirring bar containing 11.6 mg (0.1 mmol) of fumaric acid. i-Pr<sub>2</sub>NEt (150 µL, 0.9 mmol) and PyBrOP (140 mg, 0.3 mmol) were added and the reaction mixture was stirred for 16 h at 25 °C. The reaction mixture was diluted with EtOAc (50 mL) and washed  $(3 \times 50 \text{ mL})$  with acidic saturated aqueous NaCl (10% aqueous HCl/saturated aqueous NaCl 1/1), 5%

aqueous NaHCO<sub>3</sub> (50 mL) and saturated aqueous NaCl (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under reduced pressure to provide 73 mg (89%) of the title substance as an oil, which crystallized from slowly evaporating EtOAc: <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.62 and 8.23 (two t, 2H, NH), 7.11–7.06 (m, 5H), 7.00 (s, 2H, vinyl), 6.84–6.81 (m, 4H), 4.55, 4.27, 4.04 and 3.86 (br s, or pairs of s, total 8H, NCH<sub>2</sub>CO), 3.70 (two s, 6H, OCH<sub>3</sub>), 2.61 (m, 4H, ArCH<sub>2</sub>); IR (film)  $V_{\text{max}}$  3467, 3262, 1644, 1246, 1115 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 843.4542 (M + H<sup>+</sup>, C<sub>42</sub>H<sub>62</sub>N<sub>6</sub>O<sub>12</sub> requires 843.4504).

*N*,*N*'-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N*,*N*'-bis(*N*,*N*-di(2-methoxyethyl)carboxamidomethyl)ethyne-1,2-dicarboxamide (5, A2B6C1): <sup>1</sup>H NMR (DMSO-*d<sub>6</sub>*, 250 MHz) δ 8.43 and 8.23 (br t, 2H), 7.13–7.08 (m, 4H), 6.85–6.81 (m, 4H), 4.54, 4.26, 4.08 and 3.86 (br s or pairs of s, total 8H), 3.70 (two s, 6H), 2.62 (m, 4H); IR (film)  $V_{\text{max}}$  3487, 3272, 1651, 1246, 1115 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 973.3369 (M + Cs<sup>+</sup>, C<sub>42</sub>H<sub>60</sub>N<sub>6</sub>O<sub>12</sub> requires 973.3324).

(*E*)-*N*,*N*'-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N*,*N*'-bis(*N*,*N*-di(2-methoxyethyl)carboxamidomethyl)-2-butene-1,4-dicarboxamide (5, A2B6C3): <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.69 and 8.25 (two t, 2H), 7.12–7.08 (m, 4H), 6.84–6.80 (m, 4H), 5.50 (m, 2H), 4.40, 4.16, 3.93 and 3.78 (br s, 8H), 3.69 (two s, 6H), 2.63 (m, 4H); IR (film)  $V_{\text{max}}$  3446, 3261, 1650, 1245, 1115 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1003.3841 (M+Cs<sup>+</sup>, C<sub>44</sub>H<sub>66</sub>N<sub>6</sub>O<sub>12</sub> requires 1003.3793).

*N*,*N*'-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N*,*N*'-bis(*N*,*N*-di(2-methoxyethyl)carboxamidomethyl)benzene-1,3-dicarboxamide (5, A2B6C4): <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.45, 8.41 and 8.29 (t, t and m, 2H), 7.45–7.33 (m, 4H), 7.15–7.09 (m, 4H), 6.84–6.81 (m, 4H), 4.31, 4.22, 3.94 and 3.77 (br s, 8H), 3.70 (s, 6H), 2.65 (m, 4H); IR (film)  $V_{\text{max}}$  3487, 3262, 1651, 1246, 1113 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1025.3678 (M + Cs<sup>+</sup>, C<sub>46</sub>H<sub>64</sub>N<sub>6</sub>O<sub>12</sub> requires 1025.3637).

*N*,*N*'-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N*,*N*'-bis(*N*,*N*-di(2-methoxyethyl)carboxamidomethyl)benzene-1,4-dicarboxamide (5, A2B6C5): <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.40 and 8.28 (two m, 2H), 7.38–7.34 (m, 4H), 7.14–7.08 (m, 4H), 6.85–6.81 (m, 4H), 4.31, 4.23, 3.93 and 3.77 (br s or d, 8H), 3.70 (br s, 6H), 2.65 (m, 4H); IR (film)  $V_{\text{max}}$  3497, 3272, 1644, 1244, 1115 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1025.3677 (M + Cs<sup>+</sup>, C<sub>46</sub>H<sub>64</sub>N<sub>6</sub>O<sub>12</sub> requires 1025.3637).

N,N'-Bis(N-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-N,N'-bis(N,N-di(2-methoxyethyl)carboxamidomethyl)napthalene-1,4-dicarboxamide (5, A2B6C6): <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.31, 8.20 and 8.09 (m,

1365

4H), 7.70–7.59 (m, 2H), 7.38–7.28 (m, 2H), 7.18–7.16 (m, 2H), 7.02–6.95 (m, 2H), 6.87–6.78 (m, 4H), 4.85, 4.40, 4.15, and 4.02 (br s, 4H), 3.70 (m, 6H), 2.69 (m, 4H); IR (film)  $V_{\text{max}}$  3282, 1650, 1241, 1113 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1075.3835 (M+Cs<sup>+</sup>, C<sub>50</sub>H<sub>66</sub>N<sub>6</sub>O<sub>12</sub> requires 1075.3793).

*cis*- and *trans-N,N*-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N,N'*-bis(*N,N*-di (2-methoxyethyl)carboxamidomethyl)cyclohexane-1,3-dicarboxamide (5, A2B6C7,8): (mixture of *cis*- and *trans*-isomers) <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.78, 8.67, 8.51 and 8.19 (m, 2H), 7.17–7.10 (m, 4H), 6.86–6.83 (m, 4H), 4.50– 3.75 (several m, 8H), 3.72 (br s, 6H), 2.64 (m, 4H); IR (film)  $V_{max}$  3487, 3262, 1642, 1246, 1113 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 1031.4147 (M+Cs<sup>+</sup>, C<sub>46</sub>H<sub>70</sub>N<sub>6</sub>O<sub>12</sub> requires 1031.4106).

*cis*- and *trans-N,N*-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N,N'*-bis(*N,N*-di(2-methoxyethyl)carboxamidomethyl)cyclohexane-1,4-dicarboxamide (5, A2B6C9,10): (mixture of *cis*- and *trans*-isomers) <sup>1</sup>H NMR (DMSO- $d_6$ , 250 MHz)  $\delta$  8.67, 8.23 and 8.17 (m, 2H), 7.13–7.08 (m, 4H), 6.85–6.80 (m, 4H), 4.50–3.75 (several m, 8H), 3.70 (br s, 6H), 2.62 (m, 4H); IR (film) *V*<sub>max</sub> 3477, 3262, 1644, 1246, 1115 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 1031.4148 (M+Cs<sup>+</sup>, C<sub>46</sub>H<sub>70</sub>N<sub>6</sub>O<sub>12</sub> requires 1031.4106).

**Preparation of the 5, sublibrary A2B6C1–10.** A stock solution was prepared through diluting a mixture of 0.5 mmol of each diacid C1–10 and 45 mmol of *i*-Pr<sub>2</sub>NEt to 100 mL in anhydrous DMF. A 2 mL sample of this stock solution (0.1 mmol of diacid) was added to 2 mL of the solution containing **A2B6·HCI** (0.3 mmol). After the addition of PyBrOP (140 mg, 0.3 mmol), the mixture was stirred for 16 h. Work-up as described above provided 84.5 mg (95%) of the mixture as an off-white solid. TLC (10% CH<sub>3</sub>OH–CHCl<sub>3</sub>)  $R_f$ =0.47–0.62. The results from HPLC-MS analysis of this mixture (including selective ion monitoring) were in good agreement with those obtained using a mixture produced by pooling the individual compounds.

General procedure for 15: sublibrary A1B3C31–37. A sample of 4, A1B3 (0.083 g, 0.157 mmol) in CHCl<sub>3</sub> (1 mL) was treated with 4 N HCl–dioxane (1 mL) in a 4 mL vial and this mixture was allowed to stand for 3 h. The solvent and excess acid were removed by evaporation. The resulting residue is dissolved in 1 mL of DMF and 0.25 mL (1.5 mmol, 10 equiv) of *i*-Pr<sub>2</sub>NEt was added. After dissolution, 0.1 mL (0.035 mmol) of a triacid stock solution (prepared by diluting a mixture of 0.45 mmol of each triacid C31–C37<sup>37</sup> in 9 mL of a mixture DMF/CHCl<sub>3</sub> 8:1) was added, followed by 74 mg (0.157 mmol) of PyBrOP. After stirring for 16 h, the reaction mixture was

diluted with EtOAc (90 mL) and washed with 10% aqueous HCl ( $3 \times 90$  mL), saturated aqueous NaHCO<sub>3</sub> ( $2 \times 90$  mL) and saturated aqueous NaCl (90 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 0.0441 g (81%) of the sublibrary.

ESMS data confirming the integrity of the mixtures with the inclusion of each expected member was collected for the following **15** mixtures: A1B1C31–37, A1B2/C31–37, A1B3C31–37, A1B9/C31–37, A2B3C31–37, A2B8/C31– 37, A3B2/C31–37, A3B4C31–37, A4B6C31–37, A5B7/ C31–37, A5B10C31–37, A6B8/C31–37, A7B9/C31–37, A8B10C31–37. The seven components **15**: A1B3C31– A1B3C37 were individually prepared following the procedure detailed above and combined to provide an authentic equimolar mixture. The individual coupling yields were comparable with that of the mixture synthesis (Table 6) and the mass spectrum of the mixture synthesis and authentic mixture material were indistinguishable and the HPLC revealed no distinguishable features between the two mixtures (Fig. 10).

**15, A1B3C31:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.17 (m, 18H), 6.72 (m, 9H), 3.80 (m, 30H), 3.40 (m, 12H), 2.75 (m, 12H); IR (film)  $V_{\text{max}}$  3260, 3063, 2933, 1650, 1515, 1454, 1261, 1236, 1156, 1141, 1027 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 1355, M+Na<sup>+</sup> 1377; neg: M-H<sup>+</sup> 1353, M+Cl<sup>-</sup> 1389.

**15, A1B3C32:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.52 (m, 15H), 7.10 (m, 9H), 4.10 (m, 30H), 3.75 (m, 12H), 3.10 (m, 12H); IR (film)  $V_{\text{max}}$  3262, 2926, 2359, 1658, 1515, 1454, 1261, 1236, 1141, 1027 cm<sup>-1</sup>; ESMS pos: M + H<sup>+</sup> 1361, M + Na<sup>+</sup> 1383; neg: M-H<sup>+</sup> 1359, M + Cl<sup>-</sup> 1395.

**15, A1B3C33:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.20 (m, 18H), 6.72 (m, 9H), 3.80 (m, 36H), 3.45 (m, 12H), 2.80 (m, 12H); IR (film)  $V_{\text{max}}$  3279, 2932, 1658, 1515, 1261, 1158, 1027 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 1445, M+Na<sup>+</sup> 1467; neg: M-H<sup>+</sup> 1443, M+Cl<sup>-</sup> 1478.

**15, A1B3C34:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.40 (m, 3H), 7.25 (m, 15H), 6.75 (m, 9H), 4–4.40 (m, 6H), 3.85 (m, 30H), 3.50 (m, 12H), 2.80 (m, 12H); IR (film)  $V_{\text{max}}$  3278, 2932, 1658, 1515, 1453, 1261, 1235, 1119, 1027 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 1560, M+Na<sup>+</sup> 1582; neg: M-H<sup>+</sup> 1557, M+Cl<sup>-</sup> 1594.

Table 6. Individual and mixture coupling yields, 15

A1B3C31	100%	A1B3C35	94%			
A1B3C32	47%	A1B3C36	88%			
A1B3C33	89%	A1B3C37	85%			
A1B3C34	73%	average	82%			
A1B3C31–C37 81%						



Figure 10. Reconstituted equimolar (left) and combinatorial synthesis (right) mixture of 15, A1B3C31–37. Reverse-phase HPLC separation of the mixture:  $3.9 \times 300$  mm C18, 1 mL/min, CH<sub>3</sub>CN–H<sub>2</sub>O (containing 0.035% TFA) 50–50% to 65–35% (30 min linear gradient), with monitored detection at 254 nm. All desired components of the mixture elute within the retention times of 9–20 min.

**15, A1B3C35:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.20 (m, 27H), 6.78 (m, 9H), 4.50 (m, 6H), 3.80 (m, 30H), 3.50 (m, 12H), 3.25 (m, 3H), 2.80 (m, 12H), 2.40 (m, 3H); IR (film)  $V_{\text{max}}$  3273, 2934, 1650, 1515, 1453, 1261, 1082, 1027 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 1680, M+Na<sup>+</sup> 1702; neg: M-H<sup>+</sup> 1677.

**15, A1B3C36:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.20 (m, 27H), 6.80 (m, 9H), 4.50 (m, 6H), 3.80 (m, 30H), 3.50 (m, 30H), 2.80 (m, 12H), 2.20 (m, 1H); IR (film)  $V_{\text{max}}$  3278, 2928, 2359, 1660, 1515, 1453, 1261, 1096, 1027 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 1786, M+Na<sup>+</sup> 1808; neg: M-H<sup>+</sup> 1783, M+Cl<sup>-</sup> 1819.

**15, A1B3C37:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.55 (m, 9H), 7.25 (m, 15H), 6.90 (m, 6H), 6.75 (m, 9H), 4.60 (m, 6H), 4.10 (m, 5H), 3.80 (m, 25H), 3.50 (m, 12H), 2.80 (m, 12H); IR (film)  $V_{\text{max}}$  3274, 2932, 2360, 1659, 1518, 1453, 1235, 1026 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 1674, M+Na<sup>+</sup> 1696; neg: M-H<sup>+</sup> 1672, M+Cl<sup>-</sup> 1709.

General procedure for 16: N,N-bis(N-(2-(3,4-dimethoxyphenyl)ethyl)carboxamidomethyl)-N,N-bis((N-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-N''-((*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A7B3). A sample of 4 (A7B3, 3.36 g, 5.00 mmol) was stirred in a solution of 4 N HCl–dioxane (26 mL) at 25 °C for 4 h. <sup>1</sup>H NMR showed the disappearance of the diagnostic BOC group ( $\delta$  1.3, s, 9H). Removal of the solvent under N<sub>2</sub> and in vacuo gave the deprotected material as a pale yellow solid, which was dissolved in anhydrous DMF (20 mL). N-((*tert*-Butyloxy)carbonyl)iminodiacetic acid (2, 0.388 g,

1.66 mmol), *i*-Pr<sub>2</sub>NEt (2.60 mL, 14.98 mmol) and PyBrOP (2.32 g, 5.00 mmol) were added sequentially. The reaction mixture was stirred for 16 h at 25 °C before being diluted with EtOAc (200 mL) and washed with 10% aqueous HCl (2×100 mL), saturated aqueous NaHCO<sub>3</sub> ( $2 \times 100 \text{ mL}$ ), saturated aqueous NaCl (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under reduced pressure to provide 2.09 g (94%) of the title substance as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.38 (br s, 10H), 6.75 (br s, 6H), 5.80–5.50 (m, 2H), 5.06 (s, 4H), 4.35 (br s, 2H), 4.21–3.62 (m, 28H), 3.50 (s, 4H), 3.20 (br s, 4H), 2.72 (br s, 4H), 1.72 (m, 4H), 1.60 (m, 4H), 1.35 (br s, 13H); IR (film) V<sub>max</sub> 3292, 3066, 2938, 2868, 1655, 1516, 1455, 1262, 1157, 1027, 846, 735, 699 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1474.5527  $(M + Cs^+, C_{67}H_{91}N_9O_{20}$  requires 1474.5435).

N,N'-Bis(N-(2-(4-fluorophenyl)ethyl)carboxamidomethyl)-N,N'-bis(N,N-di(2-methoxyethyl)carboxamidomethyl)-N''-((*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A6B6): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.13 (m, 4H), 6.89 (m, 4H), 4.51–3.82 (m, 12H), 3.45–3.21 (m, 32H), 2.73 (m, 4H), 1.34 (br s, 9H); IR (film)  $V_{max}$  3261, 2930, 1659, 1509, 1450, 1365, 1217, 1118, 965, 844 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1068.3894 (M+Cs<sup>+</sup>, C<sub>45</sub>H<sub>67</sub>N<sub>7</sub>O<sub>12</sub>F<sub>2</sub> requires 1068.3870).

*N*,*N*'-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N*,*N*'-bis(*N*-(3,4,5-trimethoxybenzyl)carboxamidomethyl)-*N*''-((*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A2B4): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ 7.08 (m, 4H), 6.78 (m, 4H), 6.48 (m, 4H), 4.28 (m, 4H), 3.93 (m, 4H), 3.82–3.50 (m, 32H), 3.43 (m, 4H), 2.72 (m, 4H), 1.34 (m, 9H); IR (film) *V*<sub>max</sub> 3271, 3062, 2936, 1667, 1592, 1512, 1462, 1329, 1248, 1126, 1033, 823 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1220.4132 (M + Cs<sup>+</sup>, C<sub>55</sub>H<sub>73</sub>N<sub>7</sub>O<sub>16</sub> requires 1220.4168).

*N*,*N*'-Bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N*,*N*'-bis(*N*,*N*-di(2-methoxyethyl)carboxamidomethyl)-*N*"-(*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A2B6): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ 7.10 (s, 4H), 6.80 (s, 4H), 4.40–3.65 (m, 14H), 3.60–3.30 (m, 36H), 2.75 (m, 4H), 1.33, (two s, 9H); IR (film) *V*<sub>max</sub> 3263, 3066, 2937, 1664, 1592, 1512, 1459, 1423, 1329, 1246, 1176, 1129, 1012, 822, 734 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1092.4302 (M+Cs<sup>+</sup>, C<sub>47</sub>H<sub>73</sub>N<sub>7</sub>O<sub>14</sub> requires 1092.4270).

N,N'-Bis(N-(2-(3-methoxyphenyl)ethyl)carboxamidomethyl)-N,N'-bis((N-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-N''-((tertbutyloxy)carbonyl)iminodiacetic acid diamide (16, A7B2''): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.27 (s, 10H), 7.12 (m, 2H), 6.68 (m, 6H), 5.60 (m, 2H), 5.02 (s, 4H), 4.23 (br m, 2H), 4.00 (m, 6H), 3.65 (m, 14H), 3.40 (m, 4H), 3.12 (m, 6H), 2.72 (m, 4H), 1.70 (m, 4H), 1.40 (br s, 4H) 1.39 (br s, 4H), 1.33 (s, 9H); IR (film)  $V_{max}$  3298, 3068, 2949, 1657, 1546, 1454, 1258, 1166, 1038, 845, 739, 698 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 1304.6143 (M + Na<sup>+</sup>, C<sub>65</sub>H<sub>87</sub>N<sub>9</sub>O<sub>18</sub> requires 1304.6066).

*N*,*N*'-Bis(*N*-(3,4,5-trimethoxybenzyl)carboxamidomethyl)-*N*,*N*'-bis((*N*-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-*N*"-((*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A7B4): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.28 (s, 10H), 6.55 (s, 4H), 5.90–5.70 (m, 2H), 5.06 (s, 4H), 4.35 (br s, 8H), 4.10– 3.60 (m, 34H), 3.20 (br s, 2H), 1.80 (m, 4H), 1.60 (m, 4H), 1.34 (m, 13H); IR (film) *V*<sub>max</sub> 3291, 3070, 2941, 1659, 1592, 1460, 1329, 1234, 1120, 1005, 845, 739, 699 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1506.5428 (M + Cs<sup>+</sup>, C<sub>67</sub>H<sub>91</sub>N<sub>9</sub>O<sub>22</sub> requires 1506.5333).

N, N'-Bis(N-(2-(4-fluorophenyl)ethyl)carboxamidomethyl)-N,N'-bis((N-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-N"-((tert-butyloxy)carbonyl)iminodiacetic acid diamide (16, A7B13): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.28 (s, 10H), 7.08 (br s, 4H), 6.86 (m, 4H), 5.83 (m, 2H), 5.04 (s, 4H), 4.26 (br s, 2H), 4.02-3.63 (m, 10H), 3.62-3.42 (m, 6H), 3.35 (m, 4H), 3.15 (br s, 4H), 2.70 (br s, 4H), 1.72 (m, 4H), 1.48 (br s, 4H), 1.33 (br s, 13H); IR (film) V<sub>max</sub> 3295, 3069, 2946, 1660, 1547, 1510, 1455, 1253, 1220, 1160, 1046, 845, 739, 699 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z1280.5596  $(M + Na^+)$  $C_{63}H_{81}N_9O_{16}F_2$ requires 1280.5667).

N,N'-Bis(N,N-di(2-methoxyethyl)carboxamidomethyl)-N,N'-bis((N-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-N''-((*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A7B6): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.21 (s, 10H), 5.80–5.60 (m, 2H), 5.06 (s, 4H), 4.50–3.80 (m, 14H), 3.62 (s, 4H), 3.45 (m, 18H), 3.28 (m, 12H), 1.70 (m, 4H), 1.45 (br s, 4H), 1.30 (m, 13H); IR (film)  $V_{max}$  3290, 3066, 2936, 1651, 1537, 1454, 1271, 1231, 1118, 845, 739, 700 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1378.5513 (M+Cs, C<sub>59</sub>H<sub>91</sub>N<sub>9</sub>O<sub>20</sub> requires 1378.5435).

N,N'-Bis(N,N'-(2-(2-thienyl)ethyl)carboxamidomethyl)-N,N'-bis((N-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-<math>N''-((*tert*-butyloxy)-carbonyl)iminodiacetic acid diamide (16, A7B8'): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.80–7.40 (m, 4H), 7.25 (s, 10H), 7.02 (s, 2H), 6.82 (s, 2H), 6.72 (s, 2H), 5.82 (m, 2H), 5.06 (s, 4H), 4.22 (s, 2H), 4.10–3.32 (m, 22H), 3.22 (m, 4H), 2.90 (m, 4H), 1.68 (m, 4H), 1.55 (m, 4H), 1.40 (m, 13H); IR (film)  $V_{max}$  3291, 3065, 2945, 1660, 1537, 1454, 1402, 1252, 1164, 1045, 846, 737, 697 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1234.5097 (M+H<sup>+</sup>, C<sub>59</sub>H<sub>79</sub>N<sub>9</sub>O<sub>16</sub>S<sub>2</sub> requires 1234.5164).

N,N'-Bis(N-(4-(1',4'-dioxolano)piperidino)carboxamidomethyl)-N,N'-bis((N-(((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-N''-((*tert*butyloxy)carbonyl)iminodiacetic acid diamide (16, A7B14): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.26 (s, 10H), 5.80–5.60 (m, 2H), 5.06 (s, 4H), 4.20–3.80 (m, 18H), 3.60 (m, 10H), 3.33–3.13 (m, 14H), 1.68 (m, 8H), 1.45 (m, 4H), 1.39 (m, 13H); IR (film)  $V_{max}$  3275, 2955, 2871, 1658, 1535, 1453, 1402, 1365, 1337, 1211, 1165, 1015, 843 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 1288.5892 (M + Na<sup>+</sup>, C<sub>61</sub>H<sub>87</sub>N<sub>9</sub>O<sub>20</sub> requires 1288.5965).

*N*,*N*'-Bis(*N*-(2-furanyl)methylcarboxamidomethyl)-*N*,*N*'-bis((*N*-((5-benzyloxycarbonyl)amino)-5-(methoxycarbonyl)pentyl)carboxamidomethyl)-*N*"-((*tert*-butyloxy)carbonyl)iminodiacetic acid diamide (16, A7B15): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.23 (m, 10H), 6.20 (m, 6H), 5.70 (m, 2H), 5.00 (s, 4H), 4.38–4.18 (m, 6H), 4.10–3.72 (m, 12H), 3.70–3.50 (m, 6H), 3.12 (s, 2H), 1.68 (m, 4H), 1.48 (m, 4H), 1.39 (m, 4H), 1.34 (s, 9H); IR (film)  $V_{max}$  3292, 3065, 2950, 2869, 2667, 1544, 1455, 1402, 1368, 1343, 1253, 1212, 1164, 1081, 1016, 845, 738, 699 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 1196.5199 (M+Na<sup>+</sup>, C<sub>57</sub>H<sub>75</sub>N<sub>9</sub>O<sub>18</sub> requires 1196.5127).

General procedure for the synthesis of individual sublibrary entries for 17: A2B4C43. The BOC derivative 16, A2B4 (0.104 g, 0.11 mmol) was stirred in a solution of 4 N HCl-dioxane (1 mL) at 25 °C for 4 h. Removal of the solvent under  $N_2$  and in vacuo gave the deprotected material as a pale yellow solid, which was dissolved in anhydrous DMF (0.5 mL). Diglycolic acid (C43, 4.97 mg, 0.037 mmol), *i*-Pr<sub>2</sub>NEt (0.058 mL, 0.33 mmol) and PyBrOP (51.9 mg, 0.11 mmol) were added sequentially. The reaction mixture was stirred for 16h at 25 °C before being diluted with EtOAc (50 mL) and washed with 10% aqueous HCl (2×50 mL), saturated aqueous NaHCO<sub>3</sub> (2×50 mL), saturated aqueous NaCl (50 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under reduced pressure to provide 42.3 mg (65%) of the title substance as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.08 (m, 8H), 6.75 (m, 8H), 6.50 (m, 8H), (br s, 8H), 4.30 (m, 8H), 4.05–3.61 (m, 68H), 3.50 (m, 8H), 2.71 (m, 8H); IR (film) V<sub>max</sub> 3263, 3071, 2937, 2837, 1668, 1592, 1512, 1461, 1424, 1329, 1246, 1178, 1126, 1032, 1006, 964, 823 cm<sup>-1</sup>; MALDI-FTMS (NBA–NaI) m/z 2095.9087 (M + Na<sup>+</sup>, C<sub>104</sub>H<sub>132</sub>N<sub>14</sub>O<sub>31</sub> requires 2095.9081).

**17, A2B4C1:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.08 (m, 8H), 6.72 (m, 8H), 6.49 (m, 8H), 4.30 (br s, 8H), 4.09–3.65 (m, 72H), 3.45 (br s, 8H), 2.70 (m, 8H); IR (film)  $V_{\text{max}}$  3279, 3073, 2937, 2837, 1652, 1592, 1512, 1463, 1423, 1329, 1301, 1245, 1126, 1032, 1005, 965, 824, 733 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2075.8848 (M + Na<sup>+</sup>, C<sub>104</sub>H<sub>128</sub>N<sub>14</sub>O<sub>30</sub> requires 2075.8818).

**17, A2B4C2:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.06 (m, 8H), 6.77 (m, 8H), 6.54 (m, 8H), 4.37–3.84 (m, 18H), 3.83–3.67 (m, 64H), 3.42 (br s, 8H), 2.70 (br s, 8H); IR (film)  $V_{\text{max}}$  3274, 3067, 2937, 2836, 1659, 1592, 1512, 1462, 1423, 1328, 1244, 1193, 1126, 1032, 966, 822 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2077.8980 (M + Na<sup>+</sup>, C<sub>104</sub>H<sub>130</sub>N<sub>14</sub>O<sub>30</sub> requires 2077.8975).

**17, A2B4C3:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.07 (br s, 8H), 6.78 (m, 8H), 6.52 (m, 8H), 4.32 (br s, 8H), 4.16–3.69 (m, 74H), 3.41 (br s, 8H), 2.72 (m, 8H), 2.42 (s, 4H); IR (film)  $V_{\text{max}}$  3279, 3062, 2932, 2832, 1652, 1593, 1557, 1512, 1463, 1423, 1329, 1298, 1244, 1183, 1126, 1028, 1004, 969, 824 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2105.9273 (M+Na<sup>+</sup>, C<sub>106</sub>H<sub>134</sub>N<sub>14</sub>O<sub>30</sub> requires 2105.9287).

**17, A2B4C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.60–7.20 (m, 4H), 7.06 (br s, 8H), 6.67 (m, 8H), 6.54 (m, 8H), 4.32 (m, 8H), 4.12–3.69 (m, 72H), 3.40 (m, 8H), 2.72 (m, 8H); IR (film)  $V_{\text{max}}$  3268, 3076, 2936, 2838, 1651, 1592, 1557, 1512, 1462, 1423, 1329, 1298, 1244, 1178, 1125, 1031, 999, 964, 822 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2127.9107 (M+Na<sup>+</sup>, C<sub>108</sub>H<sub>132</sub>N<sub>14</sub>O<sub>30</sub> requires 2127.9131).

**17, A2B4C5:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.31–7.20 (m, 4H), 7.08 (m, 8H), 6.78 (m, 8H), 6.54 (m, 8H), 4.32 (br s, 8H), 4.12–3.68 (m, 72H), 3.38 (m, 8H), 2.72 (m, 8H); IR (film)  $V_{\text{max}}$  3266, 3067, 2939, 2828, 1652, 1592, 1557, 1512, 1461, 1423, 1328, 1298, 1244, 1183, 1126, 1024, 1003, 959, 821 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2127.9062 (M+Na<sup>+</sup>, C<sub>108</sub>H<sub>132</sub>N<sub>14</sub>O<sub>30</sub> requires 2127.9131).

**17, A2B4C6:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.10–7.20 (m, 6H), 7.05 (m, 8H), 6.79 (m, 8H), 6.51 (m, 8H), 4.30 (br s, 8H), 4.08–3.68 (m, 72H), 3.40 (m, 8H), 2.72 (m, 8H); IR (film)  $V_{\text{max}}$  3273, 3074, 2937, 2837, 1655, 1593, 1512, 1463, 1423, 1328, 1298, 1244, 1195, 1126, 1030, 1009, 964, 826 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2181.9350 (M + Na<sup>+</sup>, C<sub>112</sub>H<sub>134</sub>N<sub>14</sub>O<sub>30</sub> requires 2181.9600).

**17, A2B4C7:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.08 (m, 8H), 6.79 (m, 8H), 6.52 (m, 8H), 4.33 (br s, 8H), 4.08–3.69 (m, 72H), 3.42 (m, 8H), 2.72 (m, 8H), 2.50–1.20 (m, 10H); IR (film)  $V_{\rm max}$  3277, 3076, 2935, 2838, 1652, 1592, 1557, 1512, 1463, 1423, 1328, 1298, 1244, 1178, 1126, 1033, 959, 869, 822 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2133.9500 (M+Na<sup>+</sup>, C<sub>108</sub>H<sub>138</sub>N<sub>14</sub>O<sub>30</sub> requires 2133.9601).

**17, A2B4C8:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.07 (m, 8H), 6.79 (m, 8H), 6.53 (m, 8H), 4.32 (m, 8H), 4.12–3.69 (m, 72H), 3.40 (m, 8H), 2.73 (m, 8H), 2.50–1.20 (m, 10H); IR (film)  $V_{\text{max}}$  3275, 2938, 1654, 1593, 1512, 1451,

1423, 1329, 1303, 1245, 1126, 1031, 999, 965, 821, 735 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2133.9620 (M + Na<sup>+</sup>, C<sub>108</sub>H<sub>138</sub>N<sub>14</sub>O<sub>30</sub> requires 2133.9601).

**17**, **A2B4C9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.06 (m, 8H), 6.78 (m, 8H), 6.51 (m, 8H), 4.33 (m, 8H), 4.12–3.67 (m, 72H), 3.40 (m, 8H), 2.72 (m, 8H), 2.50–1.20 (m, 10H); IR (film)  $V_{\text{max}}$  3266, 3074, 2939, 2827, 1656, 1592, 1512, 1462, 1423, 1328, 1300, 1245, 1126, 1030, 964, 844 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2133.9516 (M+Na<sup>+</sup>, C<sub>108</sub>H<sub>138</sub>N<sub>14</sub>O<sub>30</sub> requires 2133.9601).

**17, A2B4C10:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.08 (m, 8H), 6.79 (m, 8H), 6.52 (m, 8H), 4.32 (m, 8H), 4.17–3.68 (m, 72H), 3.41 (m, 8H), 2.70 (m, 8H), 2.50–1.20 (m, 10H); IR (film)  $V_{\rm max}$  3272, 3073, 2938, 2827, 1651, 1593, 1557, 1512, 1463, 1423, 1329, 1301, 1245, 1182, 1126, 1031, 1003, 964, 823, 733 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2133.9574 (M+Na<sup>+</sup>, C<sub>108</sub>H<sub>138</sub>N<sub>14</sub>O<sub>30</sub> requires 2133.9601).

**17, A2B4C41:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.02 (br s, 8H), 6.75 (br s, 8H), 6.52 (br s, 8H), 4.30 (br s, 8H), 4.10–3.70 (m, 72H), 3.40 (br s, 8H), 2.71 (br s, 8H), 2.02 (br s, 8H); IR (film)  $V_{\text{max}}$  3270, 3077, 2936, 1658, 1592, 1512, 1461, 1423, 1329, 1245, 1126, 1033, 964, 733 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 2246.8790 (M + Cs<sup>+</sup> + <sup>13</sup>C, C<sub>107</sub>H<sub>136</sub>N<sub>14</sub>O<sub>31</sub> requires 2246.8584).

**17, A2B4C42:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.02 (br s, 8H), 6.75 (br s, 8H), 6.52 (br s, 8H), 4.30 (br s, 8H), 4.10–3.70 (m, 72H), 3.40 (br s, 8H), 2.71 (br s, 8H), 2.02 (m, 8H), 1.60 (br s, 4H); IR (film)  $V_{\text{max}}$  3270, 3075, 2937, 1658, 1592, 1512, 1462, 1422, 1328, 1244, 1181, 1126, 1033, 823, 734 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 2274.9110 (M+Cs<sup>+</sup> + <sup>13</sup>C, C<sub>109</sub>H<sub>140</sub>N<sub>14</sub>O<sub>31</sub> requires 2274.8897).

**17, A2B4C44:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.02 (br s, 8H), 6.75 (br s, 8H), 6.52 (br s, 8H), 4.30 (br s, 8H), 4.10–3.70 (m, 80H), 3.40 (br s, 8H), 2.71 (br s, 8H); IR (film)  $V_{\text{max}}$  3270, 3069, 2937, 2837, 1657, 1592, 1512, 1461, 1423, 1328, 1244, 1182, 1126, 1032, 964, 823, 733 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 2249.8351 (M+Cs<sup>+</sup>, C<sub>106</sub>H<sub>136</sub>N<sub>14</sub>O<sub>32</sub> requires 2249.8499).

**17, A2B4C45:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.02 (br s, 8H), 6.75 (br s, 8H), 6.52 (br s, 8H), 4.30 (br s, 8H), 4.10–3.70 (m, 84H), 3.40 (br s, 8H), 2.71 (br s, 8H); IR (film)  $V_{\text{max}}$  3291, 2938, 1659, 1592, 1512, 1462, 1423, 1328, 1244, 1126, 845 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 2293.8973 (M+Cs<sup>+</sup>, C<sub>108</sub>H<sub>140</sub>N<sub>14</sub>O<sub>33</sub> requires 2293.8762).

**17, A2B4C46:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.01 (br s, 8H), 6.78 (br s, 8H), 6.51 (br s, 8H), 4.30 (br s, 8H),

1369

4.10–3.70 (m, 86H), 3.40 (br s, 10H), 2.71 (br s, 8H); IR (film)  $V_{\text{max}}$  3507, 3263, 3072, 2936, 2837, 1667, 1592, 1557, 1512, 1462, 1423, 1329, 1301, 1246, 1178, 1129, 1032, 1006, 965, 901, 824, 733 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2227.9926 (M + Na<sup>+</sup>, C<sub>110</sub>H<sub>144</sub>N<sub>14</sub>O<sub>34</sub> requires 2227.9867).

**17, A2B4C47:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.02 (br s, 8H), 6.73 (br s, 8H), 6.50 (br s, 8H), 4.32 (m, 8H), 4.12– 3.70 (m, 90H), 3.40 (br s, 10H), 2.71 (br s, 8H); IR (film)  $V_{\text{max}}$  3507, 3264, 3071, 2935, 2837, 1741, 1670, 1611, 1592, 1561, 1542, 1461, 1424, 1367, 1329, 1301, 1246, 1178, 1163, 1128, 1032, 1006, 964, 901, 823 cm<sup>-1</sup>; MALDI–FTMS (NBA–NaI) m/z 2272.0250 (M + Na<sup>+</sup>, C<sub>112</sub>H<sub>148</sub>N<sub>14</sub>O<sub>35</sub> requires 2272.0129).

**17**, **A6B6C48**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.12 (m, 8H), 6.92 (m, 8H), 4.43–3.70 (m, 20H), 3.50–3.18 (m, 70H), 2.78 (m, 8H); IR (film)  $V_{\text{max}}$  3278, 2932, 1654, 1508, 1457, 1220, 1117, 824, 668 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1917.7758 (M+Cs<sup>+</sup>, C<sub>84</sub>H<sub>120</sub>N<sub>14</sub>O<sub>24</sub>F<sub>4</sub> requires 1917.7590).

**17, A2B4C49:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.03–6.75 (two br s, 20H), 6.45 (m, 8H), 4.29 (br s, 8H), 4.10–3.60 (m, 76H), 3.35 (m, 8H), 2.70 (br s, 8H); IR (film) *V*<sub>max</sub> 3568, 3268, 3071, 2936, 2837, 1743, 1670, 1611, 1592, 1560, 1548, 1461, 1424, 1367, 1329, 1301, 1246, 1178, 1126, 1031, 1006, 965, 901, 823, 779, 733, 668 cm<sup>-1</sup>; MALDI-FTMS (NBA–NaI) *m*/*z* 2187.9455 (M+Na<sup>+</sup>, C<sub>110</sub>H<sub>136</sub>N<sub>14</sub>O<sub>32</sub> requires 2187.9343).

**17, A2B4C50:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.02 (br s, 8H), 6.75 (br s, 8H), 6.52 (br, 8H), 4.30 (br s, 8H), 4.10– 3.70 (m, 80H), 3.40 (br s, 8H), 2.71 (br s, 8H), 2.01 (s, 6H); IR (film)  $V_{\text{max}}$  3278, 3068, 2937, 2837, 1657, 1592, 1512, 1461, 1423, 1328, 1244, 1195, 1126, 1031, 841 cm<sup>-1</sup>, FABHRMS (NBA–CsI) m/z 2355.9190 (M+Cs<sup>+</sup>, C<sub>112</sub>H<sub>142</sub>N<sub>16</sub>O<sub>32</sub> requires 2355.9030).

General procedure for 17 (C1-C10 and C41-C50): sublibrary A2B4C1-10 and A2B4C41-50. CHCl<sub>3</sub> (1 mL) and 4 N HCl-dioxane (1 mL) were added to 16, A2B4 (0.1041 g, 0.09577 mmol) in a 4 mL vial and this mixture was allowed to stand for 4h at 25°C. TLC (15% CH<sub>3</sub>OH–EtOAc) then indicated that conversion to the amine was complete. The solvent and excess acid were removed by evaporation. A stock solution was prepared by diluting a mixture of 0.5 mmol of each diacid (C1-C10 and C41–C50), and 45 mmol of *i*-Pr<sub>2</sub>NEt to 100 mL in anhydrous DMF. This stock solution (0.638 mL, 0.00318 mmol of each diacid, 0.45 mmol of *i*-Pr<sub>2</sub>NEt) was added to the diamide and the mixture was shaken to effect dissolution. PyBrOP (44.7 mg, 0.096 mmol) was added and the mixture was capped and stirred for 12h at 25°C. The reaction mixture was diluted with EtOAc

(25 mL) washed with 20% aqueous HCl saturated with NaCl  $(3 \times 25 \text{ mL})$ , saturated aqueous NaHCO<sub>3</sub>  $(1 \times 25 \text{ mL})$  and saturated aqueous NaCl  $(1 \times 25 \text{ mL})$ , dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 60 mg (90%) of the sublibrary. MS exhibited all the expected molecular ion for 17, A2B4CI-C10: MALDI-MS (M+H<sup>+</sup> or M+Na<sup>+</sup>) m/z 2050, 2052, 2079, 2106, 2129, 2180 (10 components, 6 different molecular weights). Similarly, for 17, A2B4C41-C50, the yield is 71%. MS exhibited all the expected molecular ions: MALDI–MS  $(M+H^+)$  or  $M + Na^+$ ) m/z 2090, 2094, 2134, 2138, 2162, 2182, 2186, 2226, 2244, 2270. A summary of the individual and mixture coupling yields is provided in Table 7.

Similarly, seven tetra-amides 16: A6B6, A2B4, A2B6, A7B15, A7B4, A7B6, A7B14 have been individually coupled with each of the eight diacids in group C21–C28, so that 56 single compounds of 17 have been made. <sup>1</sup>H NMR of each ensured the integrity of each compound and full characterization has been carried out on A6B6C21, A2B6C26 and A2B4C28.

**17, A6B6C21:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.08 (br s, 8H), 6.91 (br s, 8H), 4.48–3.75 (m, 24H), 3.57–3.12 (m, 64H), 2.70 (br s, 8H), 1.45 (br s, 4H), 1.19 (m, 8H); IR (film)  $V_{\text{max}}$  3272, 3073, 2932, 1655, 1560, 1509, 1471, 1219, 1194, 1158, 1117, 1015, 965, 843 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1941.8205 (M+Cs<sup>+</sup>, C<sub>88</sub>H<sub>128</sub>N<sub>14</sub>O<sub>22</sub>F<sub>4</sub> requires 1941.8318).

**17, A2B6C26:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.10 (m, 8H), 6.78 (m, 8H), 4.55–3.78 (s, 28H), 3.55–3.18 (m, 72H), 2.72 (m, 8H), 1.60 (br s, 4H), 1.23 (br s, 28H); IR (film)  $V_{\text{max}}$  3439, 2925, 2852, 1654, 1513, 1465, 1300, 1246, 1193, 1116, 1032, 962, 844 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 2130.0541 (M+Cs<sup>+</sup>, C<sub>102</sub>H<sub>160</sub>N<sub>14</sub>O<sub>26</sub> requires 2130.0683).

**17, A2B4C28:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.03 (br s, 8H), 6.72 (br s, 8H), 6.60 (m, 8H), 4.31 (br s, 8H),

 Table 7. Representative individual and mixture coupling yields, 17

A2B4C1	95%	A2B4C41	80%
A2B4C2	95%	A2B4C42	77%
A2B4C3	78%	A2B4C43	79%
A2B4C4	93%	A2B4C44	41%
A2B4C5	78%	A2B4C45	62%
A2B4C6	80%	A2B4C46	59%
A2B4C7	78%	A2B4C47	79%
A2B4C8	69%	A2B4C48	48%
A2B4C9	76%	A2B4C49	40%
A2B4C10	95%	A2B4C50	44%
average	84%	average	61%
A2B4C1-10	92%	A2B4C41-50	71%

4.10–3.67 (m, 72H), 3.32 (br s, 8H), 2.72 (br s, 8H), 1.40 (br m, 4H), 1.20 (m, 36H); IR (film)  $V_{max}$  3046, 3073, 2924, 2849, 1656, 1593, 1512, 1462, 1423, 1329, 1301, 1245, 1180, 1126, 953, 844, 556 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 2442.1273 (M+Cs<sup>+</sup>, C<sub>122</sub>H<sub>168</sub>N<sub>14</sub>O<sub>30</sub> requires 2442.1105).

General procedure for the synthesis of individual sublibrary entries for 17: preparation of A2B1C19. The BOC derivative 16 (A2B1, 82 mg, 0.078 mmol) was stirred in a solution of 4 N HCl-dioxane (2 mL) at 25 °C for 4 h. Removal of the solvent under N2 and in vacuo gave the deprotected material as a yellow oil. The crude amine hydrochloride was dissolved in anhydrous DMF (2mL) and C19 (10mg, 0.026 mmol), *i*-Pr<sub>2</sub>NEt (0.041 mL, 0.234 mmol) and PyBrOP (36 mg, 0.078 mmol) were added sequentially. The mixture was stirred for 16h at 25° before being diluted with EtOAc (20 mL) and washed with 10% aqueous HCl  $(2 \times 20 \text{ mL})$ , saturated aqueous NaHCO3 (2×20 mL), saturated aqueous NaCl (20 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under reduced pressure to provide 39 mg (66%) of the title substance as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.38–7.25 (m, 4H), 7.08–7.05 (m, 8H), 6.80– 6.65 (m, 24H), 4.11-3.68 (m, 60H), 3.45 (m, 16H), 2.80 (m, 16H); IR (film) V<sub>max</sub> 3282, 3067, 2923, 2831, 1651, 1569, 1508, 1462, 1246, 1221, 1174, 1036, 969, 841, 810, 733, 703 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 2399.8858  $(M + Cs^+, C_{117}H_{136}F_6N_{14}O_{26}$  requires 2399.8709).

**17, A2B11C14:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.96 (m, 2H), 7.50 (m, 4H), 7.25–7.05 (m, 28H), 6.80–6.74 (m, 8H), 4.10–3.70 (m, 36H), 3.46 (m, 16H), 2.80 (m, 16H); IR (film)  $V_{\text{max}}$  3282, 3067, 2923, 1651, 1574, 1513, 1456, 1301, 1246, 1179, 1031, 823, 739 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1983.7941 (M+Cs<sup>+</sup>, C<sub>104</sub>H<sub>118</sub>N<sub>14</sub>O<sub>18</sub> requires 1983.7803).

General procedure for 17: sublibrary A2B2"C11-20. The BOC derivative 16 (A2B2", 55 mg, 0.0552 mmol) was stirred in a solution of 4 N HCl-dioxane (2 mL) at 25 °C for 4h. Removal of the solvent under N<sub>2</sub> and in vacuo gave the deprotected material as a yellow oil. A diacid stock solution was prepared through diluting a mixture of 0.5 mmol of each diacid C11-C20 to 80 mL DMF and 20 mL DMSO. The crude amine hydrochloride was dissolved in anhydrous DMF (2mL), and the diacid stock solution (0.368 mL, 0.0184 mmol of C11–C20), *i*-Pr<sub>2</sub>NEt (0.029 mL, 0.166 mmol) and PyBrOP (26 mg, 0.0552 mmol) were added sequentially. The reaction mixture was stirred for 16h at 25 °C before being diluted with EtOAc (20 mL) and washed with 10% aqueous HCl  $(2 \times 20 \text{ mL})$ , saturated aqueous NaHCO<sub>3</sub>  $(2 \times 20 \text{ mL})$ , and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under reduced pressure to provide 30 mg (83%) of the title substance as an oil. The MS exhibited all the expected

molecular ions (10 different components which have eight different molecular weights): ESMS  $(M + Cl^{-}) m/z$  2184, 2034, 2009, 2007, 1985, 1976, 1964, 1933.

Selected characterization for 5, AXB10C4 (A scan). <sup>1</sup>H NMR of each of the 114 compounds, A8B10C4–A123B10C4, ensured the integrity of each compound in the A scan. Full characterization has been carried out on the following 11 compounds.

**5**, **A8B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.29 (s, 10H), 5.80 (m, 2H), 5.05 (s, 4H), 4.30 (br s, 4H), 4.15–3.40 (m, 20H), 3.20 (m, 4H), 2.60–2.20 (m, 6H), 1.90–1.30 (m, 20H); IR (film)  $V_{\text{max}}$  3288, 2946, 1715, 1643, 1535, 1453, 1237, 1102, 1028 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1331.4420 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>78</sub>N<sub>8</sub>O<sub>18</sub> requires 1331.4488).

**5**, **A12B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.25(s, 10H), 7.10 (m, 2H), 6.75 (m, 4H), 5.60–5.40 (m, 2H), 5.02 (br s, 4H), 4.23–3.80 (m, 8H), 3.60 (br s, 6H), 3.40–2.70 (m, 12H), 1.80–1.30 (m, 12H); IR (film)  $V_{\text{max}}$  3288, 2934, 1651, 1540, 1454, 1249, 1026, 698 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1299.3571 (M + Cs<sup>+</sup>, C<sub>58</sub>H<sub>70</sub>N<sub>8</sub>O<sub>14</sub>S, requires 1299.3507).

**5**, **A13B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.31 (s, 12H), 6.30 (m, 4H), 5.78 (br s, 2H), 5.06 (s, 4H), 4.40–4.30 (m, 6H), 4.10–3.80 (m, 6H), 3.70 (s, 6H), 3.20 (m, 4H), 1.80 (m, 4H), 1.41 (m, 4H), 1.35 (m, 4H); IR (film)  $V_{\text{max}}$  3278, 3055, 2949, 1658, 1545, 1453, 1248, 1025, 739, 699 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1239.3589 (M+Cs<sup>+</sup>, C<sub>56</sub>H<sub>66</sub>N<sub>8</sub>O<sub>16</sub> requires 1239.3651).

**5**, **A15B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.29 (br s, 10H), 5.65 (m, 2H), 5.05 (s, 4H), 4.30 (m, 4H), 4.15–3.60 (m, 16H), 3.30–2.50 (m, 10H), 1.95–1.40 (m, 8H), 1.40–1.30 (m, 20H); IR (film) *V*<sub>max</sub> 2948, 1720, 1636, 1453, 1213, 1039 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z*, 1359.4871 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>82</sub>N<sub>8</sub>O<sub>18</sub> requires 1359.4801).

**5**, **A29B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.50–7.05 (m, 20H), 5.70 (m, 2H), 5.02 (s, 4H), 4.50–3.45 (m, 22H), 3.20 (m, 4H), 2.50 (m, 4H), 1.90–1.35 (m, 22H); IR (film)  $V_{\text{max}}$  3276, 2930, 1718, 1637, 1452, 1249, 842 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1395.5390 (M + Cs<sup>+</sup>, C<sub>70</sub>H<sub>86</sub>N<sub>8</sub>O<sub>14</sub> requires 1395.5318).

**5**, **A33B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.55 (m, 4H), 7.50–6.85 (m, 30H), 5.60 (m, 2H), 5.02 (s, 4H), 4.80 (m, 4H), 4.30–3.30 (m, 18H), 1.80–1.30 (m, 12H); IR (film)  $V_{\text{max}}$  3288, 2944, 1716, 1648, 1540, 1496, 1454, 1267, 1028, 700 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1411.4617 (M + Cs<sup>+</sup>, C<sub>72</sub>H<sub>78</sub>N<sub>8</sub>O<sub>14</sub> requires 1411.4692).

**5, A38B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.30 (m, 10H), 6.70 (m, 6H), 5.90–5.60 (m, 6H), 5.01 (s, 4H), 4.30–3.50 (m, 18H), 3.28 (m, 4H), 1.80–1.20 (m, 12H); IR (film)  $V_{\text{max}}$  3287, 3056, 2924, 1718, 1648, 1544, 1490, 1444, 1250, 1037, 662 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1347.3794 (M+Cs<sup>+</sup>, C<sub>6</sub>:H<sub>70</sub>N<sub>8</sub>O<sub>18</sub>

**5**, **A51B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 8.65 (br s, 2H), 8.45 (br s, 2H), 8.24 (br s, 2H), 7.56 (two s, 6H), 7.28 (br s, 10H), 5.80 (m, 2H), 5.02 (br s, 4H), 4.28 (br s, 2H), 3.70 (br s, 6H), 3.20 (br s, 10H), 2.80 (s, 8H), 1.80–1.10 (m, 28H); IR (film)  $V_{\text{max}}$  3263, 2933, 1648, 1454, 1324, 1163, 1138, 1013, 793 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1725.4730 (M+Cs<sup>+</sup>, C<sub>78</sub>H<sub>94</sub>Cl<sub>2</sub>N<sub>10</sub>O<sub>18</sub>S<sub>2</sub> requires 1725.4620).

requires 1347.3862).

**5**, **A52B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.30 (m, 22H), 5.56 (m, 2H), 5.05 (m, 4H), 4.30 (br s, 4H), 3.65 (m, 10H), 3.30 (m, 6H), 2.20 (m, 6H), 1.78 (m, 4H), 1.48 (br s, 4H), 1.30 (br s, 4H); IR (film)  $V_{\text{max}}$  3275, 2948, 1683, 1582, 1528, 1491, 1452, 1402, 1266, 1092, 1015, 686 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1625.3360 (M+Cs<sup>+</sup>, C<sub>76</sub>H<sub>76</sub>Cl<sub>4</sub>N<sub>10</sub>O<sub>14</sub> requires 1625.3351).

**5**, **A68B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.35 (m, 30H), 6.70 (m, 6H), 5.65 (m, 2H), 5.12 (s, 12H), 3.90–3.60 (m, 14H), 3.40 (m, 4H), 3.20 (m, 4H), 2.75 (m, 4H), 1.80–1.30 (m, 12H); IR (film) *V*<sub>max</sub> 3262, 3064, 2937, 1719, 1648, 1512, 1453, 1261, 1136, 1025, 736, 696 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 1711.6155 (M + Cs<sup>+</sup>, C<sub>90</sub>H<sub>98</sub>N<sub>8</sub>O<sub>18</sub> requires 1711.6053).

**5**, **A79B10C4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.50–7.50 (m, 4H), 7.30 (m, 12H), 6.40 (br s, 4H), 5.65 (m, 2H), 5.02 (br s, 4H), 4.30 (m, 6H), 3.70 (m, 20H), 3.25 (m, 4H), 2.20 (m, 4H), 1.80–1.20 (m, 12H); IR (film) *V*<sub>max</sub> 3293, 2948, 1718, 1654, 1543, 1508, 1454, 1208, 1129, 1035 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1379.4418 (M + Cs<sup>+</sup>, C<sub>64</sub>H<sub>78</sub>N<sub>8</sub>O<sub>18</sub> requires 1379.4488).

*N*,*N*<sup>-</sup>**Bis**(*N*,*N***-di(benzyloxycarbonylmethyl))benzene-1,3dicarboxamide (18).** Dibenzyl*N*-BOC-iminodiacetale acid (7.8 g, 20 mmol) was treated with 4 N HCl–dioxane (100 mL) for 6 h at 25 °C. After removal of the solvent under a stream of N<sub>2</sub>, the crude amine hydrochloride was suspended in THF (170 mL) and Et<sub>3</sub>N (22 mL, 160 mmol) was added. Isophthaloyl dichloride (2.1 g, 10 mmol) dissolved in THF (8 mL) was added and the mixture was stirred for 4 h at 25 °C. The reaction mixture was diluted with Et<sub>2</sub>O (200 mL) and washed with 10% aqueous HCl (2×200 mL), 1 N aqueous NaOH (2×200 mL), saturated aqueous NaCl (1×200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography (SiO<sub>2</sub>, 50% EtOAc–hexanes) afforded **18** (550 mg, 77%) as a viscous oil: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.31 (m, 24H), 5.16 (s, 4H), 5.13 (s, 4H), 4.32 (s, 4H), 4.08 (s, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$  171.4, 168.8, 168.6, 135.2, 135.1, 134.8, 129.1, 128.7, 128.6, 128.7, 125.5, 67.5, 67.2, 51.8, 47.8; IR (film)  $V_{\text{max}}$  1747, 1655, 1455, 1185 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 889.1759 (M+Cs<sup>+</sup>, C<sub>44</sub>H<sub>40</sub>N<sub>2</sub>O<sub>10</sub> requires 889.1737).

*N*,*N*'-Bis(*N*,*N*-di(carboxymethyl))benzene-1,3-dicarboxamide (19). A solution of 18 (5.5 g, 7.8 mmol) in THF– EtOH (100 mL, 1:1) was treated with 10% Pd–C (500 mg), and the suspension was stirred under a H<sub>2</sub> atmosphere for 6 h at 25 °C. The mixture was filtered through a pad of Celite and the solvent removed in vacuo to provide 19 (2.9 g, 95%) as a white foam: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.40 (m, 4H), 5.25 (br s, 8H), 4.28 (s, 4H), 4.05 (s, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 173.6, 172.2, 172.1, 136.9, 130.4, 129.4, 126.1, 52.8; IR (film)  $V_{max}$  2998, 1728, 1620, 1225 cm<sup>-1</sup>; FABHRMS (NBA–NaI) *m*/*z* 397.0875 (M+H<sup>+</sup>, C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>10</sub> requires 397.0883).

N,N'-Bis(N-(carboxymethyl))-N,N'-bis(N-2-(4-fluorophenyl)ethyl)carboxamidomethyl)benzene-1,3-dicarboxamide (20). A solution of 19 (1.6 g, 3.9 mmol) in DMF (20 mL) was treated with EDCI (1.6 g, 8.0 mmol). After stirring for 1 h at 25 °C, 4-fluorophenethylamine (1.0 mL, 8.0 mmol) was added and the mixture was stirred for another 4h. The solvent was removed in vacuo, and flash chromatography (SiO<sub>2</sub>, 1% HOAc, 5%  $CH_3OH-CHCl_3$ ) afforded 20 (1.7 g, 70%) as a white foam: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.50 (m, 4H), 7.22 (m, 4H), 6.98 (m, 4H), 4.20-3.98 (m, 8H), 3.38 (t, 4H, J=7.3 Hz), 2.77 (t, 4H, J=7.3 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 173.6, 172.8, 172.4, 170.8, 170.4, 164.2, 136.8, 136.2, 131.5, 130.2, 126.4, 129.5, 116.3, 116.0, 54.6, 53.6, 51.7, 42.0; IR (film) V<sub>max</sub> 3481, 2935, 1732, 1645, 1510 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z771.1268 (M + Cs<sup>+</sup>, C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>8</sub> requires 771.1243).

General procedure for the B-scan: 5, A6B23C4. A solution of 20 (25 mg, 0.039 mmol) in DMF (1 mL) was treated with the amine hydrochloride (25 mg, 0.098 mmol), PyBrOP (56 mg, 0.18 mmol) and *i*-Pr<sub>2</sub>NEt (55 mL, 0.3 mmol) and the mixture was stirred for 12 h at 25 °C. EtOAc (50 mL) was added and the mixture was washed with 10% aqueous HCl  $(3 \times 50 \text{ mL})$ , saturated aqueous NaHCO<sub>3</sub>  $(1 \times 50 \text{ mL}),$ saturated aqueous NaCl  $(1 \times 50 \text{ mL})$  and dried  $(Na_2SO_4)$ . The solvent was removed in vacuo affording 36 mg (90%) of 5, A6B23C4 as a vellow foam: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.60-7.40 (m, 4H), 7.33 (m, 10H), 7.20 (m, 4H), 6.97 (m, 4H), 5.09 (s, 4H), 4.21–4.00 (m, 8H), 3.50– 3.35 (m, 4H), 3.28 (m, 2H), 3.15 (m, 2H), 2.80-2.69 (m, 4H), 2.39 (m, 4H), 1.75–1.40 (m, 8H); IR (film) V<sub>max</sub> 3420, 1652, 1558, 1508, 1456 cm<sup>-1</sup>; FABHRMS (NBA-CsI) m/z 1149.3485 (M+Cs<sup>+</sup>, C<sub>56</sub>H<sub>62</sub>F<sub>2</sub>N<sub>6</sub>O<sub>10</sub> requires 1149.3550).

Full characterization of selected A6B88C4 members follow and the remaining 5, A6B49C4–A6B88C4 have also been characterized by <sup>1</sup>H NMR, IR, and HRMS.

**5**, **A6B16C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.55–7.35 (m, 4H), 7.30 (m, 20H), 7.20 (m, 4H), 6.97 (m, 4H), 5.15 (s, 4H), 5.00 (s, 4H), 4.50–4.28 (m, 2H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.10 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.50 (m, 8H); IR (film)  $V_{\text{max}}$  3421, 1652, 1508, 1253, 1020 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1447.4597 (M + Cs<sup>+</sup>, C<sub>72</sub>H<sub>76</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1447.4503).

5, A6B17C4: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.55–7.35 (m, 4H), 7.30 (m, 10H), 7.20 (m, 4H), 6.97 (m, 4H), 5.02 (s, 4H), 4.29 (m, 2H), 4.21–3.97 (m, 8H), 3.44–3.36 (m, 4H), 3.11 (m, 4H), 2.80–2.70 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H), 1.44 (s, 18H); IR (film) *V*<sub>max</sub> 3421, 1841, 1653, 1406, 1018 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1407.5222 (M+Cs<sup>+</sup>, C<sub>68</sub>H<sub>84</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1407.5129).

**5**, **A6B18C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.55–7.35 (m, 4H), 7.22 (m, 4H), 6.98 (m, 4H), 4.56 (m, 1H), 4.35 (m, 1H), 4.21–3.00 (m, 8H), 3.73 (s, 6H), 3.41–3.39 (m, 4H), 3.03 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H), 1.41 (s, 18H); IR (film) *V*<sub>max</sub> 3411, 1734, 1652, 1508, 1019 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1255.4572 (M + Cs<sup>+</sup>, C<sub>56</sub>H<sub>76</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1255.4503).

5, A6B19C4: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.55–7.35 (m, 4H), 7.31 (m, 10H), 7.20 (m, 4H), 6.97 (m, 4H), 5.06 (s, 4H), 4.14 (m, 2H), 4.2–3.98 (m, 8H), 3.44–3.37 (m, 4H), 3.21 (m, 2H), 3.09 (m, 2H), 2.80–2.69 (m, 4H), 1.85–1.40 (m, 12H); IR (film) *V*<sub>max</sub> 3420, 1652, 1508, 1418, 1016 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m/z* 1293.4121 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>70</sub>F<sub>2</sub>N<sub>10</sub>O<sub>12</sub> requires 1293.4197).

**5**, **A6B20C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.55–7.35 (m, 4H), 7.30 (m, 20H), 7.15 (m, 4H), 6.94 (m, 4H), 5.16 (m, 4H), 5.00 (br s, 4H), 4.49 (m, 1H), 4.35 (m, 1H), 4.15–3.92 (m, 8H), 3.41–3.30 (m, 4H), 3.05 (m, 4H), 2.80–2.63 (m, 4H), 1.75 (m, 4H), 1.51–1.26 (m, 8H); IR (film)  $V_{\text{max}}$  3421, 1653, 1406, 1018, 953 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1475.4721 (M+Cs<sup>+</sup>, C<sub>74</sub>H<sub>80</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1475.4816).

**5**, **A6B21C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.68 (d, 4H, J=8.2 Hz), 7.60–7.40 (m, 4H), 7.32 (d, 4H, J=8.2 Hz), 7.19 (m, 4H), 6.97 (m, 4H), 4.16–3.95 (m, 8H), 3.82 (m, 2H), 3.45–3.35 (m, 4H), 3.37, (m, 6H),

3.24–3.09 (m, 4H), 2.80–2.70 (m, 4H), 2.39 (s, 6H), 1.80– 1.30 (m, 12H); IR (film)  $V_{\text{max}}$  3420, 2936, 1740, 1652, 1160 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1363.3624 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>72</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub>S<sub>2</sub> requires 1363.3632).

**5**, **A6B22C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.40 (m, 4H), 7.30 (m, 10H), 7.20 (m, 4H), 6.97 (m, 4H), 5.03 (m, 4H), 4.21–4.00 (m, 8H), 3.95 (s, 1H), 3.86 (s, 1H), 3.50–3.32 (m, 4H), 3.09 (m, 4H), 3.10 (m, 4H), 2.80–2.69 (m, 4H), 1.65–1.30 (m, 12H); IR (film) *V*<sub>max</sub> 3396, 2937, 1652, 1508, 1019 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1267.4210 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>72</sub>F<sub>2</sub>N<sub>8</sub>O<sub>12</sub> requires 1267.4292).

**5**, **A6B24C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.40 (m, 4H), 7.31 (m, 10H), 7.22 (m, 4H), 6.97 (m, 4H), 5.03 (s, 4H), 4.47 (m, 1H), 4.36 (m, 1H), 4.21–4.00 (m, 8H), 3.70 (s, 6H), 3.45–3.35 (m, 4H), 3.13 (m, 4H), 2.80–2.69 (m, 4H), 1.95–1.45 (m, 8H); IR (film)  $V_{\text{max}}$  3292, 3057, 2934, 1652, 1540, 1507, 1219 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1295.3869 (M + Cs<sup>+</sup>, C<sub>60</sub>H<sub>68</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1295.3877).

**5**, **A6B25C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.40 (m, 4H), 7.22 (m, 4H), 6.97 (m, 4H), 4.22–4.00 (m, 8H), 3.65 (s, 6H), 3.50–3.35 (m, 4H), 3.26 (m, 2H), 3.17 (m, 2H), 2.80–2.69 (m, 4H), 2.42 (m, 2H), 2.29 (m, 2H), 1.84 (m, 2H), 1.73, (m, 2H); IR (film)  $V_{\text{max}}$  3421, 1734, 1652, 1508, 1220 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 969.2646 (M + Cs<sup>+</sup>, C<sub>42</sub>H<sub>50</sub>F<sub>2</sub>N<sub>6</sub>O<sub>10</sub> requires 969.2611).

**5**, **A6B26C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.40 (m, 4H), 7.22 (m, 4H), 6.97 (m, 4H), 4.22–4.00 (m, 8H), 3.63 (s, 6H), 3.50–3.35 (m, 4H), 3.25 (m, 2H), 3.13 (m, 2H), 2.80–2.69 (m, 4H), 2.32 (m, 4H), 1.60–1.28 (m, 12H); IR (film)  $V_{\text{max}}$  3267, 3072, 2937, 1734, 1652, 1509 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1025.2286 (M + Cs<sup>+</sup>, C<sub>46</sub>H<sub>58</sub>F<sub>2</sub>N<sub>6</sub>O<sub>10</sub> requires 1025.3234).

**5**, **A6B27C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.40 (m, 4H), 7.22 (m, 4H), 6.97 (m, 4H), 4.20–4.00 (m, 8H), 4.14 (q, 4H, *J* = 7.2 Hz), 3.90–3.70 (m, 2H), 3.50–3.35 (m, 4H), 2.96 (m, 4H), 2.80–2.69 (m, 4H), 1.90–1.75 (m, 2H), 1.48–1.26 (m, 2H), 1.25 (t, 6H, *J* = 7.2 Hz); IR (film) *V*<sub>max</sub> 3421, 1652, 1437, 1019, 953 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1079.3402 (M+Cs<sup>+</sup>, C<sub>48</sub>H<sub>60</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1079.3455).

**5**, **A6B28C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.28 (m, 4H), 7.19 (m, 4H), 6.96 (m, 10H), 4.53 (s, 4H), 4. 48 (m, 2H), 4.21–3.92 (m, 8H), 3.70 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film)  $V_{\text{max}}$  3421, 2920, 1652, 1437, 1019 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1323.4282 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>72</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1323.4190).

**5**, **A6B29C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.30 (m, 4H), 7.19 (m, 4H), 7.06–6.77 (m, 10H), 4.21 (m, 2H), 4.12–3.92 (m, 8H), 3.71 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film) *V*<sub>max</sub> 1653, 1437, 1406, 1019 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1295.3930 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>68</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1295.3877).

**5**, **A6B30C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.23 (m, 4H), 6.98 (m, 4H), 4.3 (m, 2H), 4.21–3.92 (m, 8H), 3.69 (s, 6H), 3.60 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film)  $V_{\text{max}}$  3410, 1652, 1437, 1017, 953 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1171.3622 (M+Cs<sup>+</sup>, C<sub>50</sub>H<sub>64</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1171.3564).

**5**, **A6B31C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.82 (m, 4H), 7.50–7.45 (m, 4H), 7.44 (m, 6H), 7.19 (m, 4H), 6.96 (m, 4H), 4.56 (m, 2H), 4.21–3.92 (m, 8H), 3.70 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film)  $V_{\text{max}}$  3421, 1652, 1418, 1017, 952 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1263.4045 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>68</sub>F<sub>2</sub>N<sub>8</sub>O<sub>12</sub> requires 1263.3979).

**5**, **A6B32C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.67 (m, 2H), 7.56 (m, 2H), 7.50–7.45 (m, 4H), 7.44 (m, 2H), 7.19 (m, 4H), 7.16 (m, 2H), 6.96 (m, 4H), 4.56 (m, 2H), 4.21–3.92 (m, 8H), 3.70, (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film) *V*<sub>max</sub> 3420, 1684, 1653, 1540, 1017 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1299.3879 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>66</sub>F<sub>4</sub>N<sub>8</sub>O<sub>12</sub> requires 1299.3791).

**5**, **A6B33C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.89 (m, 4H), 7.50–7.45 (m, 4H), 7.19 (m, 4H), 7.16 (m, 4H), 6.96 (m, 4H), 4.56 (m, 2H), 4.21–3.92 (m, 8H), 3.70 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film)  $V_{\text{max}}$  3419, 1652, 1437, 1019, 953 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 1189.4635 (M + Na<sup>+</sup>, C<sub>60</sub>H<sub>66</sub>F<sub>4</sub>N<sub>8</sub>O<sub>12</sub> requires 1189.4634).

**5**, **A6B34C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.19 (m, 4H), 7.17 (m, 4H), 6.96 (m, 4H), 4.56 (dd, 2H, *J*=9.2, 5.2 Hz), 4.21–3.92 (m, 8H), 3.84 (s, 12H), 3.78 (s, 6H), 3.70, (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film) *V*<sub>max</sub> 3422, 1654, 1407, 1018, 953 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1444.5000 (M + Cs<sup>+</sup>, C<sub>66</sub>H<sub>80</sub>F<sub>2</sub>N<sub>8</sub>O<sub>18</sub> requires 1444.4613).

**5, A6B35C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.50–7.45 (m, 4H), 7.26 (m, 10H), 7.19 (m, 4H), 6.96 (m, 4H), 4.26

(m, 4H), 4.24 (m, 2H), 4.21–3.92 (m, 8H), 3.67 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.40 (m, 12H); IR (film)  $V_{\text{max}}$  1652, 1437, 1318, 1019, 953 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z1321.4564 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>74</sub>F<sub>2</sub>N<sub>10</sub>O<sub>12</sub> requires 1321.4510).

**5**, **A6B36C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.22 (m, 4H), 6.96 (m, 4H), 4.33 (m, 2H), 4.21–3.92 (m, 8H), 3.67 (s, 6H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.80 (m, 10H), 1.61–1.40 (m, 8H), 1.34 (m, 12H); IR (film) *V*<sub>max</sub> 3406, 1654, 1437, 1407, 1020 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1275.4999 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>80</sub>F<sub>2</sub>N<sub>8</sub>O<sub>12</sub> requires 1275.4918).

**5**, **A6B37C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.38 (s, 10H), 7.22 (m, 4H), 6.96 (m, 4H), 5.15 (m, 4H), 4.91 (m, 2H), 4.11–4.06 (m, 4H), 3.97 (br s, 4H), 3.71 (s, 6H), 3.41–3.32 (m, 4H), 3.28–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.84 (m, 4H), 1.61–1.36 (m, 8H); IR (film) *V*<sub>max</sub> 3266, 3071, 1748, 1652, 1509, 1221 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1325.3940 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>70</sub>F<sub>2</sub>N<sub>6</sub>O<sub>16</sub> requires 1325.3871).

**5**, **A6B38C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.02 (m, 4H), 7.50–7.45 (m, 4H), 7.47 (m, 6H), 7.22 (m, 4H), 6.96 (m, 4H), 5.19 (m, 2H), 4.11–3.97 (m, 8H), 3.71 (s, 6H), 3.41–3.32 (m, 4H), 3.28–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.99 (m, 4H), 1.61–1.36 (m, 8H); IR (film) *V*<sub>max</sub> 3648, 1717, 1653, 1508 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1265.3659 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>66</sub>F<sub>2</sub>N<sub>6</sub>O<sub>14</sub> requires 1265.3733).

**5**, **A6B39C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.08 (m, 4H), 7.50–7.45 (m, 4H), 7.22 (m, 4H), 7.19 (m, 4H), 6.96 (m, 4H), 5.19 (m, 2H), 4.11–3.97 (m, 8H), 3.71 (s, 6H), 3.41–3.32 (m, 4H), 3.28–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.99 (m, 4H), 1.61–1.36 (m, 8H); IR (film) *V*<sub>max</sub> 3261, 3070, 2937, 1718, 1653, 1508 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1301.3539 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>64</sub>F<sub>4</sub>N<sub>6</sub>O<sub>14</sub> requires 1301.3471).

**5**, **A6B40C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.33 (m, 4H), 7.20 (m, 4H), 6.95 (m, 4H), 5.02 (m, 2H), 4.11–3.97 (m, 8H), 3.82 (m, 18H), 3.71 (s, 6H), 3.41–3.32 (m, 4H), 3.28–3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.99 (m, 4H), 1.61–1.36 (m, 8H); IR (film) *V*<sub>max</sub> 3267, 2942, 1716, 1652, 1506, 1220, 1127 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1445.4386 (M+Cs<sup>+</sup>, C<sub>66</sub>H<sub>78</sub>F<sub>2</sub>N<sub>6</sub>O<sub>20</sub> requires 1445.4293).

**5**, **A6B41C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.50–7.45 (m, 4H), 7.31 (m, 6H), 7.22 (m, 4H), 7.19 (m, 4H), 6.94 (m, 4H), 5.19 (m, 4H), 4.91 (m, 2H), 4.11–4.06 (m, 4H), 3.97 (br s, 4H), 3.71 (s, 6H), 3.41–3.32 (m, 4H), 3.28–3.09

(m, 4H), 2.80–2.69 (m, 4H), 1.84 (m, 4H), 1.61–1.36 (m, 8H); IR (film)  $V_{\text{max}}$  3266, 3071, 1748, 1652, 1509, 1221 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1325.3940 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>70</sub>F<sub>2</sub>N<sub>6</sub>O<sub>16</sub> requires 1325.3871).

**5**, **A6B42C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 8H), 2.80–2.69 (m, 4H), 1.66–1.58 (m, 4H); IR (film)  $V_{\text{max}}$  3284, 3069, 2937, 1652, 1509, 1254 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1151.3510 (M+Cs<sup>+</sup>, C<sub>54</sub>H<sub>60</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1151.3455).

**5**, **A6B43C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.24–3.09 (m, 8H), 2.80–2.69 (m, 4H), 1.55 (br s, 4H), 1.44 (br s, 4H); IR (film)  $V_{\text{max}}$  3280, 3068, 2936, 1652, 1509, 1254 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1179.3702 (M+Cs<sup>+</sup> C<sub>56</sub>H<sub>64</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1179.3768).

**5**, **A6B44C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.22–3.08 (m, 8H), 2.80–2.69 (m, 4H), 1.66–1.28 (m, 12H); IR (film)  $V_{\text{max}}$  3279, 3070, 2936, 1652, 1509, 1248 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1207.4012 (M+Cs<sup>+</sup>, C<sub>58</sub>H<sub>68</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1207.4081).

**5, A6B45C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.22–3.08 (m, 8H), 2.80–2.69 (m, 4H), 1.66–1.28 (m, 16H); IR (film)  $V_{\text{max}}$  3278, 2936, 1652, 1508, 1254 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1235.4470 (M+Cs<sup>+</sup>, C<sub>60</sub>H<sub>72</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1235.4394).

**5**, **A6B46C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.22–3.08 (m, 8H), 2.80–2.69 (m, 4H), 1.66–1.28 (m, 20H); IR (film)  $V_{\text{max}}$  3285, 3071, 2933, 1652, 1509, 1248 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1263.4632 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>76</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1263.4707).

**5**, **A6B47C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.22–3.08 (m, 8H), 2.80–2.69 (m, 4H), 1.66–1.28 (m, 24H); IR (film)  $V_{\text{max}}$  3284, 3071, 2931, 1652, 1509, 1252 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1291.5095 (M+Cs<sup>+</sup>, requires C<sub>64</sub>H<sub>80</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> 1291.5020).

**5**, **A6B48C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.50–7.45 (m, 4H), 7.31 (m, 10H), 7.18 (m, 4H), 6.96 (m, 4H), 5.04 (s, 4H), 4.21–3.92 (m, 8H), 3.41–3.32 (m, 4H), 3.22–3.08

(m, 8H), 2.80–2.69 (m, 4H), 1.66–1.28 (m, 32H); IR (film)  $V_{\text{max}}$  3286, 3071, 2928, 1652, 1510, 1251 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1347.5559 (M+Cs<sup>+</sup>, C<sub>68</sub>H<sub>88</sub>F<sub>2</sub>N<sub>8</sub>O<sub>10</sub> requires 1347.5646).

**5**, **A6B89C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.55–7.45 (m, 4H), 7.30 (m, 20H), 7.15 (m, 4H), 6.94 (m, 4H), 5.16 (m, 4H), 5.00 (br s, 4H), 4.50–4.28 (m, 2H), 4.15–3.92 (m, 8H), 3.41–3.30 (m, 4H), 3.05 (m, 4H), 2.80–2.63 (m, 4H), 1.75 (m, 4H), 1.51–1.26 (m, 8H); IR (film) *V*<sub>max</sub> 3421, 1653, 1540, 1508, 1252 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1475.4723 (M + Cs<sup>+</sup>, C<sub>74</sub>H<sub>80</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1475.4816).

**5**, **A6B90C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.10 (d, 4H, *J*=6.8 Hz), 7.60–7.45 (m, 4H), 7.30 (m, 10H), 7.17 (m, 4H), 6.94 (m, 4H), 6.87 (d, 4H, *J*=6.8 Hz), 5.08 (s, 4H), 4.50–4.28 (m, 2H),4.15–3.92 (m, 8H), 3.41–3.30 (m, 4H), 3.25–3.16 (m, 4H), 2.80–2.63 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film) *V*<sub>max</sub> 3422, 1652, 1509, 1292 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1475.4723 (M+Cs<sup>+</sup>, C<sub>72</sub>H<sub>74</sub>F<sub>2</sub>N<sub>10</sub>O<sub>18</sub> requires 1475.4816).

**5**, **A6B91C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.45 (m, 4H), 7.30 (m, 10H), 7.20 (m, 4H), 6.97 (m, 4H), 5.02 (s, 4H), 4.50–4.28 (m, 2H), 4.21–3.92 (m, 8H), 3.69, (s, 6H), 3.41–3.32 (m, 4H), 3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film)  $V_{\text{max}}$  3422, 1652, 1508, 1219 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1323.4112 (M + Cs<sup>+</sup>, C<sub>62</sub>H<sub>72</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1323.4190).

**5**, **A6B92C4:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.60–7.45 (m, 4H), 7.30 (m, 10H), 7.20 (m, 4H), 6.97 (m, 4H), 5.02 (s, 4H), 4.50–4.28 (m, 2H), 4.21–3.92 (m, 8H), 3.69, (s, 6H), 3.41–3.32 (m, 4H), 3.09 (m, 4H), 2.80–2.69 (m, 4H), 1.96–1.74 (m, 4H), 1.61–1.40 (m, 8H); IR (film)  $V_{\text{max}}$  3421, 1652, 1508, 1456, 1221 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1323.4269 (M+Cs<sup>+</sup>, C<sub>62</sub>H<sub>72</sub>F<sub>2</sub>N<sub>8</sub>O<sub>14</sub> requires 1323.4190).

Dimethyl 5-((2-((*tert*-butyloxy)carbonyl)amino)ethoxy)benzene-1,3-dicarboxylate (21). A solution of *N*-BOC-2bromoethylamine (986 mg, 4.4 mmol) in butanone (17 mL) was treated with dimethyl 5-hydroxyisophthalate (840 mg, 4.0 mmol), NaI (660 mg, 4.4 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.44 g, 4.4 mmol), and the resulting suspension was stirred vigorously at 70 °C for 8 h. The cooled reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed with saturated aqueous NaCl (2×100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (SiO<sub>2</sub>, 5% EtOAc–CH<sub>2</sub>Cl<sub>2</sub>) provided **21** (1.13 g, 80%) as a white amorphous solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.97 (s, 1H), 7.45 (s, 2H), 3.99 (m, 2H), 3.91 (t, 2H, *J*=5 Hz), 3.73 (s, 6H), 1.26 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  165.6, 158.4, 155.8, 131.4,

1375

122.9, 119.4, 79.1, 67.5, 52.2, 39.8, 28.2; IR (film)  $V_{\text{max}}$ 3387, 2953, 1732, 1595, 1518, 1434, 1340, 1248 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 354.1564 (M+H<sup>+</sup>, C<sub>17</sub>H<sub>23</sub>NO<sub>7</sub> requires 354.1553).

5-(2-(((tert-Butyloxy)carbonyl)amino)ethoxy)benzene-1,3dicarboxylic acid (22). A solution of 21 (780 mg, 2.2 mmol) in THF-CH<sub>3</sub>OH-H<sub>2</sub>O (15 mL, 3:1:1) was treated with LiOH·H<sub>2</sub>O (464 mg, 11.1 mmol) and stirred for 1.5 h at 25 °C. The solution was concentrated to a volume of 3 mL and diluted with 35 mL H<sub>2</sub>O. Concentrated aqueous HCl (1.0 mL) was slowly added while stirring at 0 °C. The precipitate that formed was filtered, washed with 50 mL H<sub>2</sub>O, and dried in vacuo to provide 22 (550 mg, 77%) as a white powder: <sup>1</sup>H NMR (DMSO*d*<sub>6</sub>, 400 MHz) δ 13.32 (s, 2H), 8.09 (s, 1H), 7.65 (s, 2H), 7.06 (t, 1H, J = 5.0 Hz), 4.09 (t, 2H, J = 5.0 Hz), 3.33 (m, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (DMSO- $d_6$ , 100 MHz)  $\delta$ 166.4, 158.7, 155.7, 132.6, 122.4, 119.3, 77.8, 67.2, 39.8, 28.3; IR (film) V<sub>max</sub> 2978, 2361, 1699, 1507, 1266, 1168 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 348.1076  $(M + Na^+, C_{15}H_{19}NO_7 \text{ requires } 348.1059).$ 

General procedure for the synthesis of 23, A6B23. The N-BOC-iminodiacetic acid diamide 4, A6B23 (345 mg, 0.66 mmol) was treated with 4 N HCl-dioxane (5 mL) and allowed to stand at 25 °C for 2 h. The solvent was removed under a stream of  $N_2$ , and the resulting residue was treated with a solution of 22 (97.5 mg, 0.3 mmol) in DMF (6 mL), followed by PyBrOP (420 mg, 0.9 mmol), and *i*-Pr<sub>2</sub>NEt (420 µL, 2.40 mmol) and the mixture was stirred for 12 h at 25 °C. The solution was diluted with EtOAc (100 mL) and washed with 10% aqueous HCl  $(3 \times 75 \text{ mL})$ , saturated aqueous NaHCO<sub>3</sub>  $(1 \times 75 \text{ mL})$ , and saturated aqueous NaCl  $(1 \times 75 \text{ mL})$ . Drying (Na<sub>2</sub>SO<sub>4</sub>), and evaporation provided 210 mg (88%) of 23, A6B23 as a yellow foam: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) & 7.36-7.28 (m, 11H), 7.18 (m, 4H), 7.08 (m, 2H), 6.96 (m, 4H), 5.07 (s, 4H), 4.12-3.90 (m, 8H), 3.43 (m, 4H), 3.36 (m, 4H), 3.26–3.10 (m, 4H), 2.84 – 2.69 (m, 4H), 2.37 (m, 4H), 1.70–1.42 (m, 8H), 1.40 (s, 9H); IR (film) V<sub>max</sub> 3423, 3077, 2941, 1649, 1507, 1223, 1161 cm<sup>-1</sup>; FABHRMS (NBA–NaI) m/z 1198.5359  $(M + Na^+, C_{63}H_{75}F_2N_7O_{13}$  requires 1198.5288).

**23, A2B10:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.29 (m, 11H), 7.12 (m, 4H), 7.07 (m, 2H), 6.78 (m, 4H), 5.06 (s, 4H), 4.19–3.90 (m, 10H), 3.71 (s, 6H), 3.65 (s, 6H), 3.40 (m, 4H), 3.35 (m, 4H), 3.26–3.12 (m, 4H), 2.72 (m, 4H), 1.84–1.48 (m, 12H), 1.40 (s, 9H); IR (film) *V*<sub>max</sub> 3455, 2951, 2467, 1646, 1430 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1506.5522 (M+Cs<sup>+</sup>, C<sub>71</sub>H<sub>91</sub>N<sub>9</sub>O<sub>19</sub> requires 1506.5486).

**23**, **A5B10**: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.31 (m, 11H), 7.24 (m, 4H), 7.16 (m, 4H), 7.11 (m, 2H), 6.84 (m,

4H), 5.08 (s, 4H), 4.37–4.21 (m, 4H), 4.17–4.06 (m, 10H), 3.73 (s, 6H), 3.67 (s, 6H), 3.40–3.29 (m, 4H), 3.27–3.12 (m, 4H), 1.80–1.45 (m, 12H), 1.40 (s, 9H); IR (film)  $V_{\text{max}}$  3260, 2940, 1651, 1512, 1250 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1478.5206 (M+Cs<sup>+</sup>, C<sub>69</sub>H<sub>87</sub>N<sub>9</sub>O<sub>19</sub> requires 1478.5173).

**23, A6B10:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.31 (m, 11H), 7.24–7.12 (m, 4H), 7.06 (m, 2H), 6.98 (m, 4H), 5.05 (s, 4H), 4.18–3.92 (m, 10H), 3.67 (s, 6H), 3.46 (m, 4H), 3.38 (m, 4H), 3.26–3.12 (m, 4H), 3.28–3.07 (m, 4H), 1.83–1.44 (m, 12H), 1.41 (s, 9H); IR (film) *V*<sub>max</sub> 3363, 2970, 1717, 1537, 1245 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1482.5184 (M+Cs<sup>+</sup>, C<sub>69</sub>H<sub>85</sub>N<sub>9</sub>O<sub>17</sub> requires 1482.5086).

**23, A7B10:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.30 (m, 21H), 7.08 (m, 2H), 5.08, (s, 8H), 4.20–3.90 (m, 12H), 3.67 (s, 12H), 3.37 (m, 4H), 3.25–3.06 (m, 8H), 1.83–1.45 (m, 12H), 1.41 (s, 9H); IR (film)  $V_{\text{max}}$  3328, 2951, 1700, 1653, 1540 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1792.6494 (M+Cs<sup>+</sup>, C<sub>83</sub>H<sub>109</sub>N<sub>11</sub>O<sub>25</sub> requires 1792.6650).

**23**, **A8B10**: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.33 (m, 11H), 7.13–7.04 (m, 2H), 5.06 (s, 4H), 4.42 (m, 2H), 4.30 (m, 2H), 4.19–4.08 (m, 4H), 4.02–3.88 (m, 10H), 3.70 (s, 6H), 3.59 (m, 4H), 3.43 (m, 2H), 3.26–3.12 (m, 4H), 1.80–1.45 (m, 20H), 1.43 (s, 9H); IR (film) *V*<sub>max</sub> 3438, 2953, 1645, 1456, 1240 cm<sup>-1</sup>; FABHRMS (NBA–CsI) *m*/*z* 1490.5487 (M+Cs<sup>+</sup>, C<sub>67</sub>H<sub>91</sub>N<sub>9</sub>O<sub>21</sub> requires 1490.5384).

**23, A12B10:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.30 (m, 11H), 7.19 (m, 2H), 7.08 (m, 2H), 6.88 (m, 4H), 5.04 (s, 4H), 4.18–3.90 (m, 10H), 3.67 (s, 6H), 3.49 (m, 4H), 3.42 (m, 4H), 3.26–3.10 (m, 4H), 3.01 (m, 4H), 1.80–1.46 (m, 12H), 1.41 (s, 9H); IR (film)  $V_{\text{max}}$  3316, 2938, 1652, 1540, 1252 cm<sup>-1</sup>; FABHRMS (NBA–CsI) m/z 1458.4503 (M+Cs<sup>+</sup>, C<sub>65</sub>H<sub>83</sub>N<sub>9</sub>O<sub>17</sub>S<sub>2</sub> requires 1458.4403).

General procedure for 24, A6B23C4. A sample of 23 (A6B23, 55 mg, 0.044 mmol) was treated with 4 N HCl-dioxane (1 mL) and this mixture was allowed to stand for 3 h before solvent and excess acid were removed under a stream of N<sub>2</sub>. The resulting residue was dissolved in DMF ( $300 \mu$ L) and *i*-Pr<sub>2</sub>NEt ( $20 \mu$ L, 0.12 mmol) was added. After dissolution,  $100 \mu$ L of diglycolic acid stock solution (prepared by dissolving 2 mmol of diglycolic acid in 10 mL DMF) was added followed by PyBrOP (28 mg, 0.06 mmol). After stirring for 12 h at 25 °C the reaction mixture was diluted with EtOAc (50 mL) and washed with 10% aqueous HCl ( $3 \times 50 \text{ mL}$ ), saturated aqueous NaCl ( $1 \times 50 \text{ mL}$ ), and saturated aqueous NaCl ( $1 \times 50 \text{ mL}$ ), and saturated aqueous NaCl ( $1 \times 50 \text{ mL}$ ), and

evaporation provided **24**, **A6B23C4** (47 mg, 88%) as a yellow foam: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.50–7.33 (m, 4H), 7.32–7.24 (m, 14H), 7.24–7.05 (m, 20H), 6.97–6.91 (m, 8H), 5.07 (s, 8H), 4.14–3.94 (m, 20H), 3.59 (m, 4H), 3.45–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film) *V*<sub>max</sub> 3251, 2926, 1722, 1638, 1458, 1223 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 2282; neg: M–H<sup>+</sup> 2280.

**24, A6B23C2:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.34–7.24 (m, 14H), 7.22–7.03 (m, 20H), 6.97–6.91 (m, 8H), 6.85 (m, 2H), 5.07 (s, 8H), 4.14–3.94 (m, 20H), 3.61 (m, 4H), 3.45–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film) *V*<sub>max</sub> 3249, 2940, 1718, 1636, 1507, 1219 cm<sup>-1</sup>; ESMS pos: M + H<sup>+</sup> 2233; neg: M–H<sup>+</sup> 2232.

**24, A6B23C5:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.32–7.24 (m, 18H), 7.24–7.02 (m, 20H), 6.96–6.91 (m, 8H), 5.05 (s, 8H), 4.14–3.94 (m, 20H), 3.58 (m, 4H), 3.45–3.30 (m, 8H), 3.23–3.13 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  3274, 2926, 1728, 1633, 1458, 1223 cm<sup>-1</sup>; ESMS pos: M + Na<sup>+</sup> 2305; neg: M + Cl<sup>-</sup> 2317.

**24, A6B23C16:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.32–7.24 (m, 14H), 7.24–7.05 (m, 20H), 6.97–6.91 (m, 10H), 6.24 (m, 2H), 5.07 (s, 8H), 4.14–3.94 (m, 20H), 3.59 (m, 4H), 3.45–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  3251, 2926, 1727, 1638, 1453, 1223 cm<sup>-1</sup>; ESMS pos: M+Na<sup>+</sup> 2281; neg: M+Cl<sup>-</sup> 2293.

**24, A6B23C19:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.83 (m, 4H), 7.42 (m, 4H), 7.34–7.22 (m, 14H), 7.24–7.05 (m, 20H), 6.97–6.88 (m, 8H), 5.07 (s, 8H), 4.14–3.94 (m, 20H), 3.59 (m, 4H), 3.45–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  2940, 1631, 1502, 1464, 1217 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 2509; neg: M–H<sup>+</sup> 2507.

**24, A6B23C43:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.32–7.24 (m, 14H), 7.24–7.05 (m, 20H), 6.97–6.91 (m, 8H), 5.07 (s, 8H), 4.14–3.94 (m, 24H), 3.59 (m, 4H), 3.45–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  3296, 2948, 1722, 1638, 1464, 1217 cm<sup>-1</sup>; ESMS pos: M + Na<sup>+</sup> 2273; neg: M + Cl<sup>-</sup> 2285.

**24, A6B23C44:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.36–7.23 (m, 14H), 7.23–7.13 (m, 8H), 7.08–7.02 (m, 6H), 6.97–6.91 (m, 8H), 5.07 (s, 8H), 4.14–3.94 (m, 24H), 3.65–3.52 (m, 8H), 3.46–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  3274, 2936, 2365, 1733, 1649, 1458 cm<sup>-1</sup>; ESMS pos: M+Na<sup>+</sup> 2317; neg: M+Cl<sup>-</sup> 2329.

**24, A6B23C45:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.33–7.25 (m, 14H), 7.22–7.13 (m, 8H), 7.08–7.01 (m, 6H), 6.97–6.91 (m, 8H), 5.08 (s, 8H), 4.14–3.94 (m, 24H), 3.72–3.52 (m, 12H), 3.46–3.30 (m, 8H), 3.23–3.14 (m, 8H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  2930, 1733, 1646, 1466, 1219 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 2339; neg: M–H<sup>+</sup> 2337.

**24, A6B23C50.** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.32–7.24 (m, 14H), 7.24–7.05 (m, 20H), 6.97–6.91 (m, 8H), 5.07 (s, 8H), 4.14–3.94 (m, 20H), 3.59 (m, 4H), 3.46 (m, 4H), 3.42–3.30 (m, 8H), 3.23–3.08 (m, 12H), 2.78 (m, 4H), 2.73 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  3270, 2940, 1733, 1656, 1507, 1224 cm<sup>-1</sup>; ESMS pos: M + H<sup>+</sup> 2401; neg: M–H<sup>+</sup> 2399.

**24, A6B23C51:** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.32–7.24 (m, 14H), 7.24–7.05 (m, 20H), 6.97–6.91 (m, 12H), 5.07 (s, 8H), 4.14–3.94 (m, 20H), 3.69 (m, 4H), 3.47 (m, 4H), 3.48 (m, 4H), 3.43–3.30 (m, 8H), 3.23–3.14 (m, 12H), 2.75 (m, 8H), 2.38 (m, 8H), 1.68–1.40 (m, 16H); IR (film)  $V_{\text{max}}$  2930, 1713, 1631, 1466, 1218 cm<sup>-1</sup>; ESMS pos: M+H<sup>+</sup> 2239; neg: M–H<sup>+</sup> 2237.

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37. The tricarboxylic acids **C31** and **C32** are commercially available. Experimental details for the preparation of **C33–C37** will be supplied upon request. Similarly, details of the % conversions (mg amounts) of products obtained from the deconvolution resynthesis, library syntheses, the tetramer libraries, A-scan, B-scan, and related studies has been compiled and is available upon request.