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A Solution-Phase Strategy for the Synthesis of Chemical Libraries Containing Small Organic Molecules: A Universal and Dipeptide Mimetic Template

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Abstract—A general approach to the solution phase, parallel synthesis of chemical libraries, which allows the preparation of multi-milligram quantities of each individual member, is exemplified with both a universal and dipeptide mimetic template. In each step of the sequence, the reactants, unreacted starting material, reagents and their byproducts are removed by simple liquid/liquid or liquid/solid extractions providing the desired intermediates and final compounds in high purities ($\geq$90–100%) independent of the reaction yields and without deliberate reaction optimization. Copyright © 1996 Elsevier Science Ltd

The use of combinatorial libraries for the identification of novel chemical leads or for the optimization of promising lead candidates has emerged as a powerful method for the acceleration of the drug discovery process.[1–4] Initially explored with peptide or oligonucleotide libraries and related structures,[2,5–13] recent efforts have been directed at exploiting the diversity and range of useful properties embodied in small molecule libraries.[11–17] A number of approaches to the generation of chemical libraries have been disclosed including split or mixed,[18] encoded,[19] indexed,[20] or parallel and spatially addressed synthesis on pins,[5,15] beads,[21] chips[22] and other solid supports[23] while solution phase synthesis has not been embraced as a useful alternative.[20,24] This may be attributed to the natural extension of the methodology from solid-phase peptide and oligonucleotide synthesis where supported phase synthesis has emerged as the method of choice for the repetitive coupling reactions and its two key advantages of product isolation and sample manipulation. The resin bound product isolation by simple filtration permits the use of large reagent excesses to effect high yield conversions required for each of the repetitive steps. Nonetheless, the disadvantages of solid-phase synthesis are well recognized.[25] The scale is restricted by the required amount of solid support and its loading capacity. Even for medium sized libraries (1000–5000 members), the production of multi-milligram quantities of each member can be cumbersome, expensive, and potentially prohibitive.[26] Its use is also restricted by the repertoire of reactions presently extended to the solid phase and requires functionalized substrates and solid supports,[23] compatible spacer linkers, and orthogonal attachment and detachment chemistries often with the release of spectator functional groups. More problematic, it requires the use of specialized protocols for monitoring the individual steps of a multistep synthesis[27] including orthogonal capping strategies for blocking unreacted substrate and does not permit the purification of resin bound intermediates. This latter feature necessarily produces the released product of a multistep sequence in an impure state and requires that each reaction on each substrate proceed with an unusually high efficiency. Like the efforts on even the repetitive steps of the solid-phase synthesis of peptides or oligonucleotides, the optimization of the reactions for assuring the required reaction efficiencies is time consuming and challenging. For even a modest criterion of final product purity (85% pure), this requires that each step of even a two-step reaction sequence proceed in 92% yield on each substrate or that each step of a three-step reaction sequence proceed in 95% yield on each substrate. Our experience has been that such generalized reaction efficiencies with a wider range of chemistries and substrates are not routinely obtainable and require both an extensive investment in reaction optimization and purification of the released solid-phase product.[28]

A complement to adapting solution-phase chemistry to solid-phase combinatorial synthesis is the development of protocols for solution-phase combinatorial synthesis. Given that solution- and solid-phase sample manipulation are both convenient and easily automated, the only limitation to the solution-phase parallel synthesis of chemical libraries is the isolation or purification of the library members. If the advantages of sample isolation attributed to solid-phase synthesis may be embodied in a solution-phase synthesis, its non-limiting scale, expanded and non-limiting repertoire of chemical reactions, direct production of soluble inter-

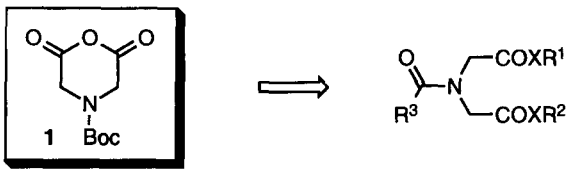


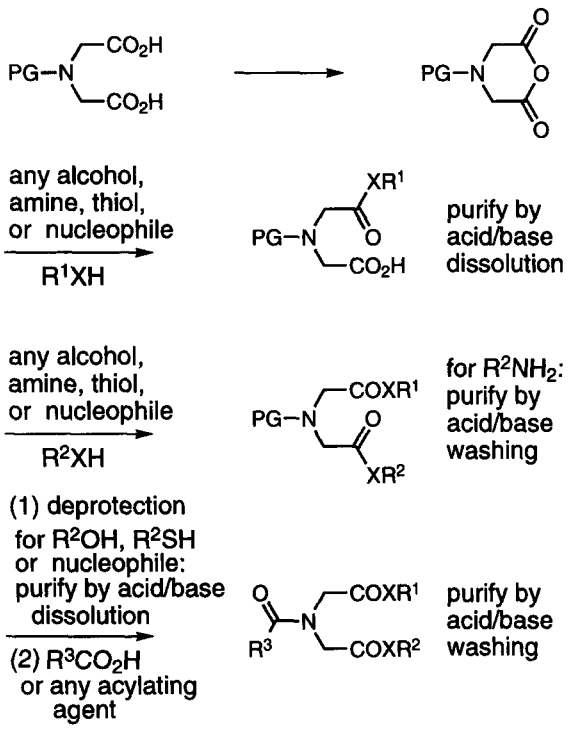
Figure 1.

mediates and final products for assay or for purification, and the lack of required linking, attachment/detachment, or capping strategies make solution-phase combinatorial synthesis an attractive alternative. A number of techniques are available for such purposes and one of the most attractive is liquid/liquid or solid/liquid extraction. Herein, we provide a review summary and details of a high-purity solution-phase parallel synthesis of chemical libraries which implements a simple purification protocol at each step.[29]

A general or universal template

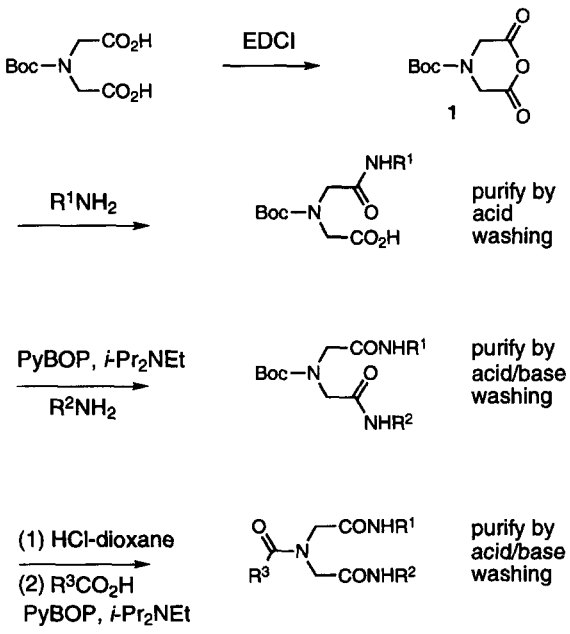
The template **1**, which is representative of a set of six-membered cyclic anhydride-based templates that have been examined, consists of a densely functionalized core which imposes little structural or conformational bias which might limit its use. The added pendant groups provide the molecular diversity and libraries built upon **1** may prove applicable to many biological targets. Its symmetrical structure contains three positions which can be sequentially functionalized enabling the synthesis of libraries with up to three variable regions (Fig. 1). The template is activated for the first functionalization as an anhydride which upon reaction liberates a free carboxylic acid as its second functionalization site. Thus, no orthogonal protecting groups are required for the template functionalization and only four chemical steps are required for the N^3 diversification (Scheme 1). At each step, the same released functionality may be used for both the *isolation and purification* of each of the intermediates and final products from the starting material, reactants, reagents and their reaction byproducts by simple liquid/liquid or solid/liquid extraction providing highly pure materials ($\geq$90–100%) independent of the reaction efficiencies.

In our recent disclosure,[29] we provided full details of our initial efforts which were conducted with **1** without optimization and that provided a fully characterized 27 member library constructed as a $3 \times 3 \times 3$ matrix affording 39 unique components in individual vessels (Scheme 2, Fig. 2). Including enantiomer and diastereomer mixtures, 51 unique entities were contained in the library. Although this has been subsequently expanded to much larger libraries, the disclosure of its initial implementation served to highlight a number of the advantages of the approach. Each of the expected library members was obtained in a purified form ($\geq$90–100% pure) independent of the reaction efficiencies in amounts ranging from 5 to 60 mg *without prior optimization*. In situ closure of *N*-BOC-iminodiacetic acid to the anhydride **1** (1 equiv EDCI, DMF,



Scheme 1.

25 °C, 1 h) followed by treatment with one of three R^1NH_2 (1 equiv, DMF, 25 °C, 20 h, 84–86%) cleanly afforded the monoamides which were purified by simple acid extraction to remove unreacted R^1NH_2, EDCI, and its reaction byproducts. The three monoamides were each partitioned into three portions with one smaller portion being retained for archival purposes. Each of the equal three portions were treated with three R^2NH_2 (1 equiv) and PyBOP (1



Scheme 2.

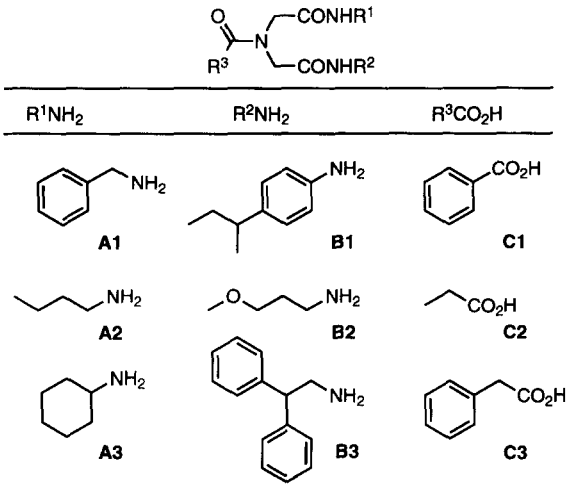


Figure 2.

equiv, 2 equiv *i*-Pr_2NEt, DMF, 20 °C, 25 h, 65–99%) to afford nine diamides which were effectively purified by acid and base extractions to remove reaction byproducts. the unreacted starting material and R^2NH_2, PyBOP, and its reaction byproducts. Although this is illustrated in Scheme 2 with primary amines, secondary amines as well as aryl amines have been found to work as well. Following the second functionalization and N-BOC deprotection (4 N HCl-dioxane, 25 °C, 45 min), reaction of three equal portions of each amine with three R^3CO_2H (1 equiv) in the presence of PyBOP (1 equiv, 3 equiv *i*-Pr_2NEt, DMF, 25 °C, 20 h, 16–100%) provided 27 agents which were purified by aqueous acid and base extractions to remove unreacted starting materials, reagents, and their reaction byproducts. Overall yields for the 27 agents ranged from 9 to 84% with an average overall yield of 61% for the three derivatizations. Importantly, and independent of individual yields, all intermediates and final products were ≥90% pure with an average 95.3% purity. Without optimization in these first efforts, most of the final library products were obtained in 20–60 mg quantities as individual samples at this exceptional level of purity suitable for direct use in screening efforts without further purification.

Subsequent extensions of these efforts to the preparation of a 125 member library constructed as a $5 \times 5 \times 5$ matrix afforded 155 unique compounds (Fig. 3) and provided comparable observations. Each library member was obtained as an individual entity in 30–100 mg quantities in pure form (>90%, generally ≥95% pure) in overall yields ranging from 32 to 85% (64% average).

One of the largest libraries based on **1** addressed to date by manual manipulation of the reactions was a 960 member library constructed in a $6 \times 8 \times 20$ matrix affording 1014 final components in individual vessels including intermediates constituting a library of 1158 compounds including diastereomers and enantiomers (Fig. 4). Each library member was obtained in amounts

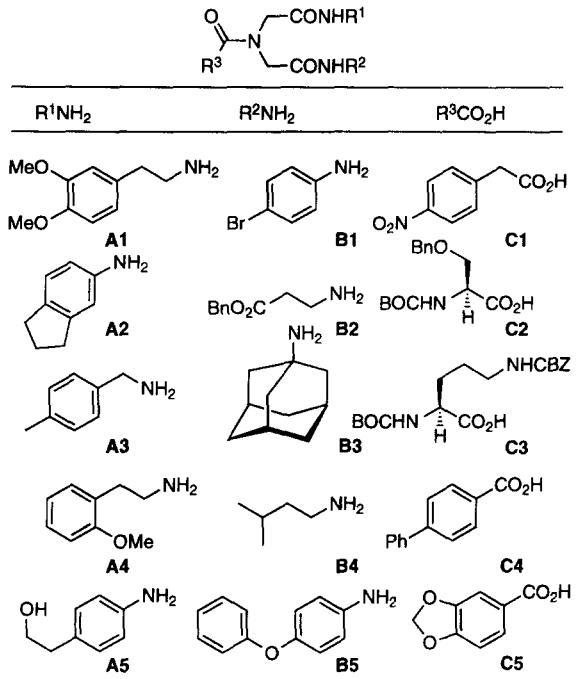


Figure 3.

ranging from 30 to 150 mg in yields ranging from 10 to 71% with an average overall yield of 52%.

A generalized dipeptidomimetic template

Template **2** is a designed rigid core structure which contains a number of important features. When fully extended, **2** contains a rigid bicyclic core with a plane of symmetry which enables it to function as a Gly-X mimic (Fig. 5). When positions 1 and 3 are extended, the conformation mirrors that of an extended sheet. Extension of position 1 and 2 introduce a turn motif. When all three positions are utilized, an interesting core peptidomimetic which explores three-dimensional space is produced. Like **1**, its symmetrical structure contains three positions which can be sequentially functionalized enabling the synthesis of libraries with three variable units. As a five-membered cyclic anhydride, the starting template is activated for the first functionalization which upon reaction liberates a carboxylic acid its second functionalization site. Like **1**, no orthogonal protecting groups are required for the template functionalization and four chemical steps are required for N^3 diversification.

The template synthesis (Scheme 3) requires N-Boc protection of propargyl amine and subsequent alkylation effected by treatment with NaH (1.1 equiv, DMF, 25 °C, 30 min) followed by allyl bromide (1.2 equiv, 0 °C, 5 h) to generate **4** (>90% yield, two steps). Treatment of **4** with catalytic $(Ph_3P)_2Pd(OAc)_2$ (0.5 equiv, 80 °C, C_6H_6, 1 h) affords diene **5** (60%).[30] The reactive diene is immediately subjected to a Diels–Alder reaction with maleic anhydride (1 equiv, C_6H_6, 40 °C, 1 h) to yield **2** which upon deliberate hydrolysis (20% H_2O–THF, 5 h) provides the easily purified and handled diacid **6**. The anhydride **2** is regenerated in

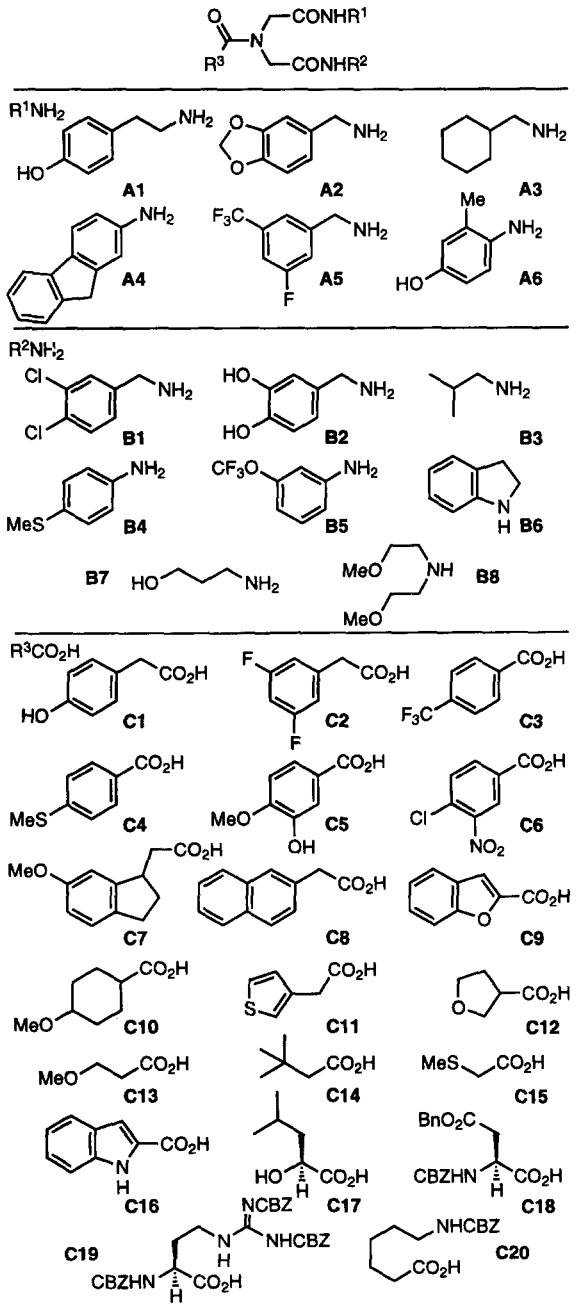


Figure 4.

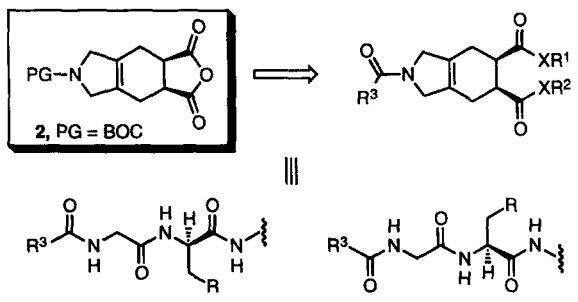
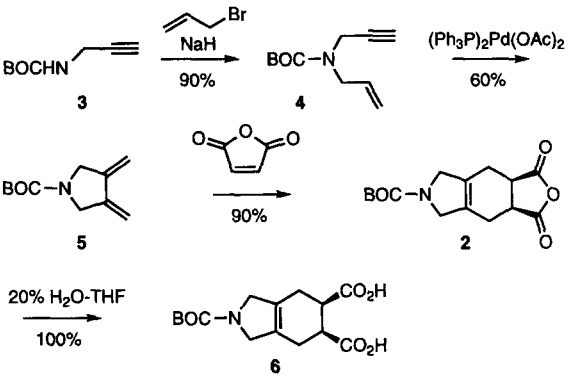


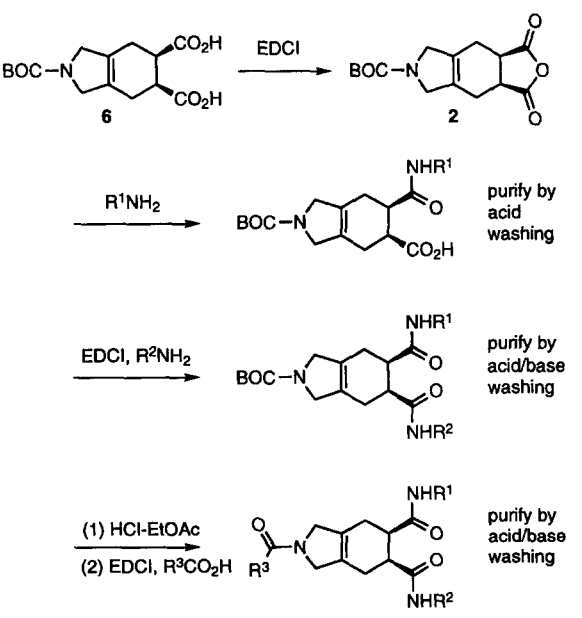
Figure 5.



Scheme 3.

situ upon treatment with EDCI (1 equiv) immediately prior to the addition of the first nucleophile.

To illustrate the library construction with **2** which is representative of efforts with related five-membered cyclic anhydrides, we have provided full details of our initial efforts which were conducted without optimization and that provided a fully characterized 27 member library constructed as a $3 \times 3 \times 3$ matrix yielding 39 unique components in individual vessels constituting a library of 78 compounds including enantiomers (Scheme 4 and Fig. 6). Treatment of **6** with EDCI (1.1 equiv, DMF, 25 °C, 20 min) followed by addition of R^1NH_2 (1 equiv, 25 °C, 16 h) afforded the monoamides which were purified by simple acid/base dissolution (80–99%). Importantly, only the monoamide product was generated indicating in situ closure of the initially generated activated carboxylate to the anhydride **2** and its subsequent reaction with the added amine. The monoamides were split into four equal components with one being retained for archival purposes. Each of the three remaining aliquots were treated with EDCI



Scheme 4.

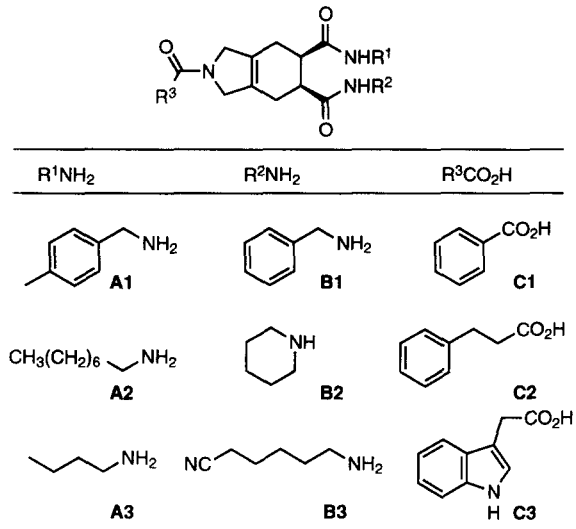


Figure 6.

(3 equiv) and R^2NH_2 (3 equiv, DMF, 25 °C, 16 h) to yield nine diamides (65–91%) which were purified by an acid/base wash removing the excess unreacted reactants, reagents and reagent byproducts. Although this has been represented in Scheme 4 with a primary amine, secondary and aryl amines also react well. One-quarter of the diamide was retained and the remaining quantity was subjected to *N*-BOC deprotection (4 N HCl–EtOAc, 25 °C, 30 min). One-third of each was treated with EDCI (2 equiv) and R^3CO_2H (2 equiv, DMF, 25 °C) such that 27 unique products were obtained. The resulting functionalized peptidomimetics were purified by washing with aqueous acid and base to yield the purified final compounds (3–89%). Irrespective of individual yields, the intermediates and final compounds were ≥90–95% pure. The only contaminant observed was a small quantity of the oxidized pyrrole which was minimized by the careful exclusion of oxygen during the *N*-BOC deprotection and subsequent acylation.

Discussion and Conclusions

Complementary to the emerging solid-phase synthesis of combinatorial libraries, a method for the rapid and simple multistep, solution-phase, parallel synthesis of chemical libraries in which each component is produced as an individual compound in unlimited quantities (typically 30–150 mg) for extensive or broad screening purposes has been developed. In each step of the sequence, intermediates and all final products were subjected to simple purification by liquid/liquid or liquid/solid extraction to remove reactants, unreacted starting material, reagents, and their byproducts providing the library members in high purities (≥90–100%) irrespective of the reaction yields and without deliberate reaction optimization. The template **1** on which this technology was first tested is unusually flexible possessing one to three functionalization sites for diversification and little inherent structural or conformational bias which might limit its use as a general or universal template. The second five-membered cyclic anhydride **2** constitutes a rigid dipeptidomimetic template capable of serving as a nonpeptide scaffold for either extended or turn peptidomimetics and possesses one to three functionalization sites. It, along with other related rigid templates, should be useful not only as lead generation libraries in their own right but as secondary libraries for further optimization and exploration of leads discovered with the more universal template **1**. Although the initial examples detailed herein enlist conventional liquid/liquid extractions, similar results employing solid-supported resins, columns, or pads have been used to effect solid/liquid extractions by simple batch, column, or filtration protocols. The one secondary amine protecting group may be easily altered to accommodate its sensitivity to selected liquid/liquid or liquid/solid extraction protocols used to remove starting materials and reaction byproducts. In addition, the approach is not limited to amide bond forming reactions. Other nucleophiles (ROH, RSH, RLi, RMgBr, R-Met) may be utilized in the first functionalization of the anhydride templates with purification of the desired product by dissolution in base. Similarly, the second functionalization may be accomplished by reaction of the activated carboxylate with other nucleophiles (ROH, RSH, R-Met) followed by purification of the desired product by dissolution in aqueous acid following *N*-BOC deprotection. Although not illustrated herein, the strategy is also not limited to the parallel synthesis of individual compounds but is also applicable to split or mixed synthesis employing stoichiometric limiting variable units and excess template to construct combinatorial libraries of compound mixtures subject to subsequent compound identification by repeat synthesis or recursive deconvolution. Studies employing larger targeted libraries with matrix characterization of each reaction type, their adaptation to automation, the development of related library templates, as well as additional approaches to the solution phase synthesis of chemical libraries will be disclosed in due time.

Experimental

General procedure for the first derivatization of compound 1: preparation of *N*-((*tert*-butyloxy)carbonyl)-iminodiacetic acid monoamides

A solution of *N*-((*tert*-butyloxy)carbonyl)iminodiacetic acid (0.349 g, 1.50 mmol) in DMF (15 mL) was treated with EDCI (0.294 g, 1.54 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h before the amine (R^1NH_2, 1 equiv) was added and the solution stirred for 20 h at 25 °C. The reaction mixture was poured into 10% aq HCl (60 mL) and extracted with EtOAc (100 mL). The organic phase was washed with 10% HCl (40 mL) and satd aq NaCl (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to yield the pure *N*-((*tert*-butyloxy)carbonyl)iminodiacetic acid monoamides (80–90%).

General procedure for the second derivatization of compound 1

Each of the *N*-((*tert*-butyloxy)carbonyl)iminodiacetic acid monoamides was dissolved in anhydrous DMF (20 mL/mmol) and divided into three equal portions in three separate vials. Each solution was treated with one of three amines (R^2NH_2, 1 equiv), diisopropyl ethylamine (2 equiv) and PyBOP (1 equiv). The solution (20 mL DMF/mmol) was stirred at 25 °C for 20 h. The mixture was poured into 10% aq HCl and extracted with EtOAc. The organic phase was washed with 10% aq HCl, satd aq NaCl, 5% aq $NaHCO_3$, and satd aq NaCl. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to yield the diamides (65–99%).

General procedure for the third derivatization of compound 1

Each of the *N'*-((*tert*-butyloxy)carbonyl)-*N*,*N*-disubstituted iminodiacetic acid diamides was dissolved in 4 N HCl–dioxane (32 mL/mmol) and the mixture was stirred at 25 °C for 45 min. The solvent was removed in vacuo and the residue was dissolved in anhydrous DMF (28 mL/mmol) and was divided into three equal portions and placed in three separate vials. The solution was treated with one of three carboxylic acids (R^3CO_2H, 1 equiv) followed by diisopropyl ethylamine (3 equiv) and PyBOP (1 equiv). The solution was stirred for 20 h at 25 °C. The mixture was poured into 10% aq HCl and extracted with EtOAc. The organic phase was washed with 10% aq HCl and extracted with EtOAc. The organic phase was washed with 10% aq HCl, satd aq NaCl, 5% aq $NaHCO_3$ and satd aq NaCl. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the final products (16–100%).

***N*-[(Dimethylethoxy)carbonyl]propynyl amine (3).** A solution of propargylamine (10.0 g, 0.182 mol) in 25% THF-H_2O (600 mL) was treated with aq satd $NaHCO_3$ (10 mL) followed by the dropwise addition of di-*tert*-butyl dicarbonate (46 mL, 0.200 mol, 1.1 equiv) and the mixture was stirred at 25 °C (5 h). The reaction mixture was concentrated, extracted with EtOAc (3 × 100 mL), and washed with aq satd NaCl (150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Recrystallization (hexanes) afforded **3** (27.4 g, 28.2 g theor, 97%) as off-white crystals: mp 41 °C (prisms, hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.76 (br s, 1H), 3.91 (d, J = 2.2 Hz, 2H), 2.22 (t, J = 2.3 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 155.2, 80.1, 79.9, 71.1, 30.2, 28.2; IR (KBr) ν_{max} 3318, 2979, 2933, 2129, 1692, 1543, 1288, 1254, 1160, 1047, 960, 948, 857, 668 cm^{-1}; Anal. calcd for $C_8H_{13}NO_2$: C, 61.90; H, 8.45; N, 9.03. Found: C, 61.90; H, 8.59; N, 9.09.

***N*-Allyl-*N*-[(dimethylethoxy)carbonyl]propynyl amine (4).** A suspension of freshly washed NaH (2.91 g, 70.9 mmol, 1.1 equiv) in DMF (165 mL) was treated with **3** (10.0 g, 64.4 mmol) in 50 mL DMF at 25 °C. The reaction mixture was stirred for 30 min, cooled to 0 °C and allyl bromide (6.7 mL, 77.3 mmol, 1.2 equiv) was added dropwise. The solution was stirred at 0 °C for 1 h before being allowed to warm to 25 °C and stirred overnight. Water (100 mL) was added and the aq phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with satd aq NaCl (1 × 200 mL), dried ($MgSO_4$), and concentrated. Chromatography (SiO_2, 4 × 20 cm, 0–10% EtOAc–hexane) afforded **4** as a clear liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.63 (m, 1H, C<u>H</u>=CH_2), 5.09 (d, J = 7.4 Hz, 1H, CH=CH*H*), 5.04 (s, 1H, CH=C*H*H), 3.91 (br s, 2H), 3.85 and 3.83 (two s, 2H), 2.12 (d, J = 0.6 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 154.6, 133.1, 116.9, 80.0, 79.3, 71.2, 48.3, 35.1, 28.1; IR (neat) ν_{max} 3299, 2978, 2931, 1694, 1454, 1405, 1367, 1248, 1170, 1147, 930, 867, 772 cm^{-1}.

3,4-Dimethylene-*N*-[(dimethylethoxy)carbonyl]pyrrolidine (5). A solution of **4** (3.15 g, 16.1 mmol) in C_6H_6 (300 mL) was treated with $(Ph_3P)_2Pd(OAc)_2$ (604 mg, 0.81 mmol, 0.05 equiv) and warmed at reflux for 1 h. The reaction mixture was cooled to 25 °C and concentrated. Chromatography (SiO_2, 4 × 20 cm, 5% EtOAc–hexane containing 2% Et_3N) yielded 5 (1.91 g, 3.15 g theoretical, 61%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.24 (s, 2H), 4.93 (m, 2H), 4.09 (m, 2H), 4.07 (s, 2H), 1.42 (s, 9H); IR (neat) ν_{max} 3086, 2975, 2929, 2863, 1702, 1477, 1454, 1401, 1365, 1174, 1113, 885 cm^{-1}.

2,3,4,5,6,7-Hexahydro-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5,6-dicarboxylic acid (6). A solution of **5** (1.3 g, 6.65 mmol) and maleic anhydride (672 mg, 6.86 mmol, 1.03 equiv) in C_6H_6 (22 mL) was warmed to 40 °C for 1 h. The reaction was cooled to 25 °C and concentrated. The crude anhydride **2** was immediately dissolved in 20% H_2O–THF and stirred at 25 °C for 5 h. The reaction was concentrated, azeotroped with EtOH, precipitated with CH_2Cl_2, and filtered to afford **6** (1.86 g, 2.07 g theor, 90%). For **2**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.74 (d, J = 0.9 Hz, 2H), 3.54 (d, J = 1.2 Hz, 2H), 2.32 (m, 2H), 1.55 (t, J = 14.6 Hz, 2H), 1.49 (m, 11H); FABHRMS (NBA–NaI) *m/z* 316.1148 (M^+Na, $C_{15}H_{19}NO_5$ requires 316.1161). For **6**: ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.73 (br s, 2H), 3.88 (br s, 4H), 2.96 (br s, 2H), 2.30 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (acetone-d_6, 300 MHz) δ 174.5, 154.5, 129.8 and 129.6, 79.2, 56.0 and 55.8, 40.4, 28.6, 24.9; IR (KBr) ν_{max} 3457, 2974, 2853, 1733, 1698, 1647, 1430, 1370, 1252, 1187, 1138, 875, 766 cm^{-1}; FABHRMS (NBA–NaI) *m/z* 334.1259 (M^+Na, $C_{15}H_{21}NO_6$ requires 334.1267).

General procedure for the first functionalization of compound 2

A solution of **6** (200 mg, 0.64 mmol) in DMF (6.5 mL) was treated with EDCI (1.1 equiv, 135 mg, 0.71 mmol) and the mixture was stirred for 20 min at 25 °C. Amines (**A1–3**, 1 equiv, neat) were added and the

reaction mixture was stirred at 25 °C for 16 h. EtOAc (6.5 mL) was added and the organic layer was washed with 5% aq HCl (1 × 6 mL) and extracted with 5% aq NaHCO3 (3 × 6 mL). The combined basic aq layers were reacidified with the addition of 5% aq HCl (pH 1) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with satd aq NaCl (1 × 10 mL), dried ($MgSO_4$), and concentrated to yield pure monoamides **A1–A3** (80–99%).

6-Carboxy-2,3,4,5,6,7-hexahydro-*N*-(4-methylbenzyl)-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5-carboxamide. 392 mg (98%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.22 (br s, 1H), 7.09 (s, 4H), 4.20 (m, 2H), 3.91 (s, 4H), 2.95 (m, 2H), 2.47 (m, 2H), 2.26 (s, 3H), 1.42 (s, 9H); FABHRMS (NBA–CsI) *m/z* 547.1223 (M^+Cs, $C_{23}H_{30}N_2O_5$ requires 547.1209).

6-Carboxy-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-*N*-octyl-1*H*-isoindole-5-carboxamide. 218 mg (80%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.67 (br t, 1H), 3.88 (br s, 4H), 3.34 (m, 2H), 2.97 (m, 2H), 2.88 (m, 2H), 2.49 (m, 2H), 1.40 (s, 9H), 1.34 (m, 2H), 1.21 (s, 10H), 0.85 (t, J=6.7 Hz, 3H); FABHRMS (NBA–CsI) *m/z* 555.1825 (M^+Cs, $C_{23}H_{38}N_2O_5$ requires 555.1836).

***N*-Butyl-6-carboxy-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5-carboxamide**. 233 mg (99%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.24 (br s, 1H), 7.60 (m, 1H), 3.89 (s, 4H), 3.01 (m, 2H), 2.87 (m, 2H), 2.45 (m, 2H), 2.28 (m, 2H), 1.45 (m, 11H), 1.25 (m, 4H), 0.84 (br t, J=7.5 Hz, 3H); FABHRMS (NBA–CsI) *m/z* 499.1221 (M^+Cs, $C_{19}H_{30}N_2O_5$ requires 499.1209).

General procedure for the second functionalization of compound 2

A solution of monoamide **AX** (0.1 mmol) in DMF (0.5 mL) was treated with EDCI (3 equiv, 0.3 mmol) and amines (B1–3, 3 equiv, neat) and the reaction mixtures were stirred at 25 °C for 16 h. The reaction mixtures were diluted with EtOAc (5 mL) and the organic layers were washed with 5% aq HCl (2 × 3 mL), H_2O (1 × 3 mL), 5% aq $NaHCO_3$ (1 × 3 mL), and satd aq NaCl (1 × 3 mL), dried ($MgSO_4$), and concentrated to yield pure diamides **A1B1–A3B3** (65–91%).

***N'*-Benzyl-2,3,4,5,6,7-hexahydro-*N*-(4-methylbenzyl)-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5,6-dicarboxamide**. 37 mg (76%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, J=7.2 Hz, 2H), 7.21 (d, J=7.2 Hz, 2H), 7.11 (s, 5H), 7.01–6.67 (m, 2H), 4.33 (m, 4H), 3.99 (q, J=13.0 Hz, 4H), 3.06 (d, J=5.8 Hz, 1H), 3.01 (d, J=5.8 Hz, 1H), 2.47 (m, 2H), 2.32 (s, 3H), 2.21 (m, 2H), 1.45 (s, 9H); FABHRMS (NBA–CsI) *m/z* 636.1825 (M^+Cs, $C_{30}H_{37}N_3O_4$ requires 636.1838).

2,3,4,5,6,7-Hexahydro-*N*-(4-methylbenzyl)-2-(dimethylethoxy)carbonyl-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 43 mg (91%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58–7.31 (m, 1H), 7.11 (m, 4H), 4.39 (d, J=5.5 Hz, 2H), 3.99 (m, 4H), 2.91 (m, 2H), 2.31 (s, 3H), 2.22 (m, 2H), 1.61–1.29 (m, 15H); FABHRMS (NBA–CsI) *m/z* 614.1983 (M^+Cs, $C_{28}H_{39}N_3O_4$ requires 614.1995).

***N'*-(5-Cyanopentyl)-2,3,4,5,6,7-hexahydro-*N*-(4-methylbenzyl)-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5,6-dicarboxamide**. 32 mg (65%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (s, 4H), 6.85 (br s, 1H), 6.67 (br s, 1H), 4.39 (m, 2H), 4.03 (s, 2H), 3.98 (s, 2H), 3.17 (m, 2H), 3.01 (m, 2H), 2.46 (m, 2H), 2.32 (s, 3H), 2.23 (m, 2H), 1.63 (m, 2H), 1.45 (s, 9H), 1.25 (t, J=7.3 Hz, 3H); FABHRMS (NBA–CsI) *m/z* 641.2119 (M^+Cs, $C_{29}H_{34}N_4O_4$ requires 641.2104).

***N'*-Benzyl-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-*N*-octyl-1*H*-isoindole-5,6-dicarboxamide**. 42 mg (87%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 5H), 7.0–6.6 (m, 2H), 4.43 (m, 2H), 4.09 (s, 2H), 3.95 (s, 2H), 3.11 (m, 4H), 2.97 (m, 2H), 2.46 (m, 2H), 2.21 (m, 2H), 1.88 (m, 2H), 1.63–1.10 (m, 19H), 0.88 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 644.2483 (M^+Cs, $C_{30}H_{45}N_3O_4$ requires 644.2464).

2,3,4,5,6,7-Hexahydro-2-(dimethylethoxy)carbonyl-*N*-octyl-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 36 mg (78%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (br s, 1H), 3.97 (m, 4H), 3.43 (m, 4H), 3.19 (dt, J=5.7, 7.1 Hz, 2H), 2.90 (m, 1H), 2.74 (m, 1H), 2.29 (m, 2H), 1.62 (m, 4H), 1.53 (m, 6H), 1.44 (s, 9H), 1.24 (br s, 10H), 0.86 (t, J=6.7 Hz, 3H); FABHRMS (NBA–CsI) *m/z* 622.2637 (M^+Cs, $C_{28}H_{47}N_3O_4$ requires 622.2637).

***N'*-(5-Cyanopentyl)-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-*N*-octyl-1*H*-isoindole-5,6-dicarboxamide**. 34 mg (69%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–6.41 (m, 2H), 4.05 (m, 4H), 3.26 (m, 4H), 3.01 (m, 2H), 2.6–2.1 (m, 6H), 1.7–1.1 (m, 25H), 0.87 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 649.2748 (M^+Cs, $C_{29}H_{48}N_4O_4$ requires 649.2730).

***N'*-Benzyl-*N*-butyl-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5,6-dicarboxamide**. 42 mg (84%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 5H), 7.1–6.8 (m, 2H), 4.39 (m, 2H), 4.03 (s, 2H), 3.98 (s, 2H), 3.10 (m, 2H), 2.48 (m, 2H), 1.70–1.50 (m, 10H), 1.44 (s, 9H), 1.21 (m, 2H), 0.89 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 588.1820 (M^+Cs, $C_{26}H_{37}N_3O_4$ requires 588.1838).

***N*-Butyl-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide**. 151 mg (75%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–6.90 (m, 2H), 4.01 (m, 2H), 3.42 (m, 4H), 3.15 (m, 2H), 2.91 (m, 2H), 2.51–2.20 (m, 2H), 1.70–1.50 (m, 10H), 1.44 (s, 9H), 1.33 (m, 2H), 0.89 (br t, J=6.8 Hz, 3H); FABHRMS (NBA–CsI) *m/z* 566.1978 (M^+Cs, $C_{24}H_{39}N_3O_4$ requires 566.1995).

***N*-Butyl-*N'*-(5-cyanopentyl)-2,3,4,5,6,7-hexahydro-2-(dimethylethoxy)carbonyl-1*H*-isoindole-5,6-dicarboxamide**. 146 mg (66%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10–6.50 (m, 2H), 4.03 (s, 2H), 3.97 (s, 2H), 3.22 (m, 4H), 2.97 (m, 2H), 2.44 (m, 2H), 2.35 (m, 2H), 2.24 (m, 2H), 1.89 (s, 2H), 1.54–1.24 (m, 10H), 1.44 (s, 9H), 0.90 (t, J=7.0 Hz, 3H); FABHRMS (NBA–CsI) *m/z* 593.2118 (M^+Cs, $C_{25}H_{40}N_4O_4$ requires 593.2104).

General procedure for the third functionalization of compound 2

Diamides **AXBX** (0.02 mmol) were treated with 4 N HCl–EtOAc (0.6 mL) and stirred for 20 min at 25 °C. The solvents were removed under a stream of N_2 and EDCI (2 equiv, 0.04 mmol), the carboxylic acids (C1–3, 2 equiv) were added to the amine hydrochloride. The reactants were slurried in DMF (0.5 mL) and stirred for 16 h at 25 °C. EtOAc (1 mL) was added and the organic layer was washed with H_2O (1 × 1 mL), 5% aq HCl (1 × 1 mL), 5% aq $NaHCO_3$ (1 × 1 mL), and satd aq NaCl (1 × 1 mL). The organic layer was dried by filtering through a plug of $MgSO_4$ (5 × 10 mm), concentrated and dried in vacuo to afford pure compounds **A1B1C1–A3B3C3** (3–89%).

2-Benzoyl-*N*-benzyl-2,3,4,5,6,7-hexahydro-*N'*-(4-methylbenzyl)-1*H*-isoindole-5,6-dicarboxamide. 2.6 mg (53%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (m, 4H), 7.41 (s, 2H), 7.30 (m, 6H), 7.13 (d, 2H), 6.85–6.45 (m, 2H), 4.35 (m, 4H), 4.13 (br q, J=13.1 Hz, 4H), 3.09 (m, 2H), 2.49 (m, 2H), 2.31 (s, 3H), 2.17 (m, 2H); FABHRMS (NBA–CsI) *m/z* 640.1596 (M^+Cs, $C_{32}H_{33}N_3O_3$ requires 640.1576).

***N*-Benzyl-2,3,4,5,6,7-hexahydro-*N'*-(4-methylbenzyl)-2-(3-phenylpropionyl)-1*H*-isoindole-5,6-dicarboxamide**. 12.5 mg (25%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (br s, 1H), 8.42 (br s, 1H), 7.37–7.09 (m, 14H), 6.93–7.19 (m, 1H), 6.14 (s, 1H), 4.45 (dd, J=5.7, 14.6 Hz, 2H), 4.33 (m, 2H), 4.11 (m, 2H), 3.09 (m, 2H), 2.96 (t, J=7.5 Hz, 2H), 2.52 (t, J=7.5 Hz, 2H), 2.33 (s, 3H), 2.23 (m, 2H); FABHRMS (NBA) *m/z* 536.2927 (M^+H, $C_{34}H_{37}N_3O_3$ requires 536.2913).

***N*-Benzyl-2,3,4,5,6,7-hexahydro-2-(1*H*-indol-3-ylacetyl)-*N'*-(4-methylbenzyl)-1*H*-isoindole-5,6-dicarboxamide**. 8.0 mg (89%); ^{1}H NMR (DMF-d_7, 300 MHz) δ 8.19 (m, 2H), 7.63 (m, 2H), 7.48–7.06 (m, 10H), 6.90–6.63 (m, 2H), 4.31 (m, 4H), 4.09 (m, 4H), 3.65 (s, 2H), 3.01 (m, 2H), 2.33 (s, 3H), 2.09 (m, 2H); FABHRMS (NBA) *m/z* 561.2860 (M^+H, $C_{35}H_{36}N_4O_3$ requires 561.2866).

2-Benzoyl-2,3,4,5,6,7-hexahydro-*N*-(4-methylbenzyl)-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 3.3 mg (46%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (m, 5H), 7.13 (br s, 5H), 4.43 (m, 2H), 4.19 (m, 4H), 3.47 (m, 4H), 2.91 (m, 2H), 2.31 (s, 3H), 2.11 (m, 2H), 1.71–1.43 (br s, 6H); FABHRMS (NBA–CsI) *m/z* 618.1754 (M^+Cs, $C_{30}H_{35}N_3O_3$ requires 618.1733).

2,3,4,5,6,7-Hexahydro-*N*-(4-methylbenzyl)-2-(3-phenylpropionyl)-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 19.2 mg (22%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (br s, 1H), 8.06 (br s, 1H), 7.31–7.09 (m, 9H), 4.43 (d, J=5.7 Hz, 1H), 4.39 (J=5.8 Hz, 1H), 4.12 (m, 4H), 3.53 (m, 2H), 3.42 (m, 2H), 2.96 (t, J=7.8 Hz, 2H), 2.66 (t, J=7.8 Hz, 2H), 2.55 (m, 2H), 2.32 (s, 3H), 2.23 (m, 2H), 1.63 (m, 2H), 1.54 (m, 4H); FABHRMS (NBA–CsI) *m/z* 646.2027 (M^+Cs, $C_{32}H_{39}N_3O_3$ requires 646.2046).

2,3,4,5,6,7-Hexahydro-2-(1*H*-indol-3-ylacetyl)-*N*-(4-methylbenzyl)-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 4.1 mg (52%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (m, 1H), 7.36 (d, J=7.5 Hz, 1H), 7.12 (m, 8H), 4.43 (m, 4H), 4.15 (m, 4H), 3.76 (s, 2H), 3.55 (m, 2H), 3.41 (m, 2H), 2.33 (m, 7H), 1.64–1.47 (m, 6H); FABHRMS (NBA–CsI) *m/z* 671.1980 (M^+Cs, $C_{33}H_{38}N_4O_3$ requires 671.1998).

2-Benzoyl-*N*-(5-cyanopentyl)-2,3,4,5,6,7-hexahydro-*N'*-(4-methylbenzyl)-1*H*-isoindole-5,6-dicarboxamide. 1.6 mg (23%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.40 (m, 2H), 7.23 (br s, 5H), 7.12 (br s, 2H), 6.73–6.40 (m, 2H), 4.37 (m, 4H), 4.13 (m, 4H), 3.04 (m, 2H), 2.33 (s, 3H), 2.16 (m, 2H), 1.64 (m, 6H); FABHRMS (NBA-CsI) *m/z* 513.2854 (M^+H, $C_{31}H_{36}N_4O_3$ requires 513.2866).

***N*-(5-Cyanopentyl)-2,3,4,5,6,7-hexahydro-*N*-(4-methylbenzyl)-2-(3-phenylpropionyl)-1*H*-isoindole-5,6-dicarboxamide**. 12.7 mg (16%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (br s, 1H), 8.46 (br s, 1H), 7.95 (br s, 1H), 7.31–7.08 (m, 9H), 6.85–6.60 (m, 1H), 6.10 (m, 1H), 4.45 (d, J=5.8 Hz, 1H), 4.13 (m, 2H), 3.30 (app q, J=6.5 Hz, 2H), 3.17 (m, 2H), 2.97 (m, 3H), 2.33 (s, 3H), 2.32 (m, 2H), 1.83–1.42 (m, 6H); FABHRMS (NBA–CsI) *m/z* 673.2173 (M^+Cs, $C_{33}H_{40}N_4O_3$ requires 673.2155).

***N*-(5-Cyanopentyl)-2,3,4,5,6,7-hexahydro-2-(1*H*-indole-3-ylacetyl)-*N'*-(4-methylbenzyl)-1*H*-isoindole-5,6-dicarboxamide**. 3.4 mg (44%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (br s, 1H), 7.65 (t, J=6.7 Hz, 1H), 7.87–7.08 (m, 8H), 6.70 (br s, 1H), 6.50 (br s, 1H), 4.49 (m, 4H), 4.18 (m, 4H), 3.81 (s, 1H), 3.76 (s, 1H), 3.15 (m, 2H), 2.95 (m, 2H), 2.36 (s, 3H), 2.10 (m, 2H), 1.59 (br s, 6H), 1.45 (br s, 2H); FABHRMS (NBA) *m/z* 566.3149 (M^+H, $C_{34}H_{39}N_5O_3$ requires 566.3131).

2-Benzoyl-*N*-benzyl-2,3,4,5,6,7-hexahydro-*N'*-octyl-1*H*-isoindole-5,6-dicarboxamide. 4.5 mg (56%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60–7.18 (m, 10H), 6.98 (br s, 1H), 6.75 (br s, 1H), 4.43 (m, 4H), 4.11 (m, 4H), 3.16 (m, 4H), 2.52–2.02 (m, 6H), 1.77–1.07 (m, 10H), 0.88 (t, J=6.3 Hz, 3H); FABHRMS (NBA-CsI) *m/z* 648.2182 (M^+Cs, $C_{32}H_{41}N_3O_3$ requires 648.2202).

***N*-Benzyl-2,3,4,5,6,7-hexahydro-*N'*-octyl-2-(3-phenylpropionyl)-1*H*-isoindole-5,6-dicarboxamide**. 16.2 mg (27%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.18 (m, 10H), 6.73–6.19 (m, 2H), 4.44 (m, 2H), 4.14 (m, 4H),

3.19 (m, 2H), 3.06 (m, 2H), 2.96 (t, $J=7.6$ Hz, 2H), 2.54 (t, $J=7.6$ Hz, 2H), 2.51 (m, 1H), 2.25 (m, 1H), 2.04 (m, 2H), 1.46 (m, 2H), 1.26 (s, 10H), 0.88 (t, $J=6.7$ Hz, 3H); FABHRMS (NBA–NaI) *m/z* 554.3518 (M^+H, $C_{34}H_{45}N_3O_3$ requires 544.3539).

***N*-Benzyl-2,3,4,5,6,7-hexahydro-2-(1*H*-indol-3-ylacetyl)-*N'*-octyl-1*H*-isoindole-5,6-dicarboxamide.** 4.6 mg (52%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (br s, 1H), 7.63 (d, $J=7.6$ Hz, 1H), 7.35–7.10 (m, 9H), 6.45 (m, 2H), 4.40 (d, $J=5.3$ Hz, 2H), 4.14 (m, 4H), 3.73 (s, 2H), 3.14 (m, 2H), 2.40 (m, 2H), 2.12 (m, 4H), 1.26 (s, 12H), 0.88 (t, $J=6.6$ Hz, 3H); FABHRMS (NBA–CsI) *m/z* 701.2440 (M^+Cs, $C_{35}H_{44}N_4O_3$ requires 701.2468).

2-Benzoyl-2,3,4,5,6,7-hexahydro-*N*-octyl-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 2.0 mg (25%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (br s, 1H), 7.50–7.33 (m, 5H), 4.36 (d, $J=13.6$ Hz, 2H), 4.15 (m, 2H), 3.46 (m, 4H), 3.23 (d, $J=5.6$ Hz, 2H), 2.98 (m, 2H), 2.49 (m, 2H), 2.30 (m, 2H), 2.11 (m, 2H), 1.75–1.49 (m, 6H), 1.27 (s, 12 H), 0.88 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 626.2345 (M^+Cs, $C_{30}H_{43}N_3O_3$ requires 626.2359).

2,3,4,5,6,7-hexahydro-*N*-octyl-2-(3-phenylpropionyl)-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 13.2 mg (21%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.17 (m, 5H), 4.13 (m, 4H), 3.44 (m, 4H), 3.22 (m, 2H), 2.96 (t, $J=7.8$ Hz, 2H), 2.92 (m, 1H), 2.77 (m, 1H). 2.67 (t, $J=7.8$ Hz, 2H), 2.57 (m, 1H), 2.44 (m, 1H). 2.25 (m, 1H), 1.64–1.36 (m, 8H), 1.26 (s, 12H), 0.87 (t, $J=6.5$ Hz, 3H); FABHRMS (NBA–CsI) *m/z* 654.2660 (M^+Cs, $C_{32}H_{47}N_3O_3$ requires 654.2672).

2,3,4,5,6,7-Hexahydro-2-(1*H*-indol-3-ylacetyl)-*N*-octyl-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 2.7 mg (30%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (br s, 1H), 7.67 (br s, 1H), 7.40–7.00 (m, 5H), 4.19 (m, 4H). 3.76 (s, 2H), 3.45 (m, 4H), 3.21 (m, 4H), 2.95 (m, 2H). 2.73 (m, 2H), 2.43–2.03 (m, 6H), 1.87–1.49 (m, 6H). 1.27 (s, 12H), 0.88 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 679.2650 (M^+Cs, $C_{33}H_{46}N_4O_3$ requires 679.2624).

2-Benzoyl-*N*-(5-cyanopentyl)-2,3,4,5,6,7-hexahydro-*N'*-octyl-1*H*-isoindole-5,6-dicarboxamide. 17.7 mg (44%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49 (m, 5H), 4.21 (m, 4H), 3.23 (m, 4H), 2.49 (m, 2H), 2.36 (m, 2H), 2.05 (m, 2H), 1.73 (br s, 6H), 1.50 (m, 4H), 1.26 (s, 10H), 0.88 (t, $J=6.8$ Hz, 3H); FABHRMS (NBA–NaI) *m/z* 543.3295 (M^+Na, $C_{31}H_{44}N_4O_3$ requires 543.3311).

***N*-(5-Cyanopentyl)-2,3,4,5,6,7-hexahydro-*N'*-octyl-2-(3-phenylpropionyl)-1*H*-isoindole-5,6-dicarboxamide.** 1.2 mg (3%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.20 (m, 5H), 4.20 (m, 4H), 3.31 (m, 4H), 2.97 (t, $J=7.6$ Hz, 2H), 2.68 (t, $J=7.8$ Hz, 2H), 2.57–2.21 (m, 4H), 2.05 (s, 2H), 1.71 (m, 6H), 1.54 (m, 4H), 1.26 (s, 10H), 0.88 (t, $J=6.9$ Hz, 3H); FABHRMS (NBA–CsI) *m/z* 681.2759 (M^+Cs, $C_{33}H_{48}N_4O_3$ requires 548.3726)

***N*-(5-Cyanopentyl)-2,3,4,5,6,7-hexahydro-2-(1*H*-indol-3-ylacetyl)-*N'*-octyl-1*H*-isoindole-5,6-dicarboxamide.** 5.1 mg (66%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.44 (br s, NH), 7.61 (dd, $J=1.2$, 6.7 Hz, 1H), 7.35–7.08 (m, 4H), 4.20 (m, 4H), 3.71 (s, 2H), 3.19 (m, 4H), 2.94 (m, 2H), 2.32 (t, $J=6.9$ Hz, 2H), 2.18 (m, 4H), 1.64 (m, 2H), 1.47 (m, 4H), 1.26 (br s, 10H), 0.88 (t, $J=6.5$ Hz, 3H); FABHRMS (NBA–CsI) *m/z* 706.2756 (M^+Cs, $C_{34}H_{47}N_3O_3$ requires 706.2733).

2-Benzoyl-*N*-benzyl-*N'*-butyl-2,3,4,5,6,7-hexahydro-1*H*-isoindole-5,6-dicarboxamide. 2.1 mg (26%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, $J=7.7$ Hz, 2H), 7.62–7.23 (m, 8H), 4.37 (m, 4H), 4.31 (m, 2H), 3.06 (m, 2H), 2.47 (m, 2H), 2.32 (m, 2H), 2.12 (m, 2H), 1.26 (m, 4H), 0.90 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 592.1552 (M^+Cs, $C_{28}H_{33}N_3O_3$ requires 592.1576).

***N*-Benzyl-*N'*-butyl-2,3,4,5,6,7-hexahydro-2-(3-phenylpropionyl)-1*H*-isoindole-5,6-dicarboxamide.** 7.8 mg (25%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (br s, 1H), 8.01 (br s, 1H), 7.37–7.17 (m, 10H), 7.08–6.29 (m, 2H), 6.10 (d, $J=1.1$ Hz, 1H), 4.50 (d, $J=5.7$ Hz, 2H), 4.42 (d, $J=5.6$ Hz, 2H), 4.40 (m, 2H), 4.13 (m, 4H), 3.30 (m, 1H), 3.17 (m, 2H), 2.96 (m, 3H), 2.89–2.61 (m, 2H), 2.52 (t, $J=7.4$ Hz, 2H), 2.25 (m, 2H), 1.44–1.22 (m, 6H), 0.93 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 620.1869 (M^+Cs, $C_{30}H_{37}N_3O_3$ requires 620.1889).

***N*-Benzyl-*N'*-butyl-2,3,4,5,6,7-hexahydro-2-(1*H*-indol-3-ylacetyl)-1*H*-isoindole-5,6-dicarboxamide.** 1.8 mg (20%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (br s, 1H), 7.64 (t, $J=6.8$ Hz, 1H), 7.37–7.10 (m, 9H), 6.98–6.54 (m, 2H), 4.38 (m, 4H), 4.17 (br s, 2H), 3.75 (s, 1H), 3.28 (s, 1H), 3.14 (m, 2H), 3.01 (m, 2H), 2.44 (m, 2H), 2.09 (m, 2H), 1.26 (s, 4H), 0.90 (br t , 3H); FABHRMS (NBA–CsI) *m/z* 648.1848 (M^+Cs, $C_{31}H_{36}N_4O_3$ requires 645.1842).

2-Benzoyl-*N*-butyl-2,3,4,5,6,7-hexahydro-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide. 1.9 mg (23%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 5H), 4.41 (m, 2H), 4.17 (m, 4H), 3.49 (m, 2H), 3.23 (m, 2H), 2.80 (m, 2H), 2.31 (m, 2H), 2.07 (m, 2H), 1.70 (m, 6H), 1.29 (br s, 4H), 0.91 (br t, 3H); FABHRMS (NBA–CsI) *m/z* 570.1753 (M^+H, $C_{26}H_{35}N_3O_3$ requires 570.1733).

***N*-Butyl-2,3,4,5,6,7-hexahydro-2-(3-phenylpropionyl)-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide.** 12.7 mg (24%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (br s, 1H), 7.30–7.18 (m, 5H), 6.94 (m, 1H), 4.13 (m, 2H), 3.46 (m, 4H), 3.21 (t, $J=6.8$ Hz, 2H), 2.96 (t, $J=7.7$ Hz, 2H), 2.90 (m, 2H), 2.74 (t, $J=7.7$ Hz, 2H), 2.67 (m, 1H), 2.54 (m, 1H), 1.65 (br s, 2H), 1.55 (s, 6H), 1.45 (m, 2H), 1.32 (m, 2H), 0.89 (t, $J=7.2$ Hz, 3H); FABHRMS (NBA–CsI) *m/z* 598.2064 (M^+Cs, $C_{28}H_{39}N_3O_3$ requires 598.2046).

***N*-Butyl-2-(1*H*-indol-3-ylacetyl)-2,3,4,5,6,7-hexahydro-6-(1-piperidinylcarbonyl)-1*H*-isoindole-5-carboxamide.** 13.7 mg (23%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37 (s,

1H), 7.63 (m, 1H), 7.52 (m, 1H), 7.34 (m, 1H), 7.19–6.94 (m, 3H), 4.15 (m, 2H), 3.74 (s, 2H), 3.57–3.21 (m, 6H), 2.90 (m, 2H), 2.75 (m, 2H), 2.18 (m, 2H), 1.46 (m, 6H), 1.26 (m, 4H), 0.90 (t, $J=7.1$ Hz, 3H); FABHRMS (NBA) *m/z* 491.3037 (M^+H, $C_{29}H_{38}N_4O_3$ requires 491.3022).

2-Benzoyl-*N*-butyl-*N'*-(5-cyanopentyl)-2,3,4,5,6,7-hexahydro-1*H*-isoindole-5,6-dicarboxamide. 9.0 mg (16%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.34 (m, 5H), 6.98 (s, 1H), 6.59 (m, 1H), 4.36 (s, 2H), 4.16 (m, 2H), 3.24 (m, 4H), 3.03 (m, 2H), 2.84 (m, 2H), 2.35 (s, 4H), 1.56 (m, 6H), 1.25 (m, 4H), 0.91 (br t, 3H); FABHRMS (NBA) *m/z* 465.2852 (M^+H, $C_{27}H_{36}N_4O_3$ requires 465.2866).

***N*-Butyl-*N'*-(5-cyanopentyl)-2,3,4,5,6,7-hexahydro-2-(3-phenylpropionyl)-1*H*-isoindole-5,6-dicarboxamide.** 4.1 mg (20%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.20 (m, 5H), 6.99 (s, 1H), 4.15 (m, 2H), 3.23 (m, 4H), 2.99 (m, 4H), 2.55 (m, 2H), 2.36 (m, 4H), 1.68 (br s, 6H), 1.49 (m, 4H), 1.28 (m, 4H), 0.90 (t, $J=6.8$ Hz, 3H); FABHRMS (NBA–CsI) *m/z* 625.2175 (M^+Cs, $C_{29}H_{40}N_4O_3$ requires 625.2155).

***N*-Butyl-*N'*-(5-cyanopentyl)-2,3,4,5,6,7-hexahydro-2-(1*H*-indol-3-ylacetyl)-1*H*-isoindole-5,6-dicarboxamide.** 13.5 mg (21%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66 (br s, NH), 7.60 (d, $J=7.7$ Hz, 1H), 7.30 (d, $J=7.8$ Hz, 1H), 7.21–7.07 (m, 3H), 6.98 (s, 1H), 6.62 (br s, 1H), 4.14 (m, 2H), 3.71 (m, 2H), 3.71 (m, 2H), 3.22 (m, 4H), 2.92 (m, 4H), 2.06 (m, 2H), 1.70–1.23 (m, 10H), 0.90 (t, $J=7.1$ Hz, 3H); FABHRMS (NBA) *m/z* 518.3148 (M^+H, $C_{30}H_{39}N_5O_3$ requires 518.3131).

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