Article

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Solid-Phase Convergent Synthesis of a Benzimidazolone Library via the Combination of Two Smaller Arrays of Carboxylic Acids and Secondary Amines

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The concept of convergent synthesis can be extended to combinatorial chemistry in order to obtain collections of products characterized by considerable chemical diversity and a certain molecular complexity. In this work, a library consisting of three carboxylic acids containing a benzimidazolonic functionality with variations at two positions was synthesized on solid phase. After cleavage, this library was combined with a second library consisting of 16 solid-supported amines containing two points of variation. IRORI technology was used for the split-and-mix synthesis of the final 48 members library.

Introduction

Benzimidazolonic scaffolds containing an amidic functionality have been reported to have pharmacological activity against a variety of molecular targets. There is a wealth of evidence that such structures are involved not only in phosphodiesterase inhibition,[1] sodium channel blockage[2] and the regulation of adenosine uptake[3] but also in interaction with nociceptors[4] and Xa factor.[5]

In particular, benzimidazolonic scaffolds substituted with a piperidine moiety have been reported to play a role as peripheral vasodilators[6] with low pharmacological side effects to the heart, that is, a low effect on heart rate, a low hypotensive effect and a low myocardial contraction effect.

For this reason, compounds of this type are of particular interest for the development of a primary, nonfocused, library. To obtain the maximum diverse set of products, we applied the concept of convergent synthesis, widely used for the synthesis of a number of drugs, such as vitamin B_{12},[7] Perindopril,[8] and Sildenafil,[9] to combinatorial chemistry, and two libraries, instead of single compounds, were combined in the convergent pathway (Figure 1). This type of synthetic approach[10] is not commonly used, as demonstrated by the limited number of examples of libraries obtained by convergent synthesis reported in the literature.[11] In particular, to the best of our knowledge, solid-phase convergent synthesis of libraries has been described only by Nielsen and Jensen,[12] but in the example reported, the authors have synthesized a very small library (nine members), and moreover, the products were obtained as a mixture.

Using this combinatorial scheme, we were able to obtain a collection of single products characterized by a remarkable chemical diversity due to the presence of two different scaffolds, each containing their points of diversity, in the same structure. Moreover, the possibility of combining two different scaffolds allows products defined by a certain molecular complexity to be obtained, which would be much more difficult to achieve using a linear parallel synthesis.

In this work, a library of three carboxylic acids was synthesized on the solid phase, cleaved, and then coupled to a library of 16 supported amines to yield the final library of 48 amides.

IRORI's "directed sorting" technique[13] was utilized to accomplish the solid-phase synthesis of the 48 (3×16) member library using a mix-and-split[14] approach in polypropylene MacroKans.

Results and Discussion

Library of Carboxylic Acids. The array of three carboxylic acids reported in Scheme 1 was realized utilizing loose Wang resin.

These three compounds were then cleaved from the resin before the condensation reaction with the supported amines loaded in MacroKans. The synthesis of benzimidazolone-3-carboxylic acids has been reported by Phillips and Ping Wei.[15] The first step featured the anchoring of 4-fluoro-3-nitrobenzoic acid to the solid support. Through an aromatic nucleophilic substitution, the first point of diversity was introduced on the molecule (**3**), and after nitro group reduction to obtain the intermediates **4a** and **4b**, the cyclization step was accomplished using *N*,*N*′-disuccinimidyl carbonate (DSC). Total yield for these steps, calculated by weighing dried resin, was in all cases higher than 95%.

The second point of diversity was introduced by alkylation of the second ureidic nitrogen. In the case of the methyl substituent, the reaction proceeded via a nucleophilic substitution reaction of the aza anion[15] with methyl iodide to obtain **7a**. In the case of *n*-propyl substituent, alkylation was unsuccessful using the previous conditions, so the functionalization was accomplished through Mitsunobu reaction to obtain compound **7b**. Cleavage of **5a**, **7a**, and **7b** afforded the substrates **6a** (86% yield and 80.1% purity by LC/MS at 254 mn), **8a** (82% yield and 90.8% purity by LC/MS at 254 nm), and **8b** (83% yield and 84.4% purity by LC/MS at 254 nm), utilized without purification in the following coupling reaction.

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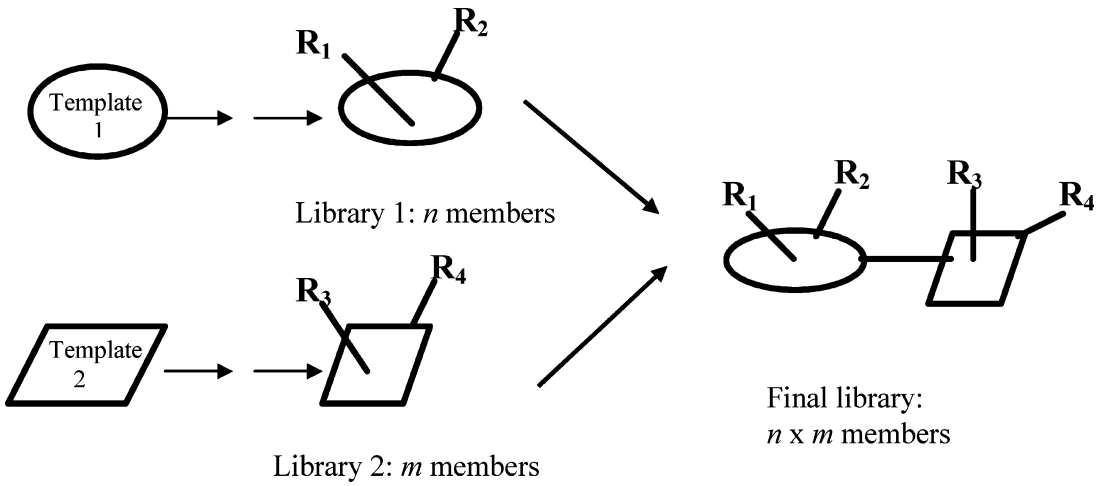
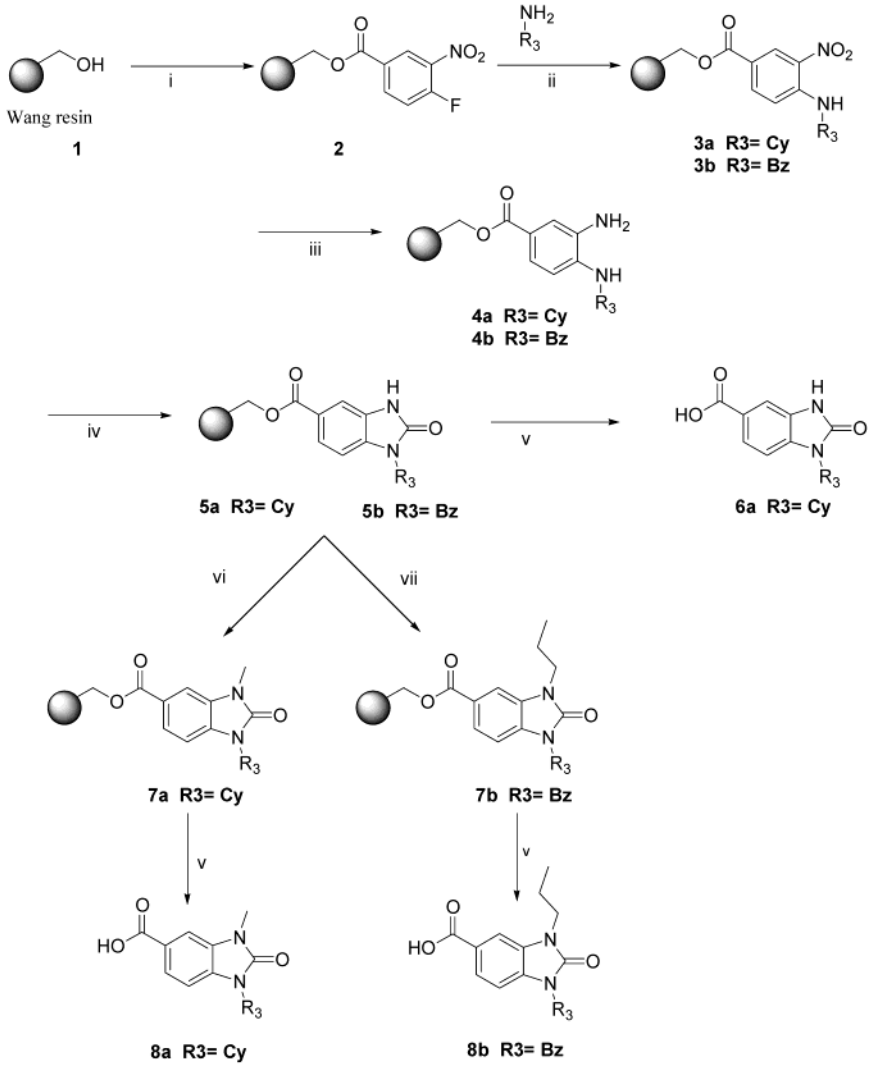


Figure 1. Convergent pathway to library synthesis.

Scheme 1. Library of Carboxylic Acids



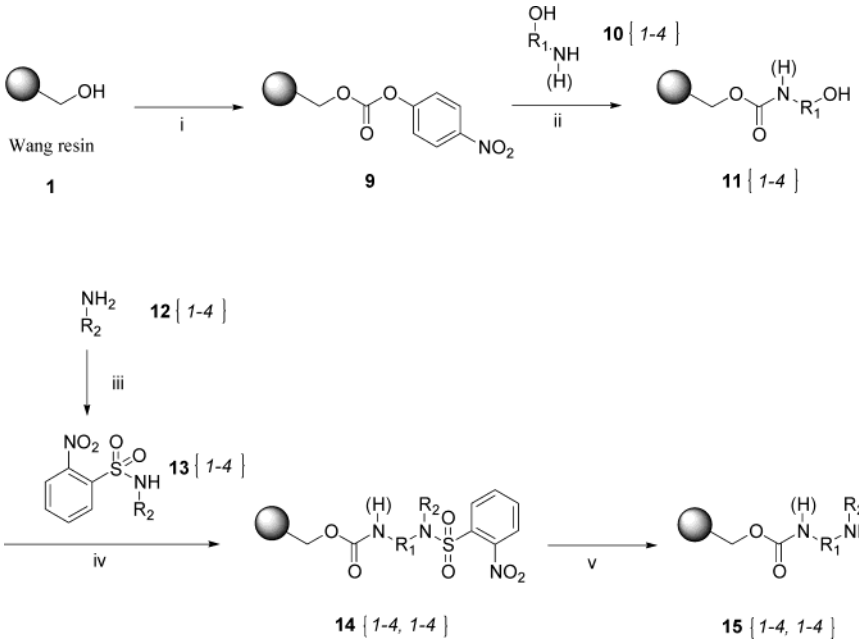
Reagents and conditions: (i) 4-Fluoro-3-nitrobenzoic acid (2.5 equiv), DIC (2.5 equiv), DCM/DMF 1/2, 2 h rt. (ii) R_3NH_2 (5 equiv), DMSO, 24 h rt. (iii) $SnCl_2 \cdot 2H_2O$ (5 equiv), DMF, 12 h 40 °C. (iv) DSC (2 equiv), THF/DCM/DMF 8/2/1, 24 h rt. (v) DCM/TFA 8/2, 2 h rt. (vi) DBU (15 equiv), CH_3I (20 equiv), DMF, 24 h rt. (vii) $CH_3CH_2CH_2OH$ (20 equiv), PPh_3 (10 equiv), DIAD (10 equiv), DCM/THF 1/1, 16 h rt.

Library of Amines. The synthesis of such structures (Scheme 2) using SynPhase lanterns as solid support has been previously reported by Renault and co-workers.[16]

Wang resin (**1**) was initially functionalized via formation of *p*-nitrophenyl carbonate (**9**) in order to allow the subsequent nucleophilic substitution with different amino alcohols **10**{*1*−*4*} (Figure 2).

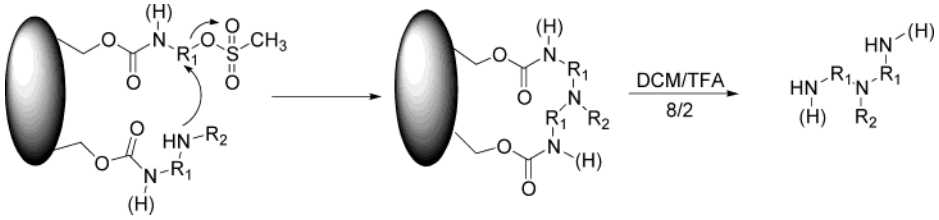
The synthesis of secondary amines was initially attempted employing nucleophilic substitution of the alcoholic functionality of the amino alcohols activated as mesylates.

Scheme 2. Library of Amines

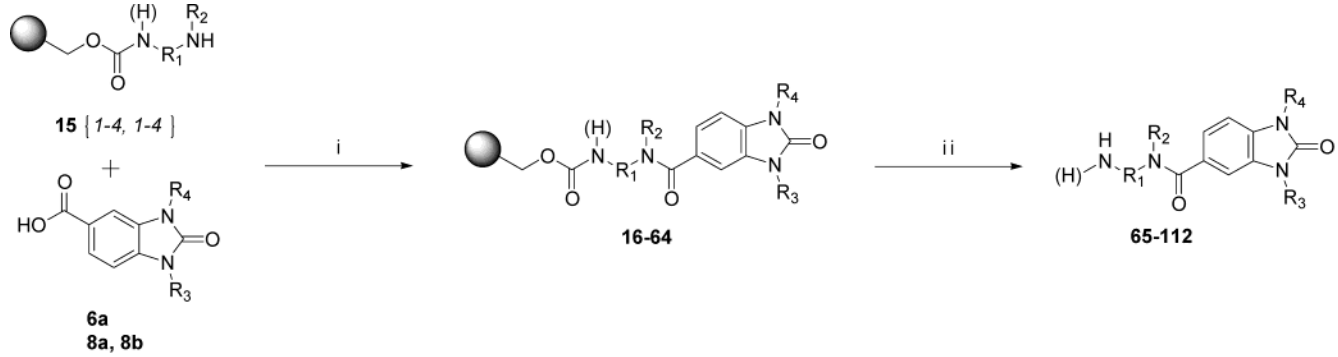


Reagent and conditions: (i) *N*-methylmorpholine (4 equiv), *p*-nitrophenylchloroformate (4 equiv), DCM, 45 min rt. (ii) amino alcohol (3.33 equiv, 0.2 M), DCM, 2 h rt. (iii) K_2CO_3 (2.2 equiv), *o*-nitrobenzensulfonyl chloride (1.2 equiv), DCM, 16 h rt. (iv) *o*-nitrobenzensulfonamide (10 equiv), PPh_3 (4 equiv), DTAD (4 equiv, 0.07 M), DCM/THF 1/1, 16 h rt. (v) DBU (20 equiv, 0.3 M), mercaptoethanol (14 equiv, 0.2 M), DMF, 75 min rt.

Scheme 3. Side Reaction, Formation of Tertiary Amine



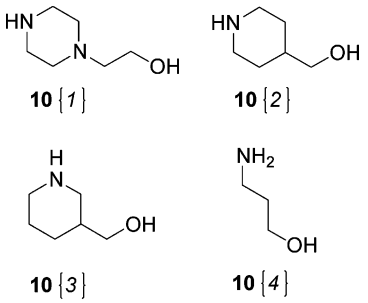
Scheme 4. Convergent Synthesis: Library of Amides



Reagents and conditions: (i) supported amine (1 equiv), carboxylic acid (3 equiv), PyBrOP (3 equiv), DIPEA (9 equiv), DMF, 3 h rt. (ii) DCM/TFA 8/2, 2 h rt.

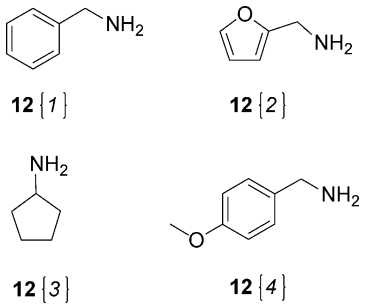
Performing this reaction, we isolated significant amounts of tertiary amine after cleavage (Scheme 3). This side reaction is due to the higher reactivity of the secondary amine that is formed on the resin during the reaction, as compared with the primary amine added as reagent in solution and to the high loading of the resin. The overalkylation side reaction normally does not occur on solid phase due to the isolation of reactive sites, but the high-loading resin used in this synthesis has previously been reported by Tang and Wareing[17] to allow intrabead reaction.

To optimize this step we explored (1) variation of the leaving group, (2) variation of the reaction solvent, (3) employment of a low-loading Wang resin, and (4) performing a Mitsunobu reaction instead of nucleophilic substitution. Changing the leaving group to bromine,[18] iodine,[19,20] or tosylate gave no improvements, yielding the same amount of overalkylation product that was isolated using the mesylate. Attempts to minimize the amount of tertiary amine utilizing CH_3CN instead of DMSO as the solvent to reduce the resin's swelling as well as using a low-loading Wang resin (0.55 mmol/g vs 1.2 mmol/g) were unsuccessful due to a considerable decrease in the reactivity. In light of these results, we decided to try the Mitsunobu reaction, functionalizing the primary amines **12**{*1*−*4*} (Figure 3) as *o*-nitroben-



10{*1*} **10**{*2*} **10**{*3*} **10**{*4*}

Figure 2. Structure of amino alcohols **10**{*1*−*4*}.



12{*1*} **12**{*2*} **12**{*3*} **12**{*4*}

Figure 3. Structure of primary amines **12**{*1*−*4*}.

zenesulfonamides[21−23] **13**{*1*−*4*} in order to have a reactive nucleophile for the Mitsunobu reaction that can be subsequently reconverted to the aminic functionality.

A variety of conditions[23] have been reported for solid-phase Mitsunobu reactions. Using nonsterically hindered azodicarboxylates, such as DIAD or DEAD, we isolated significant amounts of the product of side alkylation onto the azodicarboxylate nitrogen. This side reaction is due to competition between the nucleophile and an aza-anionic species that is forming on the azodicarboxylate during the reaction.[24] Ph_3P/di-*tert*-butyl-azodicarboxylate (DTAD, sterically hindered) was the best combination of reagents giving the most consistent results without any traces of the aforementioned byproduct. Different conditions were explored for the deprotection step,[21−23] varying the combination of nucleophile (mercaptoethanol or thiophenol) and base (K_2CO_3 or DBU) but also studying the reaction time and the concentration of nucleophile, that was found to be very important to minimize the formation of byproducts. In fact, we noticed that reaction times longer than 90 min and a concentration of nucleophile higher than 0.2 M led to the formation of a complex reaction mixture. The optimum result was obtained using DBU as the base and mercaptoethanol as the nucleophile at a 0.2 M concentration in DMF. The combination of two amino alcohols (**10**{*1*} and **10**{*4*}) with two primary amines (**12**{*1*} and **12**{*3*}) was explored during the setup both in the Mitsunobu reaction and in the deprotection step on loose resin in order to determinate yields and purities. In all cases, LC/MS of cleaved products revealed purities higher than 80%, and the total reaction yields (from step i to step v), calculated by weighing the dried resin, were in the 75−90% range. These conditions were then applied to the synthesis of the whole amine library **15**{*1*−*4*, *1*−*4*} in MacroKans, as described in the Experimental section.

Convergent Synthesis: Library of Amides. The convergent synthesis of the final library of amides entails the coupling of acids **6a**, **8a**, and **8b** with the polymer-supported amines **15**{*1*−*4*, *1*−*4*} in MacroKans, as depicted in Scheme 4.

Many coupling conditions were explored during the setup by modifying the coupling reagents but keeping constant the molar ratio of the supported amines and the acids in solution. We found that using coupling reagents, such as *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) or *N*-hydroxybenzotriazole (HOBt) in association with DIC or DIPEA led to a low conversion of the amine, a significant amount of which was recovered after cleavage together with the corresponding trifluoroacetamide. Better results were obtained using bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP) in association with DIPEA. In this case, we obtained a good conversion of amine to amide, and only traces of unreacted amine were recovered after cleavage. It was therefore decided to use this combination of reagents to accomplish the library synthesis. The reaction was performed at room temperature for 3 h without any trace of the decomposition that occurs if the same reaction is performed at 60°C. LC/MS analysis revealed the presence of variable amounts (5−15%) of a higher-molecular-weight byproduct in most crude reactions after cleavage. The presence of such byproducts required the purification of most of the final amides through preparative HPLC. Yields and purities (LC/MS, 215 nm), of the complete library (**65**−**112**) are reported in Table 1.

Conclusion

In conclusion, a library of 48 (3 × 16) members was synthesized with success on the solid phase combining two smaller arrays of acids and amines. The mix-and-split approach applied to the IRORI Accutag technology was usefully employed and allowed us to accelerate the realization of the library. Convergent synthesis was applied for the first time, to the best of our knowledge, to the realization of combinatorial arrays of single products on the solid phase, thus obtaining more diverse final compounds. Efforts are ongoing to enlarge this work to the synthesis of a 576 (24 × 24) member library.

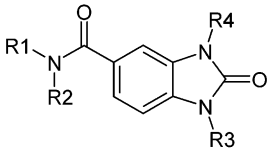
Experimental Section

All reagents were purchased from Sigma-Aldrich (Milan, Italy), Lancaster (Milan, Italy), or Maybridge (Tintagel, England) in the highest available purity and were used as such. All solvents were purchased from JT Baker and Riedel-de Häen and were used without further purification. PS-Wang (1.7 mmol/g, 50−100 mesh, 150−300 μm, 1% cross-linking divinylbenzene) was purchased from Polymer Labs (part number, 1463-6689; batch number, WANG 068). All MacroKans, Rf tags, and scanning equipment were purchased from IRORI Europe limited (Darmstadt, Germany).

Reactions with MacroKans were performed in a HIR 10M rotating hibridization incubator.

LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer equipped with an Alliance HT Waters 2790 separation module and a Waters 996 photodiode array detector using a Symmetry C18 column (3.5 μm, 4.6 × 75 mm) and X-Terra column (2.5 μm, 4.6 × 50 mm). Mixture

Table 1. Characterization of Library Members of the Final Amide Library



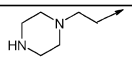
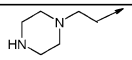
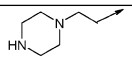
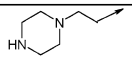
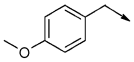
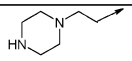
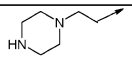
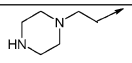
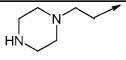
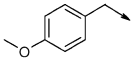
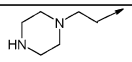
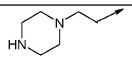
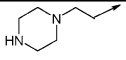
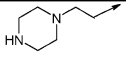
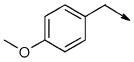
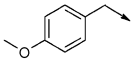
Library member	R^1	R^2	R^3	R^4	LC-MS purity %[a] before purification	LC-MS purity %[a] after purification	Yield % after purification
65			Cy	H	74.6	91.1	50.2
66			Cy	H	76.7	92.3	46.3
67			Cy	H	63.7	92.9	40.2
68			Cy	H	68.2	89.2	42.6
69			Cy	CH_3	80.2	100.0	49.2
70			Cy	CH_3	94.3	98.5	49.0
71			Cy	CH_3	87.6	90.1	42.9
72			Cy	CH_3	73.6	90.2	47.0
73			Bz	$CH_2CH_2CH_3$	86.8	93.4	43.2
74			Bz	$CH_2CH_2CH_3$	73.7	95.6	41.2
75			Bz	$CH_2CH_2CH_3$	82.7	88.5	40.2
76			Bz	$CH_2CH_2CH_3$	78.7	90.0	40.9
77			Cy	H	53.6	96.6	51.2
78			Cy	H	52.8	86.2	49.6
79			Cy	H	62.3	95.7	48.4
80			Cy	H	38.0	81.0	50.1
81			Cy	CH_3	72.7	82.8	51.2

Table 1. (Continued)

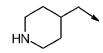
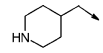
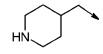
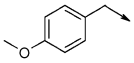
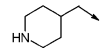
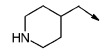
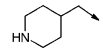
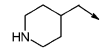
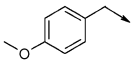
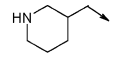
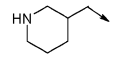
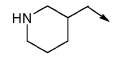
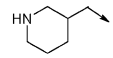
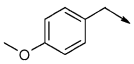
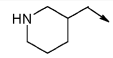
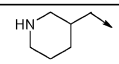
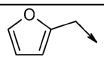
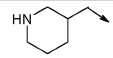
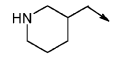
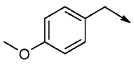
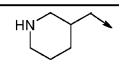
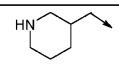
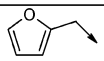
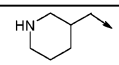
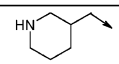
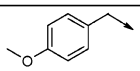
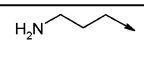
82			Cy	CH_3	59.4	81.1	50.3
83			Cy	CH_3	80.9	98.6	46.2
84			Cy	CH_3	40.0	92.5	46.9
85			Bz	$CH_2CH_2CH_3$	80.2	91.3	40.2
86			Bz	$CH_2CH_2CH_3$	59.1	90.5	406.0
87			Bz	$CH_2CH_2CH_3$	86.3	94.5	41.2
88			Bz	$CH_2CH_2CH_3$	42.7	88.0	40.3
89			Cy	H	57.9	90.4	51.2
90			Cy	H	55.3	86.2	50.0
91			Cy	H	72.9	97.9	50.1
92			Cy	H	46.7	84.0	42.9
93			Cy	CH_3	81.0	100.0	52.2
94			Cy	CH_3	71.3	83.6	51.1
95			Cy	CH_3	83.0	98.8	50.0
96			Cy	CH_3	53.6	96.0	50.1
97			Bz	$CH_2CH_2CH_3$	82.1	85.2	48.2
98			Bz	$CH_2CH_2CH_3$	66.0	85.5	47.3
99			Bz	$CH_2CH_2CH_3$	85.1	89.1	41.2
100			Bz	$CH_2CH_2CH_3$	54.5	80.8	40.2
101			Cy	H	52.6	95.6	50.3
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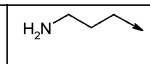
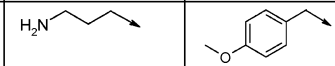
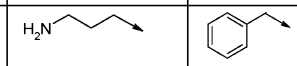
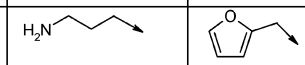
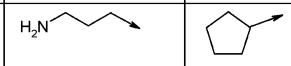
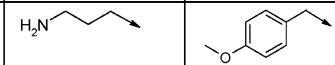
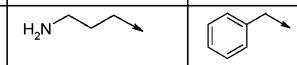
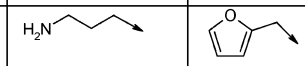
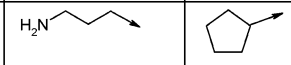
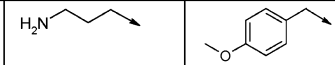
Table 1. (Continued)

103			Cy	H	72.8	100.0	50.2
104			Cy	H	53.2	85.0	48.2
105			Cy	CH_3	80.9	91.9	49.3
106			Cy	CH_3	80.1	85.5	50.8
107			Cy	CH_3	83.2	87.0	50.1
108			Cy	CH_3	60.6	85.8	49.2
109			Bz	$CH_2CH_2CH_3$	68.6	100.0	48.2
110			Bz	$CH_2CH_2CH_3$	58.6	80.8	47.0
111			Bz	$CH_2CH_2CH_3$	72.5	96.3	45.3
112			Bz	$CH_2CH_2CH_3$	56.3	91.0	41.2

[a] LC/MS purities are given as area percent (UV) at 215 nm. Conditions are reported in the Experimental Section.

A (95% water, 5% acetonitrile, 0.05% TFA) and mixture B (5% water, 95% acetonitrile, 0.05% TFA) were used as eluents as follows: 0−1 min, 5% mixture B; 1−11 min, 5−100% mixture B (linear gradient); 11.1−12 min, 100% mixture B; 12.1−15 min 5% mixture B for Symmetry column; and 0−1 min, 5% mixture B; 1−4 min, 5−100% mixture B (linear gradient); 4.1−6.0 min., 100% mixture B; 6.1−9 min 5% mixture B for X-Terra column.

Proton NMR spectra were recorded on a Bruker ARX 300-MHz instrument using TMS as internal standard.

Procedure for the Anchoring of 4-Fluoro-3-nitrobenzoic Acid: Preparation of Resin 2. Wang resin (8.47 g, loading = 1.7 mmol/g, 14.4 mmol) was suspended in DCM/DMF 1/2 (120 mL). 4-Fluoro-3-nitrobenzoic acid (6.66 g, 36.0 mmol) was dissolved in 15 mL of the same solvent mixture and added dropwise to the resin. After shaking for 10 min at room temperature, 1,3-diisopropylcarbodiimide (DIC, 5.64 mL, 36.0 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.45 g, 3.6 mmol) were added, and the reaction was allowed to proceed at room temperature for 2 h. The resin was filtered, washed once with DCM/DMF 1:2, and then subjected to a second reaction cycle utilizing the same amounts of reagents. After 2 h at room temperature, the resin was filtered, then washed with DMF (80 mL × 3), DCM (80 mL × 3), DCM/MeOH (80 mL × 1), MeOH (80 mL), DCM/MeOH (80 mL × 1), and DCM (80 mL × 3). Mini cleavage assays on 2−3 mg resin samples were used to monitor by TLC the completion of the reaction and to assess the purity of the product by LC/MS (negative ion assay, Symmetry column; purity 95.2%, 254 nm). Elemental analysis of the supported product gave a fluorine content of 2.39% (theoretical value = 2.50%). Reaction yield, determined by weighing dry resin, was 94%.

General Procedure for Aromatic Nucleophilic Substitution: Preparation of Resin 3a. Resin **2** (7.27 g, loading = 1.32 mmol/g, 9.6 mmol) was suspended in a solution of cyclohexylamine (5.49 mL, 48.0 mmol) in DMSO (50 mL), and the reaction was shaken at room temperature for 24 h. The resin was filtered and then washed with DMSO (30 mL × 5) and EtOH (50 mL × 5). Elemental analysis of the supported product gave a nitrogen content of 3.30% (theoretical value = 3.30%). Reaction yield, determined by weighing dry resin, was quantitative. Resin **3b** was prepared utilizing the same procedure.

General Procedure for Nitro Group Reduction: Preparation of Resin 4a. The resin **3a** (8.10 g, loading = 1.18 mmol/g, 9.6 mmol) was suspended in DMF (160 mL). $SnCl_2 \cdot 2H_2O$ (10.8 g, 48.0 mmol) was added, and the reaction was heated at 40°C and then shaken for 12 h. The resin was filtered and washed with DMF (100 mL × 3), DMF/H_2O (100 mL × 1), H_2O (100 mL × 3), DMF/H_2O (100 mL × 1), and DCM (50 mL × 5). Elemental analysis of the supported product gave a nitrogen content of 3.23% (theoretical value = 3.50%). Purity of **4a** was determined by LC/MS of the cleaved product (X-Terra column, 94.4%, 254 nm). Reaction yield, determined by weighing dry resin, was 95.0%. Resin **4b** was prepared following the same procedure. Purity of **4b** was determined by LC/MS of the cleaved

product (X-Terra column 93.0%, 254 nm). Reaction yield, determined by weighing dry resin, was 94.5%.

General Procedure for the Cyclization: Preparation of Resin 5a. Resin **4a** (7.80 g, loading = 1.22 mmol/g, 9.6 mmol) was suspended in a mixture of dry THF/dry DCM/dry DMF 8:2:1 (110 mL). A solution of *N*,*N*′-disuccinimidyl carbonate (DSC, 4.9 g, 19.2 mmol) in 10 mL of the same solvent mixture was added dropwise to the resin, and the reaction was shaken at room temperature for 24 h. The procedure was repeated twice under the same conditions. The resin was filtered and washed with DMF (80 mL × 5), DCM/THF (80 mL × 5), and DCM (80 mL × 5). Purity of **5a** was determined by LC/MS of the cleaved product (Symmetry column, 92.2%, 254 nm). ^{1}H NMR (300 MHz, DMSO) of the cleaved product: δ 11.1 (s, 1H), 7.65 (dd, J = 1.4, 8.6 Hz, 1H), 7.52 (d, J = 1.4 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 4.22−4.02 (m, 1H) 1.25−2.10 (m, 10H, aliphatic system). Reaction yield, determined by weighing dry resin, was 95.0%.

Resin **5b** was prepared following the same procedure. Purity of **5b** was determined by LC/MS of the cleaved product (Symmetry column, 100%, 254 nm). ^{1}H NMR (300 MHz, DMSO) on cleaved product: δ 11.2 (s, 1H), 7.68 (dd, J = 1.4, 8.6 Hz, 1H), 7.60 (d, J = 1.4 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.20−7.30 (m, 5H, aromatic system), 5.10 (s, 2H). Reaction yield, determined by weighing dry resin, was quantitative.

Procedure for Alkylation of Ureidic Nitrogen: Nucleophilic Substitution. Preparation of Resin 7a. Resin **5a** (4.0 g, loading = 1.2 mmol/g, 4.8 mmol) was suspended in dry DMF (100 mL), and a 1 M solution of 1,8-diazabicyclo-[5,4,0]undecene (10.7 mL, 72.0 mmol) in the same solvent was added dropwise. After 1 h stirring at room temperature, iodomethane (5.90 mL, 96.0 mmol) was added, and the reaction shaken for 24 h at room temperature. Upon completion of the reaction (TLC of the cleaved samples), the resin was filtered and washed with DMF (80 mL × 3), DMF/EtOH (80 mL × 1), EtOH (80 mL × 5), EtOH/DCM (80 mL × 1), and DCM (80 mL × 3), affording 3.95 g of resin **7a** (reaction yield: 97.4%). Purity was determined by LC/MS of the cleaved product (Symmetry column, 93.2%, 254 nm).

Procedure for Alkylation of Ureidic Nitrogen: Mitsunobu Coupling. Preparation of Resin 7b. *n*-Propanol (7.15 mL, 96.0 mmol) and PPh_3 (12.5 g, 48.0 mmol) were added, under shaking, to the resin **5b** (4.06 g, loading = 1.18 mmol/g, 4.8 mmol) suspended in a mixture of dry DCM/dry THF 1:1 (100 mL). The reaction mixture was cooled to 0°C, and a 0.8M solution of DIAD in the same solvent mixture was added dropwise. The reaction was then shaken overnight at room temperature. The resin was filtered and washed with DCM (80 mL × 3), DMF (80 mL × 3), DMF/H_2O (80 mL × 1), H_2O (80 mL × 3), DMF/H_2O (80 mL × 1), DMF (80 mL × 3), THF (80 mL × 3), and DCM (80 mL × 3), affording 4.1 g of resin **7b** (reaction yield: 96.5%). Purity was determined by LC/MS of the cleaved product (X-Terra column, 93.2%, 254 nm).

General Procedure for Cleavage: Preparation of Intermediates 6a, 8a, and 8b. Intermediates **5a**, **7a**, and **7b** were cleaved from the resin by treatment with 20% TFA/DCM for 2 h. The solvent was removed under vacuum, affording the substrates (**6a**, **8a**, **8b**) which were used without further purification in the following coupling reactions.

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (6a). LC/MS purity (positive ion assay, Symmetry column; 254 nm), 80.1%, reaction yield, 86.0%.

1-Cyclohexyl-3-methyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (8a). LC/MS purity (positive ion assay, Symmetry column; 254 nm), 90.8%, reaction yield, 82.0%.

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (8b). LC/MS purity (positive ion assay, Symmetry column; 254 nm), 84.4%, reaction yield, 83.0%.

Procedure for Functionalization of Wang Resin with *p*-Nitrophenyl Carbonate: Preparation of Resin 9. Loose Wang resin (3.65 g, loading = 1.2 mmol/g, 4.8 mmol), was suspended in dry DCM (90 mL). *N*-Methylmorpholine (1.71 mL, 15.5 mmol) and *p*-nitrophenylchloroformate (3.12 g, 15.5 mmol) were added, and the reaction was shaken for 45 min at room temperature. The resin was filtered and washed with DCM (50 mL × 5). Elemental analysis was performed on the supported product, giving a nitrogen content of 1.74% (theoretical N = 1.83%). Reaction yield, determined by weighing dry resin, was 94.7%.

General Reaction Conditions with MacroKans. Irori's directed sorting technique was utilized as described by Xiao and co-workers.[13c] Approximately 75 mg of the appropriate resin and an rf Tag were loaded into each MacroKan using Irori dry-resin loader. All MacroKans were sorted at each step and added to the right reaction vessel. After each reaction, the Kans were collected and washed together in a custom-built washer system (DMF × 2, DMF/H_2O × 1, H_2O × 2, DMF/H_2O × 1, DMF × 2, DCM × 3) then sorted into the assigned reaction vessel.

General Procedure for Nucleophilic Substitution: Preparation of Resin 11{*1*}. Twelve MacroKans containing activated Wang resin **9** (0.076 g, loading = 1.32 mmol/g, 0.1 mmol) were suspended in DCM (70 mL), and 1-piperazinoethanol (1.71 mL, 14.0 mmol) was added dropwise. After 2 h mixing at room temperature, the solvent was drained, and the Kans were washed with DMF × 2, DMF/H_2O × 1, H_2O × 2, DMF/H_2O × 1, DMF × 2, and DCM × 3 and dried under vacuum overnight. Intermediates **11**{*2*}, **11**{*3*}, and **11**{*4*} were prepared utilizing the same procedure.

General Procedure for Solution Synthesis of Sulfonamides: Preparation of Intermediate 13{*1*}. Benzylamine (1.96 mL, 18.0 mmol) was dissolved in dry DCM (55 mL), and K_2CO_3 (8.75 g, 39.6 mmol) was added to the solution. The obtained suspension was stirred for 15 min at room temperature and then cooled to 0 °C. A 1 M solution of *o*-nitrobenzenesulfonyl chloride (6.59 g, 21.6 mmol) in dry DCM (16 mL) was added dropwise, then the reaction mixture was stirred overnight at room temperature. After washing with water, the separated organic layer was dried over anhydrous Na_2SO_4. Filtration and removal of the solvent under reduced pressure afforded a crude product that was

redissolved in DCM (30 mL) and treated with tris(2-aminoethyl)amine polystyrene (9.5 g, loading = 2.45 mmol/g, 23.5 mmol) in order to remove the excess of sulfonyl chloride. After 2 h stirring at room temperature, the resin was removed by filtration, and the solvent was evaporated under vacuum. Purity of **13**{*1*} was determined by LC/MS (Symmetry column; 100%, 254 nm). Reaction yield, 99.4%. Intermediates **13**{*2*}, **13**{*3*}, and **13**{*4*} were prepared utilizing the same procedure.

***N*-Furan-2-ylmethyl-2-nitrobenzenesulfonamide (13{*2*}).** HPLC purity (Symmetry column; 254 nm), 97.6%; reaction yield, 99.1%.

***N*-Cyclopentyl-2-nitrobenzenesulfonamide (13{*3*}).** LC/MS purity (Symmetry column; 254 nm), 100%; reaction yield, 98.8%.

***N*-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide (13{*4*}).** HPLC purity (Symmetry column; 254 nm), 97.7%; reaction yield, 99.4%.

General Procedure for the Synthesis of Supported *o*-Nitrobenzenesulfonamide: Mitsunobu Coupling. Preparation of Resin 14{*1*−*4*,*1*}. *N*-Benzyl-2-nitrobenzenesulfonamide **13**{*1*} (3.50 g, 12.0 mmol) and PPh_3 (1.15 g, 5.0 mmol) were added to a suspension of 12 MacroKans containing supported amino alcohols **11**{*1*−*4*} (0.1 mmol) in a mixture of dry THF/dry DCM 1:1 (60 mL), and the reaction was cooled to 0°C. A 0.5 M solution of DTAD (1.15 g, 5.0 mmol) was added dropwise, and the reaction was mixed overnight at room temperature. The solvent was drained, and the Kans were washed with DMF × 2, DMF/H_2O × 1, H_2O × 2, DMF/H_2O × 1, DMF × 2, and DCM × 3 and then dried under vacuum overnight. All intermediates **14**{*1*−*4*,*1*−*4*} were prepared utilizing the same procedure.

Procedure for Deprotection: Preparation of Resins 15{*1*−*4*,*1*−*4*}. All MacroKans, each containing 0.1 mmol of supported *o*-nitrobenzenesulfonamide, were suspended in DMF (320 mL), and a 1 M solution of 1,8-diazabicyclo-[5,4,0]undecene (15.7 mL, 105.0 mmol) was added dropwise. After 10 min mixing at room temperature, 2-mercaptoethanol (4.9 mL, 70.0 mmol) was added, and the reaction was mixed for 75 min at room temperature. The reaction mixture was drained, and the Kans were washed with DMF × 2, DMF/H_2O × 1, H_2O × 2, DMF/H_2O × 1, DMF × 2, and DCM × 3 and then dried under vacuum overnight.

Procedure for Condensation Reaction: Preparation of Resins 16−64. The appropriate acid (**6a**, 1.20 g; **8a**, 1.30 g; **8b**, 1.40 g; 4.8 mmol), previously cleaved from the resin, was added to a suspension of 16 MacroKans containing the supported secondary amines **15**{*1*,*4*−*1*,*4*} (0.1 mmol), in DMF (80 mL). When the acid was completely dissolved, a 1 M solution of PyBrOP (2.24 g, 4.8 mmol) in DMF and DIPEA (2.46 mL, 14.4 mmol) were added dropwise. The MacroKans were mixed at room temperature for 3 h. The reaction mixture was drained, and the Kans were washed with DMF × 2, DMF/H_2O × 1, H_2O × 2, DMF/H_2O × 1, DMF × 2, and DCM × 3, then dried under vacuum overnight.

General Procedure for Final Cleavage: Preparation of Library Members 65−112. All products were cleaved from the resin with 20% TFA/DCM for 2 h using a 96-well cleavage station. The solvent was removed using a Genevac HT-4 vacuum centrifuge, and the residues were dissolved in CH_3CN and analyzed by LC/MS.

General Procedure for Preparative HPLC Purification. The purification was performed on a Biotage Parallex Flex preparative HPLC. Crude cleaved products were dissolved in 1 mL of MeOH (Baker HPLC Analyzed) and eluted through a Symmetry C18 column (7 μm, 19 × 300 mm). Mixture A (100% water, 0.1% TFA) and Mixture B (100% acetonitrile, 0.1% TFA) were used as eluent as follows: 0−5 min, 25% mixture B; 5−20 min, 25−95% mixture B (linear gradient); 20−22 min, 95% mixture B; and 22−23 min, 95−25% mixture B (linear gradient). The solvent was removed using a Genevac HT-4 vacuum centrifuge, and the purified library members thus obtained were analyzed by LC/MS according to the following procedure: Luna C18 column (4.6 × 50 mm, 3 μm). Mixture A (95% water, 5% acetonitrile, 0.1% formic acid) and Mixture B (5% water, 95% acetonitrile, 0.1% Formic acid) were used as eluents as follows: 0−0.5 min, 95% mixture A; 0.5−6.5 min, 95−5% mixture A (linear gradient); 6.5−11 min, 5% mixture A; and 11.1−14.2 min, 95% mixture A.

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Benzyl-(2-piperazin-1-yl-ethyl)-amide (65). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as free base): δ 7.40−7.21 (m, 5H), 7.17 (dd, J = 8.2, 1.9 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 1.9 Hz, 1H), 4.70 (s, 2H), 4.30−4.15 (m, 1H), 3.55 (dd, J = 6.6, 6.9 Hz, 2H), 2.90−2.80 (m, 4H), 2.50 (dd, J = 7.2, 7.2 Hz, 2H), 2.39−2.25 (m, 4H), 2.20−2.02 (m, 2H), 1.95−1.75 (m, 6H), 1.30−1.20 (m, 2H). LC/MS m/z = 462.3 $[M + H]^+$ (Luna column; 254 nm, 95.2%; 215 nm, 91.1%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid 4-Methoxybenzyl-(2-piperazin-1-yl-ethyl)-amide (68). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as free base): δ 9.9 (s, 1H), 7.10−6.90 (m, 5H), 6.75−6.65 (m, 2H), 4.48 (s, 2H), 4.30−4.00 (m, 1H), 3.70 (s, 3H), 3.48−3.35 (m, 2H), 3.10−3.00 (m, 4H), 2.70−2.40 (m, 6H), 2.12−1.88 (m, 2H), 1.85−1.55 (m, 5H), 1.40−1.00 (m, 3H). LC/MS m/z = 492.4 $[M + H]^+$ (Luna column; 254 nm, 95.3%; 215 nm, 89.2%).

1-Cyclohexyl-3-methyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Cyclopentyl-(2-piperazin-1-yl-ethyl)-amide (71). Beige amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as free base): δ 7.02 (d, J = 8.2 Hz, 1H), 6.93 (dd, J = 8.2, 1.6 Hz, 1H), 6.89 (d, J = 1.6 Hz, 1H), 4.20−4.02 (m, 2H), 3.35 (dd, J = 6.6, 6.6 Hz, 2H), 3.28 (s, 3H), 3.18−3.00 (m, 4H), 2.88−2.80 (m, 4H), 2.65 (dd, J = 6.6, 6.6 Hz, 2H), 2.12−1.08 (m, 18H). LC/MS m/z = 454.4 $[M + H]^+$ (Luna column; 254 nm, 97.3%; 215 nm, 90.1%).

1-Benzyl-3-propyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Benzyl-(2-piperazin-1-yl-ethyl)-amide (73). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as free base): δ 7.35−7.15 (m, 10H), 7.11 (dd, J = 7.9, 1.5 Hz, 1H), 7.09 (d, J = 1.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 5.05 (s, 2H), 4.70 (s, 2H), 3.85 (dd, J = 7.2, 7.2 Hz, 2H), 3.55 (dd, J = 6.3, 6.3 Hz, 2H), 2.88−2.76 (m, 4H), 2.56 (dd, J = 6.6, 6.6 Hz, 2H), 2.40−2.28 (m, 4H), 1.80−

1.65 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). LC/MS $m/z = 512.3$ $[M + H]^+$ (Luna column; 254 nm, 98.9%; 215 nm, 93.4%).

1-Benzyl-3-propyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Furan-2-ylmethyl-(2-piperazin-1-yl-ethyl)-amide (74). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as free base): δ 7.35 (m, 1H), 7.32−7.20 (m, 5H), 7.18−7.08 (m, 2H), 6.85 (d, $J = 7.9$ Hz, 1H), 6.45−6.40 (m, 1H), 6.32−6.20 (m, 1H), 5.03 (s, 2H), 4.50 (s, 2H), 3.85 (dd, $J = 7.2$, 7.2 Hz, 2H), 3.55 (dd, $J = 6.3$, 6.3 Hz, 2H), 3.20−3.10 (m, 4H), 2.88−2.76 (m, 4H), 2.65 (dd, $J = 6.6$, 6.6 Hz, 2H), 1.85−1.70 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). LC/MS $m/z = 502.3$ $[M + H]^+$ (Luna column; 254 nm, 98.1%; 215 nm, 95.6%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Benzyl-piperidin-4-yl-methylamide (77). Amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as free base): δ 9.38 (s, 1H), 7.38−7.22 (m, 3H), 7.22−7.08 (m, 5H), 4.65 (s, 2H), 4.30−4.10 (m, 1H), 3.50−3.30 (m, 4H), 2.98−2.78 (m, 2H), 2.20−1.12 (m, 15H). LC/MS $m/z = 447.4$ $[M + H]^+$ (Luna column; 254 nm, 99.2%; 215 nm, 96.6%).

1-Cyclohexyl-3-methyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Cyclopentyl-piperidin-4-yl-methylamide (83). Amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 7.90−7.40 (m br, 2H), 7.38−7.08 (m, 3H), 4.40−4.10 (m, 2H), 3.70−3.55 (m, 2H), 3.50 (s, 3H), 3.40−3.30 (m, 2H), 3.20−3.00 (m, 2H), 2.50 (m, 1H), 2.20−1.18 (m, 22H). LC/MS $m/z = 439.3$ $[M + H]^+$ (Luna column; 254 nm, 98.7%; 215 nm, 98.6%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Cyclopentyl-piperidin-4-yl-methylamide (87). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 7.85−7.48 (m br, 2H), 7.40−7.22 (m, 5H), 7.18 (s, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 7.00 (d, $J = 7.5$ Hz, 1H), 5.15 (s, 2H), 4.25−4.08 (m, 1H), 3.95 (t, $J = 7.0$ Hz, 2H), 3.65−3.50 (m, 2H), 3.38−3.27 (m, 2H), 3.12−2.92 (m, 2H), 2.60−2.40 (m, 1H), 2.10−1.35 (m, 14H), 0.95 (t, $J = 7.0$ Hz, 3H). LC/MS $m/z = 475.07$ $[M + H]^+$ (Luna column; 254 nm, 98.8%; 215 nm, 94.5%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid 4-Methoxybenzylpiperidin-4-yl-methylamide (88). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 8.1−7.9 (m br, 1H), 7.40−6.82 (m, 12H), 5.12 (s, 2H), 4.60 (s, 2H), 3.95−3.82 (m, 2H), 3.85 (s, 3H), 3.78−3.50 (m, 2H), 3.50−3.40 (m, 2H), 3.15−2.92 (m, 2H), 2.32−2.10 (m, 1H), 2.05−1.85 (m, 2H), 1.70−1.50 (m, 4H), 0.95 (t, 3H). LC/MS $m/z = 527.09$ $[M + H]^+$ (Luna column; 254 nm, 98.5%; 215 nm, 88.0%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Cyclopentylpiperidin-3-ylmethylamide (91). White amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 10.1−10.0 (s br, 1H), 7.95−7.6 (m br, 1H), 7.45−7.08 (m, 3H), 4.35−4.05 (m, 2H), 3.85−3.70 (m, 1H), 3.55−2.95 (m, 5H), 2.55−2.35 (m, 1H), 2.25−1.15 (m, 22H). LC/MS $m/z = 425.3$ $[M + H]^+$ (Luna column; 254 nm, 97.6%; 215 nm, 97.9%).

1-Cyclohexyl-3-methyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Cyclopentyl-piperidin-3-ylmethylamide (95). White amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 9.8−9.5 (s br, 1H), 8.65−8.40 (s br, 1H), 7.20−7.0 (m, 3H), 4.35−4.10 (m, 2H), 3.85−3.70 (m, 1H), 3.50−3.25 (m, 1H), 3.4 (s, 3H), 3.25−2.80 (m, 4H), 2.20−2.00 (m, 2H), 2.00−1.15 (m, 21H). LC/MS $m/z = 439.09$ $[M + H]^+$ (Luna column; 254 nm, 99.2%; 215 nm, 98.8%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid Furan-2-ylmethylpiperidin-3-ylmethylamide (98). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 8.15−7.95 (s br, 1H), 7.78−7.58 (s br, 1H), 7.45−7.20 (m, 8H), 7.05−6.95 (m, 1H), 6.40−6.15 (m, 2H), 5.1 (s, 2H), 4.58 and 4.50 (ABq, $J = 15.7$ Hz, 2H), 3.93 (t, $J = 7.2$ Hz, 2H), 3.40−2.90 (m, 6H), 2.22−1.35 (m, 7H), 0.95 (t, $J = 7.2$ Hz, 3H). LC/MS $m/z = 487.3$ $[M + H]^+$ (Luna column; 254 nm, 94.3%; 215 nm, 85.5%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (4-Methoxybenzyl)-piperidin-3-ylmethylamide (100). Transparent oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 9.65−9.40 (s br, 1H), 8.60−8.35 (s br, 1H), 7.35−6.75 (m, 12H), 5.05 (s, 2H), 4.63 and 4.45 (ABq, $J = 17.9$ Hz, 2H), 4.1−3.6 (m, 5H), 3.40−2.75 (m, 6H), 2.30−2.10 (m, 1H) 1.92−1.52 (m, 5H), 1.40−1.20 (m, 1H), 0.91 (t, $J = 7.2$ Hz, 3H). LC/MS $m/z = 527.3$ $[M + H]^+$ (Luna column; 254 nm, 93.7%; 215 nm, 80.8%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)benzylamide (101). White amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 10.2 (s br, 1H), 8.4 (s br, 2H), 7.35−6.92 (m, 8H), 4.58 (s, 2H), 4.25−4.08 (m, 1H), 3.6−3.4 (m, 2H), 3.10−2.85 (m, 2H), 2.12−1.60 (m, 9H), 1.45−1.10 (m, 3H). LC/MS $m/z = 407.3$ $[M + H]^+$ (Luna column; 254 nm, 97.6%; 215 nm, 95.6%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)furan-2-ylmethylamide (102). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 10.05 (s br, 1H), 8.2 (s br, 2H), 7.45−7.08 (m, 4H), 6.4−6.1 (m, 2H), 4.50 (s, 2H), 4.30−4.10 (m, 1H), 3.65−3.42 (m, 2H), 3.00−2.80 (m, 2H), 2.12−1.92 (m, 2H), 1.92−1.60 (m, 6H), 1.5−1.10 (m, 4H). LC/MS $m/z = 397.2$ $[M + H]^+$ (Luna column; 254 nm, 93.2%; 215 nm, 90.0%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)cyclopentylamide (103). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 10.12 (s br, 1H), 7.50−7.10 (m, 3H), 4.40−4.22 (m, 1H), 4.20−4.05 (m, 1H), 3.70−3.58 (m, 2H), 3.40−3.15 (m, 2H), 2.25−1.18 (m, 20H). LC/MS $m/z = 385.3$ $[M + H]^+$ (Luna column; 254 nm, 99.1%; 215 nm, 100.0%).

1-Cyclohexyl-2-oxo-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)-(4-methoxybenzyl)amide (104). Brown amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 10.0 (s br, 1H), 8.32 (s br, 2H), 7.60−7.08 (m, 7H), 4.50 (s, 2H), 4.3−4.1 (m, 1H), 3.75 (s, 3H), 3.6−3.4 (m, 2H), 3.10−2.80 (m, 2H), 2.12−1.50 (m, 8H), 1.45−1.05 (m, 4H). LC/MS $m/z = 437.3$ $[M + H]^+$ (Luna column; 254 nm, 93.4%; 215 nm, 85.0%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)benzylamide (109). Pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 8.30 (s br, 2H), 7.42−7.10 (m, 12H), 6.90−6.80 (m, 1H), 5.06 (s, 2H), 4.6 (s, 2H), 3.82−3.52 (m, 4H), 3.10−2.93 (m, 2H), 2.00−1.80 (m, 2H), 1.7−1.5 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H). LC/MS m/z = 457.3 $[M + H]^+$ (Luna column; 254 nm, 100.0%; 215 nm, 100.0%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)furan-2-ylmethylamide (110). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 8.15 (s br, 2H), 7.45−7.20 (m, 8H), 6.92−6.85 (m, 1H), 6.40−6.35 (m, 1H), 6.28−6.20 (m, 1H), 5.08 (s, 2H), 4.5 (s, 2H), 3.9 (t, J = 7.2 Hz, 2H), 3.70−3.60 (m, 2H), 3.05−2.90 (m, 2H), 1.88−1.70 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H). LC/MS m/z = 447.3 $[M + H]^+$ (Luna column; 254 nm, 96.6%; 215 nm, 80.8%).

1-Benzyl-2-oxo-3-propyl-2,3-dihydro-1*H*-benzoimidazole-5-carboxylic Acid (3-Aminopropyl)cyclopentylamide (111). White amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K as trifluoroacetate): δ 8.22 (s br, 2H), 7.38−7.20 (m, 5H), 7.08−6.88 (m, 3H), 5.09 (s, 2H), 4.20−4.00 (m, 1H), 3.9 (t, J = 7.2 Hz, 2H), 3.55−3.42 (m, 2H), 3.15−2.90 (m, 2H), 2.10−1.95 (m, 2H), 1.85−1.30 (m, 10H), 1.00 (t, J = 7.2 Hz, 3H). LC/MS m/z = 435.3 $[M + H]^+$ (Luna column; 254 nm, 98.7%; 215 nm, 96.3%).

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Supporting Information Available. HPLC traces at 215 nm for compounds **65**, **68**, **71**,**73**, **74**, **77**, **83**, **87**, **88**, **91**, **95**, **98**, **100**, **101**, **102**, **103**, **104**, **109**, **110**, and **111** before purification and LC/MS traces at 215 and 254 nm and ^{1}H NMR spectra of the same purified products. This material is available free of charge via the Internet at http://pubs.acs.org.

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