Parallel Synthesis of Tri- and Tetrasubstituted Ureas from Carbamoyl Imidazolium Salts

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Abstract: A method for producing tri- and tetrasubstituted ureas from carbamoyl imidazolium salts is presented. Carbamoyl imidazolium salts are prepared from the reaction of *N,N*'–carbonyldiimidazole (CDI) with secondary amines, followed by alkylation with iodomethane. These stable salts can be stored for extended periods and are effective electrophilic carbamoylation reagents. Primary and secondary amines add to carbamoyl imidazolium salts at room temperature to give tri- and tetrasubstituted ureas in excellent yields. This reaction was used to synthesize ureas using both liquid-liquid extraction and solid-phase extraction (cation exchange) purification techniques. Liquid-liquid extraction affords the product ureas more cleanly than cationic exchange. A series of urea compounds were synthesized using parallel synthesis techniques in high yields and with suitable purity for routine *in vitro* biological tests. These studies validate the utility of carbamoyl imidazolium salts as useful "building blocks" for combinatorial library synthesis.

INTRODUCTION

The combinatorial synthesis of small molecule libraries is now a widely applied technique in the pharmaceutical and agrochemical industries [1]. The synthesis of novel combinatorial libraries is increasingly dependant upon the development of new reactions and scaffold syntheses, as well as the ready availability of combinatorial "building blocks" for attachment to these scaffolds. Combinatorial libraries have largely been synthesized using solid-phase organic synthesis (SPOS), in which the molecules to be synthesized are bound to a polymeric support through a linker [2]. One of the main disadvantages of using SPOS however is that conversion of known solution-phase reactions to efficient solid-supported methods is often difficult and time-consuming. Indeed, incompatibility of reagents and reaction conditions with existing polymer supports often precludes the adaptation of useful synthetic reactions to a SPOS format. Moreover, the additional steps required for attachment and cleavage to polymer supports using SPOS, the expense associated with the resins and linkers, and the challenges in the analysis of polymer-supported compounds, have resulted in solution-phase methods [3] becoming increasingly used for combinatorial library synthesis. Solution-phase approaches often compliment SPOS and in some cases a combination of solution and solid-phase techniques are utilized. Solution-phase methods are most valuable for the parallel synthesis of combinatorial libraries as discrete compounds and also in cases where larger quantities of products (> 50 mg) are required. One of the major advantages of solution-phase methods is that little development is required to optimize reaction conditions of existing chemistry, and the analyses of the intermediates and products is relatively straightforward. A major challenge however in using solution-phase methods is the development of suitable purification protocols for isolation of the products, particularly for high-throughput purposes.

A variety of rapid purification techniques in solution-phase parallel syntheses [4] have proven useful in the production of large numbers of high purity compounds. Liquid-phase polymer-supported synthesis is also a useful tool incorporating the positive aspects of both classical and solid-phase chemistry by providing homogenous reaction conditions and simplified product purification techniques [5,6]. Functionalized polymers have been widely utilized both as reagents and reaction catalysts, as well as for the purification of libraries by solid-phase extraction. Side-products, unreacted reagents and other impurities which are generated from the reaction are sequestered or "scavenged" by forming covalent bonds or acid-base complexes with the functionalized polymer [7]. Additional methods utilized for the purification of compound libraries include high-performance liquid, preparative thin layer and flash chromatographic techniques [8]. Liquid-liquid phase extractions, particularly aqueous extractions, have also been routinely used [9]. Curran and coworkers have developed fluorous-phase extraction techniques to improve separation and purification efficiency [10]. The attractiveness of these methods lie in their convenience and simplicity, facilitating both manual and automated parallel solution-phase syntheses.

Despite the increasing importance of combinatorial chemistry for the synthesis of small-molecule compound libraries, there is nevertheless a critical need for the development of novel scaffolds and reagents for combinatorial functionalizations, and suitable methodology for their application to both solid and solution-phase syntheses. We now report a new class of combinatorial "building block", carbamoyl imidazolium salts (**3**), their application to parallel solution-phase synthesis of ureas, and

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the development of straightforward experimental protocols for product purification.

SYNTHESES OF UREAS

The urea functionality is a key structural element in many biologically active molecules, and is found in numerous pharmaceuticals and agrochemicals [11-13]. Consequently, efficient methods for the combinatorial synthesis of urea containing molecules are of great interest for lead discovery and optimization purposes. There are numerous methods for the synthesis of mono-, di- and tri-substituted ureas, the most significant of which involves reaction of amines with isocyanates. There are many commercially available isocyanates, which act as mono-substituted carbamoylation reagents, and these reagents constitute one of the most important classes of combinatorial "building block". Various strategies for the synthesis of urea derivatives have been reported that are appropriate for automated high-throughput synthesis of ureas in solution. These include the use of polymer-supported reagents [14], synthesis on soluble polymeric supports [15], fluorous scavenging reagents [16], polymer-supported scavenging resins [17], and ion exchange purifications [18].

Unlike unsymmetrical di- and tri-substituted ureas, there are only a few methods for the formation of unsymmetrical tetrasubstituted ureas [19]. The most well established method involves treatment of a carbamoyl chloride with a secondary amine [20]. Carbamoyl chlorides thus act as reactive di-substituted carbamoylation reagents. Unfortunately there are significant drawbacks associated with the use of carbamoyl chlorides for combinatorial purposes. There are relatively few carbamoyl chlorides that are commercially available, and their synthesis requires the use of phosgene. In addition, they are toxic, highly reactive and prone to hydrolysis. These factors have resulted in relatively few cases of their application in combinatorial chemistry. The use of proprietary libraries of carbamoyl chloride "building blocks" is therefore not a convenient option, because of the difficulties associated with their preparation and long-term storage.

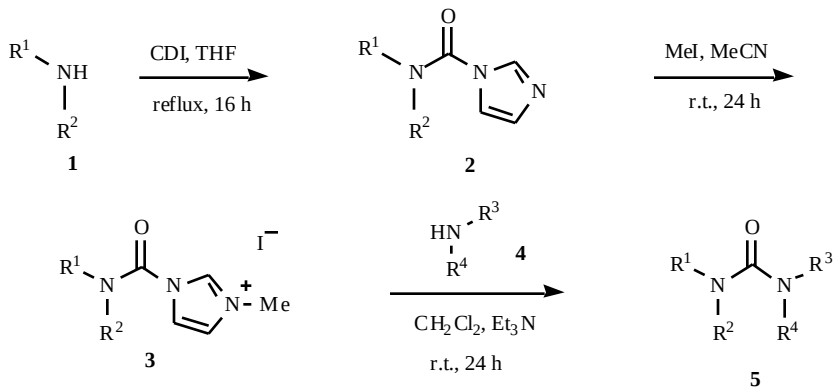
We have developed a much more stable equivalent of carbamoyl chlorides, cationic carbamoyl imidazolium salts **3**, that are readily synthesized from secondary amines **1** and *N*,*N*'-carbonyldiimidazole (CDI) via intermediate carbamoyl imidazoles **2** (Scheme 1). The salts **3** are effective reagents for trapping with a variety of nucleophiles, and can be used for the synthesis of unsymmetrical tri- and tetrasubstituted ureas, as well as carbamates and thiocarbamates [21]. Thus, addition of primary or secondary amines **4** to a solution of the salts **3** in dichloromethane with triethylamine at room temperature affords tri- or tetrasubstituted ureas **5**. Conversion of carbamoyl imidazoles **2** to the corresponding resonance-stabilized carbamoyl imidazolium salts **3**, by *N*-alkylation of the imidazole moiety, significantly increases their reactivity toward nucleophilic attack [21,22]. *N*,*N*'-Carbonyldiimidazole (CDI) the phosgene equivalent used in this synthesis is a commercially available and readily handled crystalline solid [23].

SYNTHESIS OF CARBAMOYL IMIDAZOLES 2 AND CARBAMOYL IMIDAZOLIUM SALTS 3

Stable, isolable carbamoyl imidazoles **2** were produced in high yields after refluxing 1,3,3-trimethyl-6-azobicyclo[3,2,1]octane, *N*-isopropylbenzylamine, tetrahydroisoquinoline, *N*-methylaniline and piperazine-1-carboxylic acid *tert*-butyl ester with CDI in THF for 16 h (Table 1) [24]. Tetrahydroquinoline gave the corresponding product after refluxing for 3 days. Heating of L-proline benzyl ester hydrochloride, 1,4-dioxa-8-aza-spiro[4.5]decane and morpholine with CDI afforded undesirable byproducts, but when stirred at room temperature for 2 days in dichloromethane, cleanly formed the desired carbamoyl imidazoles **2** in high yields, without the need for further purification. The imidazolium salts **3** were obtained in quantitative yield after reaction of **2** with iodomethane in acetonitrile for 24 h at room temperature. Again, imidazolium salts **3** did not require additional purification for the final conversion to the ureas **5**, and in general could be stored for extended periods without detectable decomposition.

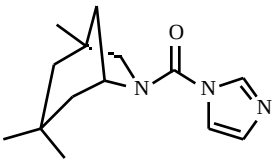
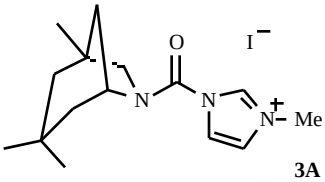
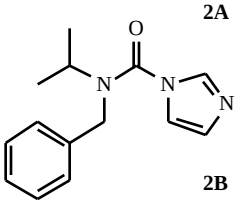
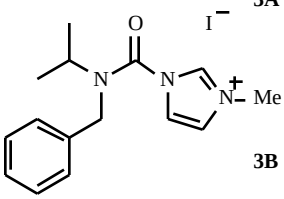
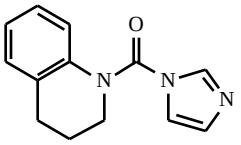
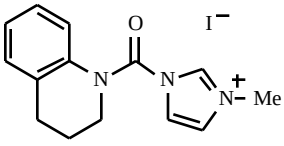
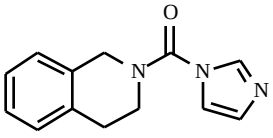
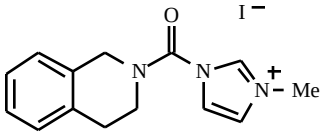
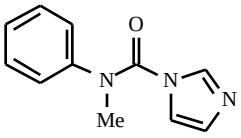
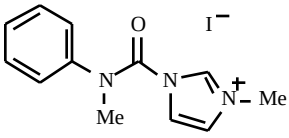
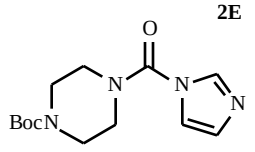
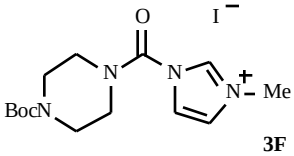
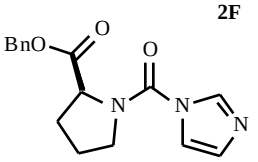
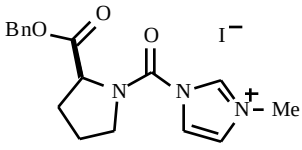
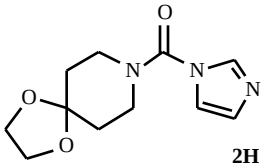
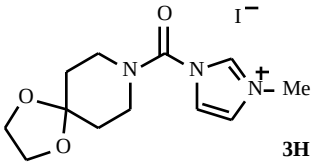
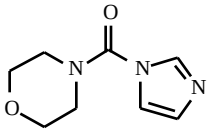
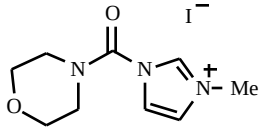
SYNTHESIS OF TRI- AND TETRASUBSTITUTED UREAS 5

Addition of secondary amines **4** to a solution of carbamoyl imidazolium salts **3** in dichloromethane with triethylamine at room temperature affords tetrasubstituted



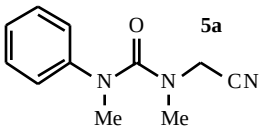
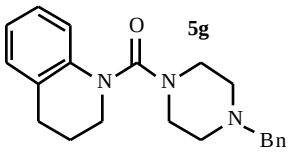
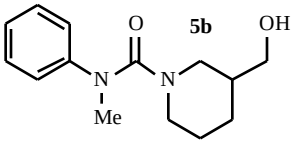
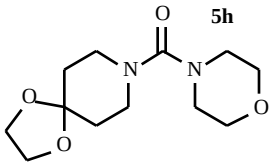
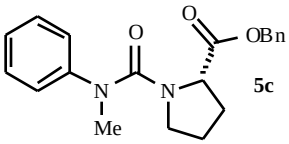
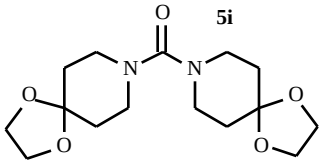
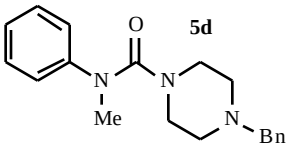
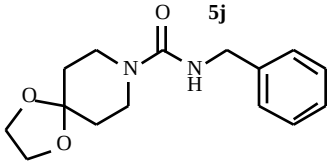
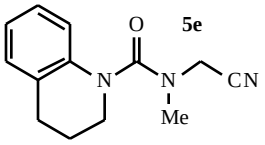
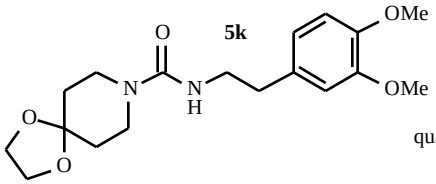
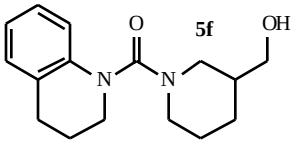
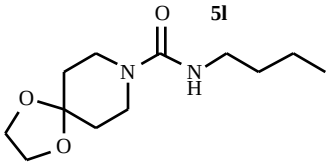
Scheme 1.

Table 1. Carbamoyl Imidazole 2[a] and Carbamoyl Imidazolium Salt 3[b] Formation

Carbamoyl Imidazole 2	Yields of 2[c]	Imidazolium Salt 3	Yields of 3[c]
 **2A**	95%	 **3A**	quant.
 **2B**	92%	 **3B**	quant.
 **2C**	88%	 **3C**	quant.
 **2D**	88%	 **3D**	quant.
 **2E**	87%	 **3E**	quant.
 **2F**	90%	 **3F**	quant.
 **2G**	96%[d]	 **3G**	98%
 **2H**	95%[d]	 **3H**	96%
 **2I**	90%[d]	 **3I**	82%

[a]Secondary amine **1** and CDI in THF were refluxed for 16 h. [b]Carbamoyl imidazole **2** and 4 equiv. of MeI in acetonitrile were stirred for 24 h. [c]Isolated yields without flash chromatography. Compounds were determined to be >95% pure by ^{1}H and ^{13}C NMR. [d]Secondary amine **2** and CDI in dichloromethane were stirred for 2 days.

Table 2. Ureas 5 Synthesized[a] From Carbamoyl Imidazolium Salts 3

Urea	Yield[b]	Urea	Yield[b]
 **5a**	84%	 **5g**	96%
 **5b**	92%	 **5h**	97%
 **5c**	98%	 **5i**	quant.
 **5d**	97%	 **5j**	quant.
 **5e**	85%	 **5k**	quant.
 **5f**	quant.	 **5l**	94%

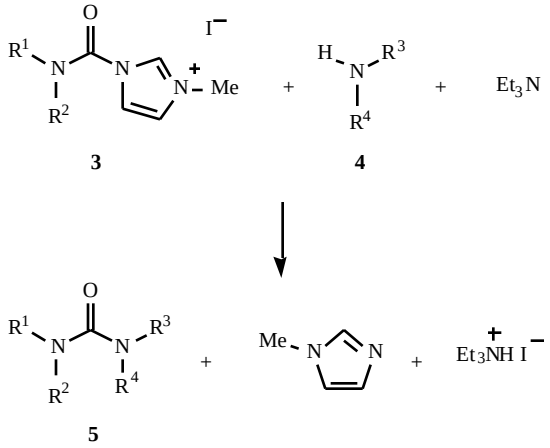
[a]Carbamoyl imidazolium salts **3**, secondary amines (or HCl salts) **4** and triethylamine (1.0 equiv., or 2.0 equiv. for HCl salts) in CH_2Cl_2 were stirred at room temperature for 24 h. Ureas **5a-d** were synthesized from **3E**, **5e-g** from **3C** and **5h-l** from **3H**. [b]Isolated yields after a standard aqueous work-up procedure. Compounds **5** were determined to be >95% pure by ^1H and ^{13}C NMR.

ureas **5a**-**5i** in high yields (Table 2). A wide array of different secondary amines including piperazine, piperidine and L-proline derivatives were successfully reacted, forming the urea products in excellent yields. The addition of the primary amines, benzylamine, 2-(3,4-dimethoxyphenyl)-ethylamine and butylamine to the salts **3** afforded the corresponding trisubstituted ureas **5j**-**5l** (Table 2).

PARALLEL SYNTHESIS OF A UREA LIBRARY USING LIQUID-LIQUID EXTRACTION AND SOLID PHASE EXTRACTION

Planning for solution-phase synthesis of libraries often begins with determining a method for purification of the intermediates and final products. Amongst a number of methods that are routinely used in high-throughput solution-phase syntheses, purification by solid-phase extraction or liquid-liquid extraction offers significant advantages. In the case of the urea synthesis by carbamoyl imidazolium salts, the byproducts of the reaction are *N*-methylimidazole, triethylamine salts, unreacted carbamoyl imidazolium salts and amines (Scheme 2). Since *N*-methylimidazole and the other amines are readily protonated by acid, all the impurities from the reaction are ionizable and dissolve in aqueous solution, while the neutral urea product stays in the organic phase (CH_2Cl_2). Thus, after being treated with 1M hydrochloric acid, the crude reaction mixture was applied to a Bond Elute Reservoir® (Varian) [25], the hydrophobic membrane of which permits separation of the more-dense

CH_2Cl_2 layer from the aqueous layer. A Bond Elute Reservoir® is a plastic syringe barrel, which is made of ultra-clean medical grade polypropylene tubes and packed with 20 micron polyethylene frits. The frits are hydrophobic and allow only the passage of the organic-phase, achieving, in essence, a "hands-off" aqueous extraction. The product containing CH_2Cl_2 phase was then collected and concentrated *in vacuo* (or on smaller scales with evaporation by passage of N_2) to give ureas **5** of high purity, with the impurity-laden aqueous phase remaining in the reservoir. This expedient reaction and purification protocol was used for the synthesis of a urea library *vide infra*.

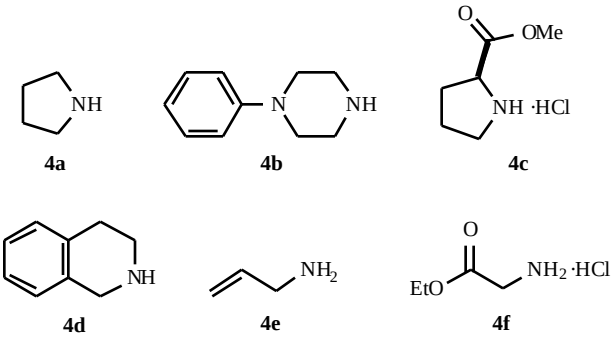


Scheme 2.

Since all the impurities are cationic after treatment with dilute acid, cation exchange chromatography was also used as a purification method. The reaction mixture was mixed with 5% TFA in methanol and poured over a strong cation exchange (SCX - Varian) column [26]. The SCX columns contain a bonded silica support functionalized ethylbenzenesulfonic acid in a disposable syringe barrel preconditioned with methanol. The SCX column was rinsed with methanol to elute the neutral urea product, while the resin retained all of the cationic impurities. In this manner, the products were obtained in high yields. However, the products were often contaminated with HI resulting in discoloration of the products over time, presumably due to iodine formation. No such discoloration was observed in the case of the products obtained using the liquid-liquid extraction method, and this method was thus chosen for the library synthesis.

For the parallel synthesis of ureas, the reactions of carbamoyl imidazolium salts **3** and amines **4** can be completed at room temperature within 24 h in almost all cases (Table 3). As a demonstration, six different amines pyrrolidine **4a**, 1-phenyl-piperidine **4b**, L-proline methyl ester **4c**, tetrahydroisoquinoline **4d**, allylamine **4e** and L-glycine ethyl ester **4f** were coupled with six different carbamoyl imidazolium salts **3A**, **3B**, **3C**, **3D**, **3E**, **3F**, which were derived from 1,3,3-trimethyl-6-azobicyclo[3,2,1]octane, *N*-isopropylbenzylamine, tetrahydroquinoline, tetrahydroisoquinoline, *N*-methylaniline, and piperazine-1-carboxylic acid *tert*-butyl ester respectively. After stirring the reaction mixture at room temperature for 24 hrs, 1M hydrochloric acid was added and mixed with the reaction mixture. The mixture was passed through a hydrophobic membrane (70 ml Bond Elute Reservoir®) and the organic dichloromethane phase collected. The procedure was then repeated to minimize contaminants, providing a matrix of 36 ureas (6 x 6) with suitable purity for routine *in vitro* biological tests. This approach was suitable for relatively large-scale syntheses, with reactions conducted on a 0.25 mmol scale, a factor that allows for broad *in vivo* agrochemical screening.

Table 3. 6x6 Matrix of Reactions Performed on Coupling of Carbamoyl Imidazolium Salts 3A-F with Secondary Amines 4a-f, using Liquid-Liquid Extraction Purification[a,b]



	4a	4b	4c	4d	4e	4f
3A	97% (>95%)[c]	90% (>99%)	89% (>90%)[c]	quant. (81%)	95% (>95%)[c]	86% (>90%)[c]
3B	98% (>90%)[d]	88% (>99%)	91% (>90%)[d]	96% (>95%)[d]	87% (>90%)[d]	85% (95%)
3C	88% (98%)	quant. (99%)	90% (99%)	quant. (97%)	85% (98%)	89% (98%)
3D	93% (86%)	75% (98%)	quant. (86%)	quant. (86%)	90% (83%)	81% (63%)
3E	93% (97%)	92% (99%)	98% (99%)	93% (94%)	90% (89%)	87% (97%)
3F	quant. (>99%)	90% (93%)	quant. (>95%)[c]	89% (93%)	95% (>95%)[c]	95% (>90%)[c]

[a]Entries given using the format: isolated yield (purity). [b]HPLC conditions: Waters millipore 7 x 330 mm column, 90% hexane/10% isopropanol, 20 min. [c]No UV detection, purity determined by 400 MHz NMR. [d]Purity determined by 400 MHz NMR.

CONCLUSION

In summary, liquid-liquid and solid-phase extraction techniques have been used for the rapid purification of ureas synthesized by the reaction of amines with carbamoyl imidazolium salts. The salts are stable and synthetically versatile, reacting with other nucleophiles such as thiols and alcohols. Carbamoyl imidazolium salts act as equivalents to carbamoyl chlorides, which are themselves undesirable electrophiles for combinatorial purposes. We therefore anticipate the adoption of carbamoyl imidazolium salts as a new and general combinatorial "building block" for carbamoylation reactions. These methods are now being used in our laboratories for the synthesis of ureas and other

proprietary compounds of agrochemical and pharmaceutical interest.

EXPERIMENTAL SECTION

General

THF was distilled from sodium metal/benzophenone ketyl under nitrogen. CH_2Cl_2 and CH_3CN were distilled from CaH_2 under nitrogen. All other commercial reagents were used as received (Aldrich, Fischer Scientific Ltd. or BDH). All glassware was flame-dried and allowed to cool under a stream of dry nitrogen. All reactions were carried out under an atmosphere of nitrogen. Melting points are uncorrected. ^1H and ^{13}C NMR were recorded at 400 and 100 MHz respectively on a Varian Unity 400 spectrometer and at 200 and 50 MHz respectively on a Gemini spectrometer. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26) or CD_3OD (δ 3.31) or DMSO-d_6 (δ 2.50). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.2) or CD_3OD (δ 49.0) or DMSO-d_6 (δ 39.5). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates or as KBr discs. Low resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer, and high resolution spectra were recorded on an AEI MS3074 spectrometer. Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates, (Alugram SIL G/UV_{254} purchased from Rose Scientific Limited), visualized with a UV_{254} lamp (Spectroline, Longlife Filter) and stained with 20% phosphomolybdic acid in ethanol. Solvent systems associated with R_f values and chromatography are reported as v/v ratios. HPLC puritites were determined with a Waters millipore 7 x 330 mm column, eluting with 90% hexane/10% isopropanol system at 1 mL/min over 20 min using UV detection at 254 nm.

General procedure for the preparation of carbamoyl imidazoles 2A-2F

To a suspension of *N*,*N*'-carbonyldiimidazole (CDI, 60 mmol) in THF (100 mL) was added amine **1** (55 mmol). The mixture was refluxed for 16 hs before cooling to room temperature. Removal of the solvent under vacuum gave a viscous oil, which was dissolved in CH_2Cl_2 (100 mL) and washed with water (2 x 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the product carbamoyl imidazole **2A-2F**.

Imidazole-1-yl-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone (2A)

White solid; Yield: 95%; mp = 72-75 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.32 (m, 1H), 7.05 (m, 1H), 4.40 (br s, 1H), 3.50 (d, 1H, *J* = 10.5 Hz), 3.33 (d, 1H, *J* = 10.5 Hz), 1.78 (m, 2H), 1.60-1.33 (m, 4H), 1.09 (s, 3H), 0.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 135.7, 123.8, 120.7, 59.7, 51.0, 42.5, 41.0, 40.3, 37.9, 36.1, 31.9, 29.9, 24.4; IR (thin film) 2954, 1693, 1408, 1203, 1102, 1065, 747 cm^{-1}; MS (EI) m/z (rel. intensity) 247 (6), 180 (100), 152 (7), 137 (16), 123 (16), 95 (27), 81 (27); HRMS (EI) m/z calcd (M^+.) 247.1688, found 247.1685.

Imidazole-1-carboxylic acid benzyl-isopropyl-amide (2B)

Foamy yellow oil; Yield: 92%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.38 (m, 2H), 7.31 (m, 3H), 7.21 (s, 1H), 7.04 (s, 1H), 4.58, (s, 2H), 4.16 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 137.2, 136.9, 129.8, 129.1, 127.8, 126.8, 117.8, 51.7, 48.6, 20.6; IR (thin film) 2975, 1690, 1414, 1217, 1069, 1020, 965, 754 cm^{-1}; MS (EI) m/z (rel. intensity) 243 (1), 176 (25), 92 (10), 91 (100), 85 (14), 83 (23), 68 (6), 65 (7), 51 (9); HRMS (EI) m/z calcd (M^+.) 243.1367, found 243.1372.

(3,4-Dihydro-2*H*-quinolin-1-yl)-imidazol-1-yl-methanone (2C)

Yellow solid; Yield: 88%; mp = 71-73 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J* = 1.0 Hz), 7.18 (m, 1H), 7.06 (m, 1H), 6.98 (m, 1H), 6.92 (m, 1H), 6.89 (m, 1H), 6.64 (m, 1H), 3.86 (t, 2H, *J* = 6.5 Hz), 2.82 (t, 2H, *J* = 6.5 Hz), 2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 137.8, 137.5, 131.9, 129.6, 129.1, 127.1, 125.9, 123.2, 118.3, 45.9, 26.7, 24.1; IR (KBr disc.) 3122, 2958, 1691, 1578, 1492, 1396, 1215, 1100, 916 cm^{-1}; MS (EI) m/z (rel. intensity) 227 (46), 160 (94), 142 (13), 132 (100), 117 (11), 77 (17); HRMS (EI) m/z calcd (M^+.) 227.1059, found 227.1051.

(3,4-Dihydro-1*H*-isoquinolin-2-yl)-imidazol-1-yl-methanone (2D)

Yellow solid; Yield: 88%; mp = 82-83 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.26-7.08 (m, 6H), 4.75 (s, 2H), 3.82 (t, 2H, *J* = 6.0 Hz), 3.04 (t, 2H, *J* = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.8, 136.6, 133.4, 131.5, 129.5, 128.6, 127.0, 126.5, 126.0, 117.6, 48.1, 44.2, 28.3; IR (KBr disc.) 3098, 2898, 1681, 1428, 1240, 1162, 1104, 1077, 1052, 933 cm^{-1}; MS (EI) m/z (rel. intensity) 227 (69), 160 (100), 142 (49), 130 (10), 117 (36), 103 (14), 91 (12); HRMS (EI) m/z calcd (M^+.) 227.1061, found 227.1059.

Imidazole-1-carboxylic acid methyl-phenyl-amide (2E): [27]

Yellow solid; Yield: 87%; mp = 62-63 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.38-7.29 (3H, m), 7.11-7.07 (2H, m), 6.81-6.76 (2H, m), 3.45 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.3, 142.0, 136.8, 129.3, 127.9, 127.1, 125.1, 117.7, 39.2; IR (KBr disc.) 3126, 3056, 2949, 1702, 1592, 1492, 1458, 1417, 1385, 1343, 1294, 1262, 1253, 1206, 1118, 1096, 1072, 1044, 1026, 983, 900 cm^{-1}.

4-(Imidazole-1-carbonyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2F)

White solid; Yield: 90%; mp = 108-110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 1H), 7.17 (1H, m), 7.08 (m,

1H), 3.56 (m, 4H), 3.50 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 151.1, 137.1, 130.2, 118.0, 80.9, 46.5, 42.5 (br), 28.5; IR (thin film) 2976, 1692, 1419, 1366, 1240, 1167, 1125, 995 cm^{-1}; MS (EI) m/z (rel. intensity) 280 (12), 224 (29), 223 (15), 207 (20), 157 (35), 113 (36), 112 (16), 95 (10); HRMS (EI) m/z calcd (M^+.) 280.1543, found 280.1535.

Preparation of 1-(imidazole-1-carbonyl)-pyrrolidine-2-carboxylic acid benzyl ester (2G)

To a solution of *N*,*N*'-carbonyldiimidazole (CDI, 0.89 g, 5.5 mmol) in CH_2Cl_2 (15.0 ml) was added L-proline benzyl ester hydrochloride (1.21 g, 5.0 mmol) and triethylamine (0.70 ml, 5.0 mmol). The mixture was stirred for 48 h at room temperature, then washed with water (2 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum to yield **2G** as colorless, viscous oil (1.44 g, 96%) was obtained. Foamy oil; Yield: 96%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.35 (br s, 6H), 7.07 (s, 1H), 5.20 (m, 2H), 4.67 (m, 1H), 3.76 (m, 2H), 2.35 (m, 1H), 2.06 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 149.4, 136.5, 135.1, 129.4, 128.3, 128.1, 127.8, 117.3, 66.8, 60.6, 49.5, 29.1, 24.6; IR (thin film) 3583, 3469, 3122, 2980, 2957, 1746, 1682, 1417, 1171, 1100, 901 cm^{-1}; MS (EI) m/z (rel. intensity) 299 (1), 232 (12), 164 (12), 160 (6), 158 (11), 91 (100), 70 (21); HRMS (EI) m/z calcd (M^+) 299.1270, found 299.1255; $[\alpha]^{23}_D$ –61° (*c* 1.00, CH_2Cl_2).

General procedure for the preparation of carbamoyl imidazoles 2H, 2I

To a solution of *N*,*N*'-carbonyldiimidazole (CDI, 44 mmol) in CH_2Cl_2 (30 mL) cooled in a cold water bath was added amine (40 mmol) dropwise. After the solids dissolved, giving a slightly yellowish clear solution, the water bath was removed. On stirring to a further 1 h, the reaction was diluted with CH_2Cl_2 (20 mL), and quenched with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL), the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield.

2H or 2I.(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-imidazol-1-yl-methanone (2H)

White solid; Yield: 95%; mp = 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.16 (m, 1H), 7.06 (m, 1H), 3.96 (s, 4H), 3.65 (m, 4H), 1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 136.7, 129.5, 117.8, 106.1, 64.4, 44.5, 34.9; IR (thin film) 3112, 2869, 2855, 1700, 1464, 1427, 1361, 1243, 1098, 1026, 913 cm^{-1}; MS (EI) m/z (rel. intensity) 237 (22), 170 (100), 142 (82), 99 (37), 98 (27), 70 (19); HRMS (EI) m/z calcd (M^+.) 237.1113, found 237.1111.

Imidazole-1-yl-morpholine-4-yl-methanone (2I): [28]

White solid; Yield: 90%; mp = 83-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.17 (m, 1H), 7.08 (m, 1H), 3.73 (m, 4H), 3.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 136.4, 129.4, 117.5, 65.9, 46.3.

General procedure for the preparation of carbamoyl imidazolium salts 3

To a solution of carbamoyl imidazole **2** (8.0 mmol) in acetonitrile (15 mL) was added methyl iodide (32 mmol). The mixture was stirred at room temperature for 24 hs. Solvent was removed under vacuum to yield the carbamoyl imidazolium salt

3.1-Methyl-3-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-3*H*-imidazol-1-ium iodide (3A)

White solid; Yield: quant.; mp = 179-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 0.75H), 10.33 (s, 0.25H), 7.78 (m, 0.75H), 7.72 (m, 0.25H), 7.67 (m, 1H), 4.76 (br s, 0.25H), 4.43 (br t, 0.75H, *J* = 4.0 Hz), 4.33-4.30 (m, 3H), 4.15 (d, 1H, *J* = 10.0 Hz), 3.65 (d, 1H, *J* = 10.0 Hz), 2.18 (br d, 1H, *J* = 13.0 Hz), 2.00 (m, 1H), 1.62–1.37 (m, 5H), 1.21 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 136.5, 135.9, 124.3, 124.1, 120.9, 120.7, 95.6, 59.9, 59.0, 51.3, 42.8, 41.3, 40.6, 38.2, 36.4, 32.2, 30.0, 24.7; IR (thin film) 3432, 1722, 1676, 1586, 1537, 1261, 1188, 1093 cm^{-1}; MS (FAB) m/z (rel. intensity) 262 (100), 152 (10), 135 (14), 123 (19), 95 (28), 83 (39); HRMS (FAB) m/z calcd (M^+. - 127) 262.1916, found 262.1919.

3-(Benzyl-isopropyl-carbamoyl)-1-methyl-3*H*-imidazol-1-ium iodide (3B)

Foamy yellow oil; Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (m, 1H), 7.31-7.07 (m, 7H), 4.88 (s, 2H), 4.44 (m, 1H), 4.14 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 136.8, 136.0, 129.3, 128.2, 126.8, 123.7, 120.4, 52.7, 49.2, 37.9, 20.6; MS (FAB) m/z (rel. intensity) 259 (9), 258 (50), 180 (5), 176 (21), 173 (17), 132 (6), 92 (9), 91 (100), 83 (14); HRMS (FAB) m/z calcd (M^+. - 127) 258.1621, found 258.1620.

3-(3,4-Dihydro-2H-quinoline-1-carbonyl)-1-methyl-3*H*-imidazol-1-ium iodide (3C)

Yellow solid; Yield: quant.; mp = 97-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.61 (s, 1H), 7.25-7.22 (m, 2H), 7.15 (m, 1H), 7.08 (m, 1H), 6.95 (d, 1H, *J* = 8.0 Hz), 4.12 (s, 3H), 3.93 (t, 2H, *J* = 6.5 Hz), 2.93 (t, 2H, *J* = 6.5 Hz), 2.11 (m, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 146.4, 138.3, 135.9, 132.2, 129.0, 126.3, 125.9, 123.3, 123.2, 121.2, 46.7, 36.4, 25.7, 22.9; IR (KBr disc.) 3438, 3074, 2937, 1722, 1583, 1535, 1493, 1459, 1356, 1014, 749 cm^{-1}; MS (FAB) m/z (rel. intensity) 242 (100), 160 (40), 154 (83), 138 (29), 137 (52), 136 (61), 132 (14), 120 (12), 107 (23), 91 (12); HRMS (FAB) m/z calcd (M^+. - 127) 242.1293, found 242.1296.

3-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)-1-methyl-3H-imidazol-1-ium iodide (3D)

Yellow solid; Yield: quant.; mp = 166-168 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.63 (br s, 1H), 8.09 (br s, 1H), 7.89 (br s, 1H), 7.22 (br s, 4H), 4.75 (br s, 2H), 3.94 (m, 3H), 3.72 (br s, 2H), 2.96 (br s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 146.8, 137.3, 133.9, 131.5, 128.1, 126.7, 126.4, 126.1, 123.5, 120.8, 47.5 (br), 44.2, 36.5, 27.6; IR (KBr disc.) 3144, 3078, 2968, 1711, 1408, 1354, 1150, 1132, 978 cm^{-1}; MS (FAB) m/z (rel. intensity) 242 (100), 190 (3), 144 (5), 117 (5), 160 (39); HRMS (FAB) m/z calcd ($M^{+\cdot}$ - 127) 242.1293, found 242.1284.

1-Methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (3E)

Yellow solid; Yield: quant.; mp = 95-98 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.55 (br s, 1H), 7.37-7.31 (m, 5H), 7.01 (br s, 1H), 4.02 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 139.7, 137.2, 129.8, 128.3, 125.7, 122.8, 120.2, 40.3, 37.1; IR (thin film) 3457, 3076, 1732, 1594, 1494, 1372, 1271, 1152, 983, 920 cm^{-1}; MS (FAB) m/z (rel. intensity) 217 (20), 216 (100), 154 (14), 136 (11), 107 (6), 93 (7); HRMS (FAB) m/z calcd ($M^{+\cdot}$ - 127) 216.1137, found 216.1130.

3-(4-*tert*-Butoxycarbonyl-piperazine-1-carbonyl)-1-methyl-3*H*-imidazol-1-ium iodide (3F)

White solid; Yield: quant.; mp = 190-195 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.55 (m, 1H), 8.00 (t, 1H, J = 2.0 Hz), 7.86 (t, 1H, J = 2.0 Hz), 3.91 (s, 3H), 3.50-3.46 (m, 8H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 153.7, 146.8, 137.7, 123.7, 121.0, 79.5, 46.0 (br), 42.5 (br), 36.4, 28.1; IR (thin film) 3441, 3050, 1728, 1675, 1462, 1376, 1247, 1171, 1126, 999 cm^{-1}; MS (FAB) m/z (rel. intensity) 295 (1), 213 (15), 157 (5), 128 (20), 113 (12), 83 (14), 82 (100); HRMS (FAB) m/z calcd ($M^{+\cdot}$ - 127) 295.1770, found 295.1761.

3-(2-Benzyloxycarbonyl-pyrrolidine-1-carbonyl)-1-methyl-3*H*-imidazol-1-ium iodide (3G)

Foamy yellow oil; Yield: 98%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.78-7.32 (m, 7H), 5.18 (br s, 2H), 4.70 (br s, 1H), 4.24 (br s, 3H), 4.12-3.93 (m, 2H), 2.49 (br s, 1H), 2.12 (m, 3H,); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 145.1, 136.2, 134.7, 128.3, 128.1, 127.7, 123.9, 120.4, 68.0, 61.5, 51.4, 37.7, 29.9, 25.4; IR (thin film) 3448, 3069, 1728, 1584, 1537, 1407, 1175, 1094 cm^{-1}; MS (FAB) m/z (rel. intensity) 314 (100), 173 (66), 154 (11), 136 (10), 107 (6), 91 (69); HRMS (FAB) m/z calcd ($M^{+\cdot}$ - 127) 314.1505, found 134.1499; $[\alpha]^{23}_D$ -44° (*c* 1.01, CH_2Cl_2).

3-(1,4-Dioxa-8-aza-spiro[4.5]decane-8-carbonyl)-1-methyl-3*H*-imidazol-1-ium iodide (3H)

White solid; Yield: 96%; mp = 169-172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.03 (m, 1H), 7.87 (m, 1H), 3.91 (m, 7H), 3.54 (s, 4H), 1.76 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 137.4, 123.5, 120.9, 105.6, 63.9, 44.4 (br), 36.5, 33.8; IR (KBr disc.) 3078, 2886, 1735, 1573, 1534, 1419, 1369, 1218, 1138, 1092, 1027 cm^{-1}; MS (FAB) m/z (rel. intensity) 252 (100), 185 (63), 170 (83), 142 (75), 126 (10); HRMS (FAB) m/z calcd ($M^{+\cdot}$ - 127) 252.1348, found 252.1355.

1-Methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide (3I)

White solid; Yield: 82%; mp = 165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 3.91 (s, 3H), 3.66 (s, 4H), 3.52 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 137.4, 123.5, 120.9, 65.3, 46.2, 36.5; IR (KBr disc) 3115, 2862, 1718, 1437, 1244, 1145, 1117, 996; MS (FAB) m/z (rel. intensity) 196 (100), 185 (14), 175 (5), 115 (10), 114 (50), 111 (5); HRMS (FAB) m/z calcd ($M^{+\cdot}$ - 127) 196.1086, found 196.1103.

General procedure for the preparation of tri- or tetrasubstituted ureas 5a-5l

To a solution of carbamoyl imidazolium salt **3** (1 mmol) in CH_2Cl_2 (10 mL) was added the primary or secondary amine **4** (1 mmol) and triethylamine (1 mmol). The mixture was stirred at room temperature for 24 hs, then washed with 1.0 N HCl (2 x 5 mL) and brine (5 mL), the organic layer dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield urea **5**.

1-Cyanomethyl-1,3-dimethyl-3-phenyl-urea (5a)

Colorless oil; Yield: 84%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.17 (m, 3H), 4.10 (s, 2H), 3.23 (s, 3H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.6, 145.3, 129.7, 125.5, 124.4, 115.5, 39.9, 38.3, 36.7; IR (thin film) 3496, 2934, 2249, 1654, 1496, 1380, 1124, 699 cm^{-1}; MS (EI) m/z (rel. intensity) 203 (84), 134 (100), 119 (11), 110 (13), 106 (48), 97 (71), 91 (9), 84 (13), 77 (42); HRMS (EI) m/z calcd ($M^{+\cdot}$) 203.1059, found 203.1056.

3-Hydroxymethyl-piperidine-1-carboxylic acid methyl-phenyl-amide (5b)

Yellow oil; Yield: 92%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.29 (m, 2H), 7.14-7.07 (m, 3H), 3.51-3.40 (m, 3H), 3.30-3.22 (m, 4H), 3.09-2.99 (m, 1H), 2.90-2.78 (m, 1H), 2.44 (br s, 1H), 1.67-1.46 (m, 3H), 1.32-1.18 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4, 146.8, 129.3, 124.3, 123.6, 63.9, 48.0, 46.8, 39.4, 37.5, 26.6, 23.5; IR (thin film) 3406, 2933, 2856, 1630, 1596, 1473, 1406, 1267, 1127, 1033 cm^{-1}; MS (EI) m/z (rel. intensity) 248 (86), 217 (13), 190 (22), 160 (5), 142 (100), 134 (39), 124 (7), 114 (12), 107 (88), 106 (54), 98 (27), 88 (56); HRMS (EI) m/z calcd ($M^{+\cdot}$) 248.1525, found 248.1531.

1-(Methyl-phenyl-carbamoyl)-pyrrolidine-2-carboxylic acid benzyl ester (5c)

Yellow oil; Yield: 98%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.08 (m, 10H), 5.20 (m, 2H), 4.56 (t, 1H, *J* = 7.0 Hz), 3.23 (s, 3H), 2.97 (m, 1H), 2.70 (m, 1H), 2.16 (m, 1H), 1.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 159.1, 145.7, 135.8, 129.2, 128.4, 128.0, 125.2, 125.1, 124.8, 66.5, 60.2, 48.8, 39.4, 29.3, 25.2; IR (thin film) 3468, 2975, 2879, 1744, 1643, 1596, 1496, 1387, 1170; MS (EI) m/z (rel. intensity) 338 (37), 203 (100), 197 (11), 134 (96), 120 (10), 106 (34), 91 (83); HRMS (EI) m/z calcd ($M^{+\cdot}$) 338.1630, found 338.1633; $[\alpha]^{23}_D$ +101° (*c* 1.02, $CHCl_3$).

4-Benzyl-piperazine-1-carboxylic acid methyl-phenyl-amide (5d)

White solid; Yield: 97%; mp = 217-219 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61-7.05 (m, 10H), 4.09 (m, 2H), 3.80 (m, 2H), 3.53 (m, 2H), 3.20 (m, 5H), 2.63 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 162.0, 146.9, 132.5, 131.3, 131.0, 130.3, 129.8, 126.9, 125.6, 61.4, 51.9, 43.8, 40.1; IR (KBr disc.) 3061, 3027, 2926, 1664, 1594, 1494, 1395, 1265, 1078 cm^{-1}; MS (EI) m/z (rel. intensity) 309 (48), 262 (6), 218 (10), 203 (28), 177 (25), 159 (27), 146 (54), 134 (100), 106 (27), 91 (96); HRMS (EI) m/z calcd ($M^{+\cdot}$) 309.1841, found 309.1852.

3,4-Dihydro-2H-quinoline-1-carboxylic acid cyanomethyl-methyl-amide (5e)

Yellow oil; Yield: 85%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-7.11 (m, 2H), 7.03-6.95 (m, 2H), 4.18 (s, 2H), 3.64 (t, 2H, *J* = 6.5 Hz), 2.77 (s, 3H), 2.76 (t, 2H, *J* = 6.5 Hz), 1.99 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.7, 139.5, 129.0, 128.8, 126.5, 123.0, 120.0, 115.5, 45.3, 37.9, 36.7, 26.5, 23.4; IR (thin film) 3500, 2947, 2298, 1650, 1605, 1581, 1494, 1380, 1294, 1023 cm^{-1}; MS (EI) m/z (rel. intensity) 229 (100), 201 (6), 160 (68), 132 (87), 117 (19), 103 (7), 97 (68); HRMS (EI) m/z calcd ($M^{+\cdot}$) 229.1215, found 229.1210.

(3,4-Dihydro-2H-quinolin-1-yl)-(3-hydroxymethyl-piperidin-1-yl)-methanone (5f)

Yellow oil; Yield: quant.; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11-7.06 (m, 2H), 6.99-6.87 (m, 2H), 3.73-3.43 (m, 5H), 3.38-3.22 (m, 2H), 3.07-2.95 (m, 1H), 2.81-2.74 (m, 3H), 2.03-1.26 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.4, 140.6, 128.9, 127.3, 126.1, 121.7, 119.5, 63.8, 48.0, 47.0, 45.7, 37.8, 26.8, 26.7, 23.9, 23.3; IR (thin film) 3414, 2930, 2857, 1626, 1579, 1474, 1349, 1258, 1087 cm^{-1}; MS (EI) m/z (rel. intensity) 274 (74), 160 (9), 142 (91), 133 (100), 117 (13), 98 (26), 88 (49); HRMS (EI) m/z calcd ($M^{+\cdot}$) 274.1681, found 274.1672.

(4-Benzyl-piperazin-1-yl)-(3,4-dihydro-2H-quinolin-1-yl)-methanone (5g)

White solid; Yield: 96%; mp = 171-173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55-6.90 (m, 9H), 4.02 (br s, 2H), 3.67-3.57 (m, 6H), 2.88-2.70 (m, 6H), 2.01-1.88 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 139.6, 130.7, 129.6, 129.2, 128.9, 128.7, 128.3, 126.4, 122.7, 119.9, 60.7, 50.9, 45.2, 42.9, 26.5, 23.3; IR (KBr disc.) 2940, 1640, 1578, 1492, 1300, 1260, 1202, 1176 cm^{-1}; MS (EI) m/z (rel. intensity) 335 (15), 203 (26), 160 (22), 146 (24), 132 (37), 91 (100); HRMS (EI) m/z calcd ($M^{+\cdot}$) 335.1998, found 335.1990.

1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl-methanone (5h)

White solid; Yield: 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 4H), 3.64 (m, 4H), 3.29 (m, 4H), 3.19 (m, 4H), 1.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 106.8, 66.3, 64.1, 47.2, 44.4, 34.6; IR (thin film) 2869, 1634, 1476, 1425, 1362, 1241, 1144, 1090 cm^{-1}.

Bis-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-methanone (5i)

White solid; Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 8H), 3.17 (m, 8H), 1.54 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 106.9, 64.0, 44.6, 34.6; IR (KBr pellet) 2983, 1626, 1422, 1216, 1096 cm^{-1}; MS (EI) m/z (rel. intensity) 312 (71), 267 (43), 170 (49), 142 (100), 99 (32), 87 (25); HRMS (EI) m/z calcd ($M^{+\cdot}$) 312.1685, found 312.1680.

1,4-Dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid benzylamide (5j)

White solid; Yield: quant.; mp = 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.77 (m, 1H), 4.40 (d, 2H, *J* = 5.5 Hz), 3.95 (s, 4H), 3.46 (m, 4H), 1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 139.5, 128.3, 127.4, 126.9, 106.8, 64.2, 44.7, 42.0, 34.6; IR (KBr disc.) 3334, 2964, 1682, 1613, 1538, 1215 cm^{-1}.

1,4-Dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid[2-(3,4-dimethoxy-phenyl)-ethyl]-amide (5k): [29]

Yellow oil; Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 1H), 6.63 (m, 2H), 4.76 (t, 1H, *J* = 5.5 Hz), 3.86 (s, 4H), 3.76 (s, 6H), 3.33 (m, 6H), 2.67 (t, 2H, *J* = 7.0 Hz), 1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 148.4, 147.0, 131.6, 120.3, 111.6, 110.9, 106.6, 63.9, 55.4, 55.3, 42.0, 41.6, 35.6, 34.3; IR (KBr pellet) 3334, 2960, 1614, 1515, 1232, 1142, 1030 cm^{-1}.

1,4-Dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid butylamide (5l)

White solid; Yield: 94%; mp = 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (t, 1H, *J* = 5.0 Hz), 3.85 (s, 4H), 3.35 (m, 4H), 3.07 (m, 2H), 1.55 (m, 4H), 1.36 (m, 2H), 1.21 (m, 2H), 0.80 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 106.9, 64.1, 41.9, 40.5, 34.6, 32.2, 19.9, 13.6; IR (KBr disc.) 3286, 2933, 1715, 1622, 1367, 1247, 1147 cm^{-1}; MS (EI) m/z (rel. intensity) 242 (100),

197 (49), 170 (85), 142 (96), 129 (39), 98 (90), 87 (62); HRMS (EI) m/z calcd ($M^{+\cdot}$) 242.1630, found 242.1636.

General procedure for the solid-phase extraction method in the synthesis of ureas

To a solution of carbamoyl imidazolium salt **3** (0.1 mmol) in CH_2Cl_2 (0.5 mL) was added the primary or secondary amine **4** (0.1 mmol) and triethylamine (0.1 mmol). The mixture was stirred at room temperature for 24 hs, then diluted with 5% TFA in methanol solution (0.5 mL). The mixture was mixed and poured into a preconditioned SCX column (i.e. washed with methanol before use). The column was eluted with methanol (2 mL). The solution was collected and concentrated *in vacuo* to give the product

5. General procedure for the liquid-liquid extraction method in the synthesis of ureas

To a solution of carbamoyl imidazolium salt **3** (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added the primary or secondary amine **4** (0.25 mmol) and triethylamine (0.25 mmol). The mixture was stirred at room temperature for 24 hs, then diluted with CH_2Cl_2 (5 mL) and 1N HCl solution (5 mL). The mixture was shaken and poured into a 70 mL Bond Elute Reservoir (Varian). The organic layer was collected while the aqueous layer was left in the reservoir. The organic phase was washed again with 1N HCl and poured into the Bond Elute Reservoir. The product **5** was obtained after concentration.

5Aa

Yield: 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (m, 1H), 3.36-3.27 (m, 4H), 3.21 (d, 1H, *J* = 1.0 Hz), 3.20 (d, 1H, *J* = 1.0 Hz), 1.94 (dt, 1H, *J* = 14.0 Hz, 2.0 Hz), 1.81-1.72 (m, 4H), 1.53 (m, 1H), 1.44 (d, 1H, *J* = 14.0 Hz), 1.32 (dd, 1H, *J* = 14.0 Hz, 1.5 Hz), 1.20 (m, 1H), 1.17 (s, 1H), 1.01 (s, 3H), 1.00 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 58.3, 56.9, 51.8, 48.0, 43.6, 42.4, 39.5, 36.4, 31.1, 29.8, 25.4.

5Ab

Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.91 (m, 2H), 6.86 (m, 1H), 4.22 (m, 1H), 3.40 (m, 4H), 3.28-3.12 (m, 6H), 2.05 (m, 1H), 1.62 (m, 1H), 1.50 (br d, 1H, *J* = 14.0 Hz), 1.40 (m, 1H), 1.26 (m, 2H), 1.06 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 151.1, 129.0, 119.9, 116.1, 58.5, 57.5, 51.5, 49.1, 46.3, 45.9, 43.7, 42.1, 39.5, 36.3, 30.7, 29.7, 25.4; HPLC purity (retention time): 100% (3.48 min).

5Ac

Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55-5.24 (m, 1H), 4.70-4.52 (m, 1H), 3.80-3.69 (m, 5H), 3.61-3.39 (m, 2H), 2.54-2.45 (m, 1H), 2.19-1.82 (m, 5H), 1.61-1.37 (m, 4H), 1.13 (m, 3H), 1.05 (m, 3H), 0.96 (m, 3H).

5Ad

Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.13 (m, 4H), 4.86 (d, 1H, *J* = 15.5 Hz), 4.65 (d, 1H, *J* = 15.5 Hz), 4.52 (m, 1H), 3.80 (m, 2H), 3.50 (s, 2H), 3.07 (m, 2H), 2.09 (m, 1H), 1.86 (m, 1H), 1.57-1.36 (m, 4H), 1.13 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 133.0, 132.2, 128.5, 127.1, 126.6, 126.3, 59.4, 59.3, 51.2, 49.1, 45.7, 43.3, 42.1, 39.8, 36.3, 31.0, 29.8, 28.8, 25.1; HPLC purity (retention time): 81% (3.53 min).

5Ae

Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92-5.83 (m, 1H), 5.26 (d, 1H, *J* = 17.0 Hz), 5.20 (d, 1H, *J* = 10.5 Hz), 4.64 (br m, 1H), 4.11 (br m, 2H), 3.59 (br d, 1H, *J* = 9.0 Hz), 3.32 (d, 1H, *J* = 9.0 Hz), 2.17-1.92 (br m, 1H), 1.81 (br m, 1H), 1.61-1.38 (m, 4H), 1.14 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H); IR (thin film) 3200, 2954, 1637, 1560, 1458, 1200, 917 cm^{-1}.

5Af

Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (br m, 1H), 4.24-4.17 (q, 2H, *J* = 7.0 Hz), 4.10-3.94 (m, 2H), 3.28 (br m, 1H), 3.05 (m, 1H), 1.99-1.88 (br m, 1H), 1.70 (br m, 1H), 1.56-1.38 (m, 2H), 1.30-1.25 (m, 5H), 1.08 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 155.4, 61.4, 56.0, 55.4, 52.0, 44.1, 42.6, 42.1, 36.6, 31.6, 30.1, 29.9, 25.3, 14.4; IR (thin film) 3436, 2956, 1744, 1639, 1523, 1410, 1265, 1193, 1026, 915 cm^{-1}.

5Ba

Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 4.31 (s, 2H), 3.98 (m, 1H), 3.34 (m, 4H), 1.76 (m, 4H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 140.0, 128.3, 126.9, 126.7, 50.1 (br), 48.3, 46.5 (br), 46.0, 25.3, 20.1; IR (thin film) 2973, 2876, 1770, 1634, 1455, 1352, 1173, 964 cm^{-1}.

5Bb

Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.09 (m, 10H), 4.29 (s, 2H), 3.90 (m, 1H), 3.65 (br m, 4H), 3.20 (m, 4H), 1.26 (s, 3H), 1.24 (s, 3H); IR (thin film) 3029, 2972, 2244, 1650, 1495, 1269, 1168, 1015, 910; HPLC purity (retention time): 100% (5.58 min).

5Bc

Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.15 (m, 5H), 4.51-4.43 (m, 2H), 4.13-3.97 (m, 2H), 3.64 (s, 3H), 3.45 (m, 2H), 2.19-1.76 (m, 4H), 1.25-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 162.5, 140.1, 128.2, 127.1, 126.8, 59.9, 51.9, 50.0, 49.4, 45.8, 29.3, 25.4, 20.8, 20.2; IR (thin film) 2967, 1747, 1634, 1400, 1173, 1050 cm^{-1}.

5Bd

Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.06 (m, 9H), 4.44 (s, 2H), 4.34 (s, 2H), 3.90 (m, 1H), 3.53 (d,

2H, *J* = 6.0 Hz), 2.88 (d, 2H, *J* = 6.0 Hz), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 139.9, 134.5, 133.9, 128.7, 128.3, 127.0, 126.5, 126.3, 126.0, 51.0, 48.5, 46.2, 44.8, 28.7, 20.5; IR (thin film) 2970, 1648, 1406, 1250, 1200, 1000, 748 cm^{-1}.

5Be

Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 5.77-5.68 (m, 1H), 4.96-4.87 (m, 2H), 4.68 (m, 1H), 4.33 (s, 2H), 4.28 (br s, 1H), 3.76 (m, 2H), 1.14 (s, 3H), 1.12 (s, 3H).

5Bf

Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.75 (br m, 1H), 4.60 (m, 1H), 4.38 (s, 2H), 4.13 (q, 2H, *J* = 7.0 Hz), 3.92 (d, 2H, *J* = 5.0 Hz), 1.22 (td, 3H, *J* = 7.0 Hz, 0.5 Hz), 1.15 (s, 3H), 1.13 (s, 3H); IR (thin film) 3359, 2979, 1732, 1651, 1538, 1128, 1028, 939, 862 cm^{-1}; HPLC purity (retention time): 95% (6.33 min).

5Ca

Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 1H), 6.93 (m, 2H), 6.86 (m, 1H), 3.59 (t, 2H, *J* = 6.5 Hz), 3.23 (br m, 4H), 2.71 (t, 2H, *J* = 6.5 Hz), 1.94 (m, 2H), 1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 140.4, 128.7, 128.6, 126.3, 121.7, 120.2, 47.8, 44.7, 26.9, 25.3, 23.8; IR (thin film) 2949, 2875, 1648, 1492, 1399, 1295, 1195, 752 cm^{-1}; HPLC purity (retention time): 98% (11.91 min).

5Cb

Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-6.89 (m, 9H), 3.63-3.58 (m, 6H), 3.18 (br m, 4H), 2.74 (t, 2H, *J* = 6.5 Hz), 1.98-1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 140.3, 129.4, 129.0, 128.2, 126.4, 122.5, 120.0, 117.6 (br), 50.5 (br), 45.4, 44.8, 26.8, 23.5; IR (thin film) 2932, 1644, 1599, 1492, 1415, 1232, 999, 753 cm^{-1}; HPLC purity (retention time): 99% (7.42 min).

5Cc

Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 1H), 7.10 (m, 2H), 6.90 (m, 1H), 4.56 (t, 1H, *J* = 7.5 Hz), 3.81-3.69 (m, 4H), 3.42-3.36 (m, 1H), 3.12-3.02 (m, 2H), 2.75-2.62 (m, 2H), 2.24 (m, 1H), 2.00 (m, 1H), 1.88-1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 158.3, 140.1, 129.2, 128.3, 126.4, 122.13, 120.8, 59.8, 51.9, 48.9, 44.8, 29.5, 26.8, 25.1, 23.8; IR (thin film) 2951, 2880, 1745, 1640, 1579, 1495, 1403, 1174, 1026 cm^{-1}; HPLC purity (retention time): 97% (13.12 min).

5Cd

Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 4H), 7.06-7.00 (m, 3H), 6.93-6.89 (m, 1H), 4.44 (s, 2H), 3.63 (t, 2H, *J* = 6.0 Hz), 3.55 (t, 2H, *J* = 6.0 Hz), 2.83 (t, 2H, *J* = 6.0 Hz), 2.78 (t, 2H, *J* = 6.5 Hz), 2.00-1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 140.6, 134.5, 133.4, 129.0, 128.6, 127.9,126.4, 126.4, 126.2, 126.1, 121.9, 119.7, 47.9, 45.4, 43.5, 28.4, 26.9, 23.5; HPLC purity (retention time): 97% (5.48 min).

5Ce

Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.12 (m, 4H), 5.84 (m, 1H), 5.18 (m, 2H), 3.92 (d, 2H, *J* = 5.0 Hz), 3.81 (t, 2H, *J* = 6.0 Hz), 2.73 (t, 2H, *J* = 6.5 Hz), 2.01-1.88 (m, 2H); IR (thin film) 3325, 2947, 1654, 1512, 1321, 1202, 912 cm^{-1}; HPLC purity (retention time): 97% (8.34 min).

5Cf

Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 1H), 7.26-7.14 (m, 2H), 7.06 (m, 1H), 5.67 (br m, 1H), 4.20 (q, 2H, *J* = 7.0 Hz), 4.05 (d, 2H, *J* = 5.5 Hz), 3.78 (t, 2H, *J* = 6.0 Hz), 2.77 (t, 2H, *J* = 6.5 Hz), 1.94 (m, 2H), 1.29 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.5, 139.1, 132.6, 129.7, 126.9, 124.7, 123.4, 61.5, 43.7, 42.9, 27.2, 24.1, 14.4; IR (thin film) 3385, 2983, 1751, 1643, 1507, 1395, 1195, 1034 cm^{-1}; HPLC purity (retention time): 98% (5.62 min).

5Da

Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.06 (m, 5H), 4.45 (s, 2H), 3.52 (t, 2H, *J* = 6.0 Hz), 3.41 (m, 4H), 2.89 (t, 2H, *J* = 6.0 Hz), 1.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 134.7, 133.8, 128.7, 126.4, 126.3, 126.1, 48.4, 48.1, 44.0, 28.8, 25.4; IR (thin film) 2971, 2875, 1774, 1634, 1418, 1306, 1173, 934 cm^{-1}; HPLC purity (retention time): 86% (13.20 min).

5Db

Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.24-7.14 (m, 3H), 7.10 (m, 1H), 6.97 (d, 2H, *J* = 8.0 Hz), 6.92 (t, 1H, *J* = 7.5 Hz), 4.49 (s, 2H), 3.56 (t, 2H, *J* = 6.0 Hz), 3.50-3.48 (m, 4H), 3.23-3.20 (m, 4H), 2.93 (t, 2H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.6, 134.5, 133.6, 129.2, 128.8, 126.5, 126.2, 126.1, 120.8, 116.6, 49.5, 48.7, 46.5, 44.5, 28.5; IR (thin film) 2842, 1643, 1600, 1416, 1228, 930 cm^{-1}; HPLC purity (retention time): 98% (6.40 min).

5Dc

Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.07 (m, 4H), 4.54 (t, 1H, *J* = 7.0 Hz), 4.45 (m, 2H), 3.68 (s, 3H), 3.63-3.47 (m, 4H), 2.93-2.84 (m, 2H), 2.22 (m, 1H), 2.02 (m, 1H), 1.89-1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 162.0, 134.6, 133.7, 128.6, 126.3, 126.2, 126.0, 60.0, 51.9, 49.5, 47.9, 44.0, 29.4, 28.8, 25.3; IR (thin film) 2949, 1740, 1636, 1419, 1173, 950, 749 cm^{-1}; HPLC purity (retention time): 86% (7.47 min).

5Dd

Yield: quant.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.08 (m, 8H), 4.49 (s, 4H), 3.55 (t, 4H, *J* = 6.0 Hz), 2.95 (t, 2H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 134.5, 133.7, 128.8, 126.4, 126.2, 126.0, 48.7, 44.6, 28.6; IR

(thin film) 2926, 1635, 1456, 1419, 1369, 1237, 1109, 931 cm^{-1}; HPLC purity (retention time): 86% (6.43 min).

5De

Yield: 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.11 (m, 4H), 5.95-5.87 (m, 1H), 5.22-5.10 (m, 2H), 4.61 (br m, 1H), 4.56 (s, 2H), 3.92 (m, 2H), 3.63 (t, 2H, *J* = 6.0 Hz), 2.88 (t, 2H, *J* = 6.0 Hz); IR (thin film) 3332, 2921, 1628, 1534, 1400, 1257, 988, 911 cm^{-1}; HPLC purity (retention time): 83% (8.87 min).

5Df

Yield: 81%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.15 (m, 4H), 5.08 (br m, 1H), 4.59 (s, 2H), 4.22 (q, 2H, *J* = 7.0 Hz), 4.06 (d, 2H, *J* = 5.0 Hz), 3.66 (t, 2H, *J* = 6.0 Hz), 2.89 (t, 2H, *J* = 6.0 Hz), 1.30 (t, 3H, *J* = 7.0 Hz); IR (thin film) 3281, 3016, 1698, 1603, 1531, 1393, 1216, 1148, 1082, 754 cm^{-1}; HPLC purity (retention time): 63% (8.43 min).

5Ea

Yield: 93%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (m, 5H), 3.60 (s, 3H), 3.30 (br m, 4H), 1.82 (m, 4H); IR (thin film) 3315, 2973, 1621, 1591, 1494, 1454, 1353, 1219, 918 cm^{-1}; HPLC purity (retention time): 97% (5.85 min).

5Eb

Yield: 92%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.12 (m, 10H), 3.51 (br m, 4H), 3.26 (s, 3H), 3.07 (br m, 4H); HPLC purity (retention time): 99% (4.28 min).

5Ec

Yield: 98%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.22 (m, 5H), 4.71 (m, 1H), 3.76 (s, 3H), 3.36 (s, 3H), 3.03 (m, 1H), 2.62 (m, 1H), 2.24 (m, 1H), 1.81-1.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 158.9, 135.6, 129.1, 125.0, 124.6, 59.9, 51.7, 48.6, 29.2, 29.1, 25.1; IR (thin film) 2952, 1746, 1600, 1495, 1400, 1176, 915 cm^{-1}; HPLC purity (retention time): 98% (6.08 min).

5Ed

Yield: 93%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-6.91 (m, 9H), 4.41 (s, 2H), 3.57 (t, 2H, *J* = 6.0 Hz), 3.51 (s, 3H), 2.71 (t, 2H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 146.6, 134.5, 133.5, 129.3, 128.4, 126.1, 126.0, 125.8, 124.4, 123.8, 47.6, 43.5, 39.5, 28.2; IR (thin film) 2928, 1594, 1493, 1440, 1403, 1259, 1113, 928 cm^{-1}; HPLC purity (retention time): 94% (5.86 min).

5Ee

Yield: 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.26 (m, 5H), 5.80 (m, 1H), 5.15-5.10 (m, 2H), 3.90 (br d, 2H), 3.39 (s, 3H); IR (thin film) 3269, 2933, 1621, 1592, 1496, 1339, 1195, 989 cm^{-1}; HPLC purity (retention time): 89% (8.45 min).

5Ef

Yield: 87%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 5H), 4.80 (br t, 1H), 4.18 (q, 2H, *J* = 7.0 Hz), 3.95 (d, 2H, *J* = 5.5 Hz), 3.29 (s, 3H), 1.26 (t, 3H, *J* = 7.0 Hz); IR (thin film) 3432, 3015, 1740, 1654, 1517, 1379, 1216, 1025, 756 cm^{-1}; HPLC purity (retention time): 97% (6.82 min).

5Fa

Yield: quant.; ^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (m, 4H), 3.34 (m, 4H), 3.20 (m, 4H), 1.80 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 154.8, 79.9, 48.3, 45.9, 42.0 (br), 28.3, 25.5.

5Fb

Yield: 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.03 (m, 2H), 6.97-6.89 (m, 1H), 3.48 (m, 4H), 3.42 (m, 4H), 3.25-3.18 (m, 8H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.6, 149.6, 129.3, 121.8, 117.1, 80.0, 49.9, 46.5, 46.2, 43.0 (br), 28.3; HPLC purity (retention time): 93% (13.18 min).

5Fc

Yield: quant.; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (m, 1H), 3.66 (s, 3H), 3.47-3.17 (m, 10H), 2.21 (m, 1H), 1.98 (m, 1H), 1.84-1.78 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 161.8, 154.7, 80.0, 60.0, 52.0, 49.8, 45.9, 46.0 (br), 29.4, 28.3, 25.4; IR (thin film) 2978, 1747, 1698, 1417, 1366, 1172, 998 cm^{-1}.

5Fd

Yield: 89%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.06 (m, 4H), 4.43 (s, 2H), 3.50 (t, 2H, *J* = 6.0 Hz), 3.43 (m, 4H), 3.23 (m, 4H), 2.89 (t, 2H, *J* = 6.0 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 154.7, 134.5, 133.5, 128.9, 126.5, 126.2, 126.1, 48.7, 44.5, 43.5 (br), 28.5, 28.3; IR (thin film) 3005, 2929, 1693, 1643, 1366, 1238, 1169, 997 cm^{-1}; HPLC purity (retention time): 93% (9.36 min).

5Fe

Yield: 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94-5.84 (m, 1H), 5.30-5.11 (m, 2H), 4.47 (br m, 1H), 3.89-3.83 (m, 2H), 3.45-3.23 (m, 8H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.8, 135.6, 116.1, 80.3, 43.6, 43.5 (br), 28.5; IR (thin film) 3361, 2981, 1685, 1534, 1420, 1245, 1168, 1125 cm^{-1}.

5Ff

Yield: 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (br s, 1H), 4.23 (q, 2H, *J* = 7.1 Hz), 4.00 (m, 2H), 3.45-3.37 (m, 8H), 1.46 (s, 9H), 1.29 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 157.1, 154.6, 80.3, 61.6, 43.8 (br), 43.0, 28.6, 14.4; IR (thin film) 3404, 2982, 1740, 1684, 1522, 1419, 1206, 1168 cm^{-1}.

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ABBREVIATIONS

CDI	=	*N*,*N*'-carbonyldiimidazole
SPOS	=	Solid-Phase Organic Synthesis
SCX	=	Strong Cation Exchange
Boc	=	*N-tert* butoxycarbonyl

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