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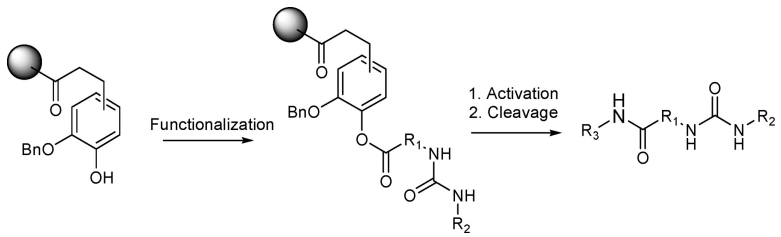

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A Versatile Synthetic Approach to Peptidyl Privileged Structures Using a "Safety-Catch" Linker

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Peptidyl privileged structures have been widely used by many groups to discover biologically active molecules. In this context, privileged substructures are used as "hydrophobic anchors", to which peptide functionality is appended to gain specificity. Utilization of this concept has led to the discovery of many different active compounds at a wide range of biological receptors. A synthetic approach to these compounds has been developed on a "safety-catch" linker that allows rapid preparation of large libraries of these molecules. Importantly, amide bond formation/cleavage through treatment with amines is the final step; it is a linker strategy that allows significant diversification to be easily incorporated, and it only requires the inclusion of an amide bond. In addition, chemistry has been developed that permits the urea moiety to be inserted at the *N*-terminus of the peptide, allowing the same set of amines (either privileged substructures or amino acid analogues) to be used at both the *N*- and *C*-termini of the molecule. To show the robustness of this approach, a small library of peptidyl privileged structures were synthesized, illustrating that large combinatorial libraries can be synthesized using these technologies.

Introduction

The recent rapid advances in proteomic and genomic technologies are uncovering an increasing number of potentially new targets for drug design and development. These discoveries are placing an increasing burden on chemists to discover new compounds that modulate these targets, for the purposes of both target validation and the discovery of potential new drugs. From empirical observations, it is evident that the use of privileged substructures (a single molecular framework able to provide ligands for diverse receptors)[1−3] is a powerful tool for discovering compounds with good affinity. One such example is the spiropiperidine−indane core that has yielded a wide range of diverse potent compounds against different receptor targets,[2] including growth hormone secretagogues,[4] neurokinin antagonists,[5] somatostatin-2 receptor agonists,[6,7] C5a partial agonists,[8] and melanocortin-4 receptor agonists[9] (see Figure 1). Molecules of this type have been labeled peptidyl privileged structures.[2]

It has been suggested that privileged substructures, or components of them, show such broad binding characteristics as they bind to conserved regions in different G-protein coupled receptors.[10] Privileged substructures have been described as "hydrophobic anchors",[4,11,12] to which peptide functionality may be appended to gain specificity, or a "design in which a privileged structure anchor is derivatized with dipeptides or capped amino acids".[2] As a result, they are a promising means to develop diverse libraries by attachment of a wide variety of natural and unnatural amino acids.[13] Combinatorial libraries utilizing these moieties are very attractive for lead compound development, and privileged substructures have been extensively reviewed.[2,3,14−17] Exploitation of peptidyl privileged structures has led to the discovery of many different active compounds[2] and some clinical candidates[4] at a wide range of biological receptors.

The objective of this work was the development of methodologies for the rapid combinatorial synthesis of this broad structural class of compounds. Existing linkers that may be suitable for this approach fall mainly into two classes: the active-ester linkers and the "safety-catch" linkers.[18] "Safety-catch" linkers are masked active-ester linkers that are stable but can be chemically modified (unmasked) to render them susceptible to cleavage. Although conceptually very attractive, the chemical requirements are high and only a few examples have been reported, such as the acylsulfonamide linker, which is known as Kenner's "safety-catch" linker[19] and Marshall's sulfone linker.[20,21] Both utilize additional chemical reagents to activate the linker (by alkylation or oxidation, respectively) that, given the diverse functionalities of amino acids, may potentially cause side reactions. Therefore, we decided upon a "safety-catch" linker that activates upon simple deprotection. The "safety-catch"

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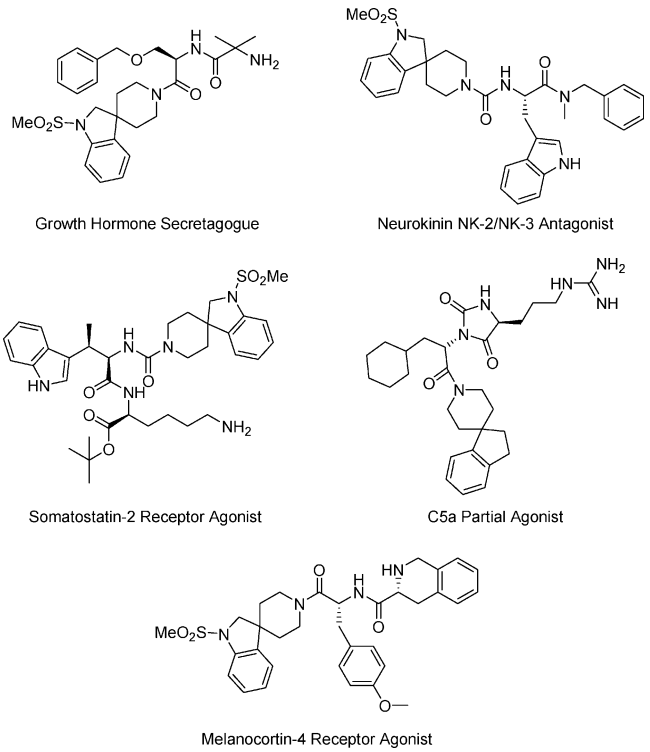


Figure 1. Peptidyl privileged structures containing the spiro-piperidine−indane moiety.

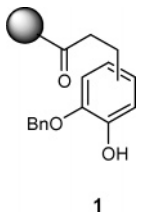


Figure 2. "Safety-Catch" linker (from the work of Bourne and co-workers[22,23]).

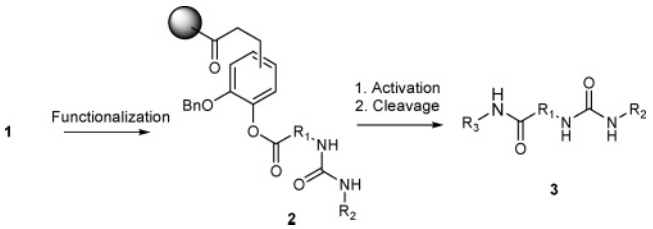
linker first reported by Bourne et al. (see Figure 2) satisfies this criteria.[22,23] This linker, which is a mixture of 3-(3-benzyloxy-4-hydroxyphenyl)propionic acid and 3-(4-benzyloxy-3-hydroxyphenyl)propionic acid (**1**), has been exploited for the synthesis of large numbers of cyclic peptide libraries.[24] However, the introduction of amide bond replacements that are orthologous to this chemistry has not been reported.

Results and Discussion

The compounds selected for synthesis were to be based on **3** (see Scheme 1), containing both an amide bond and a urea moiety. These compounds could be accessed through acylation of the "safety-catch" linker (**1**) with natural or unnatural amino acids. After removal of the protecting group on the amino functionality, a urea moiety is readily produced, to yield **2**. Activation of the linker with either hydrofluoric acid or trifluoromethanesulfonic acid to remove the catechol benzyl protecting group, followed by amine cleavage of the activated ester, should then readily yield **3**.

Privileged substructures attached to amino acids via urea functionality are found in a large number of biologically

Scheme 1. Strategy for Library Synthesis



active molecules,[2] including somatostatin agonists,[6,7,25] growth hormone secretagogues,[26] neurokinin antagonists,[5] and CGRP antagonists.[27] The choice of the urea moiety provides the capacity of attaching amines (privileged substructures or amino acid analogues) at both the *N*- and *C*-termini of the molecule, thus allowing the incorporation of these privileged substructure "hydrophobic anchors" at either one or both ends of a peptide. Most importantly, the chemistry allows a very rapid synthesis of these compounds in a combinatorial manner, and the final amine cleavage allows much diversification to occur at the final step.

Development and Optimization. The initial aim of this work was to be able to incorporate the urea moiety readily, in a fashion that is orthologous with the chemical requirements of the "safety-catch" linker. Two main strategies were applicable for urea formation on the solid-phase: activation of the amine (to moieties such as isocyanates and carbamates) on resin, followed by amine addition or prior activation of an amine in solution and addition to an amine on resin.

For ease of synthesis, the former strategy seemed to be the most attractive. This allowed all synthetic transformations to be conducted on-resin and minimized reaction workup. Initial attempts revealed that one of the main problems with urea formation on resin was competing hydantoin formation. For example, all attempts to synthesize peptide ureas through formation of the isocyanate on resin led to the exclusive formation of hydantoins, which is a discovery that was reported previously by Xiao et al. and others[28,29] (see Figure 3). Xiao et al. also reported a solution to this problem.[28] By reducing the reactivity of the isocyanate/active carbamate through the use of a phenyl carbamate, it is possible to effectively prevent the formation of hydantoins, using either 1,4-dioxane or tetrahydrofuran (THF) as the solvent for the reaction.

Although this strategy is appropriate for the formation of ureas in systems that are resistant to amines (0.5 M solutions of amines in DMF were used to convert the phenyl carbamate to the urea), it was not appropriate for use on the "safety-

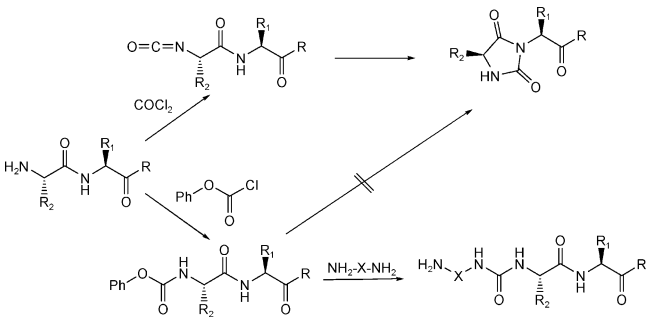


Figure 3. Synthesis of peptidyl ureas on the solid phase.

catch" linker. We found that excessive use of nucleophilic amines caused some premature cleavage of the peptidyl unit from resin, subsequently reducing the overall yields.

As a result, it was decided to synthesize the urea via the reaction of an activated amine with the unprotected amino group on resin. The first experiments to test this involved the synthesis of the isocyanate of mono-Boc-protected ethylenediamine and the addition of this with 12 equiv DIEA in DCM to the test system (Tyr(tBu)-Arg(Pbf)-Phe-TCP resin). These experiments were unsuccessful. Subsequent attempts with different solvents, such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), toluene, and THF, yielded the product in quantitative yield. All peptide coupling reactions were accomplished in DMF; therefore, it was the preferred solvent for further experiments.

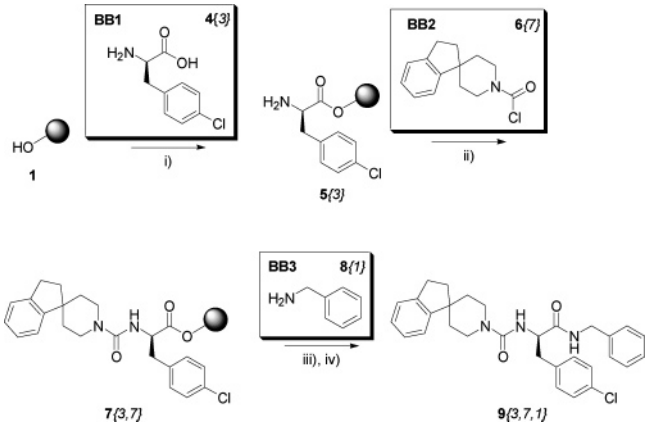
Mono-Boc-protected ethylenediamine was then functionalized to form the phenyl carbamate, the *p*-nitrophenylcarbamate, and the isocyanate (the isocyanate was always made immediately prior to urea formation). Time course experiments were then conducted with these products on the same solid-phase test system as used previously. The reaction of the *p*-nitrophenyl carbamate of Boc-ethylenediamine proceeds the fastest, and this reaction is 97% complete after 10 min (5 equiv carbamate, 4.5 equiv DIEA). In comparison, the isocyanate reaction requires at least 20 min to reach completion (3.8 equiv isocyanate, 36 equiv DIEA). The reaction of the phenyl carbamate of Boc-ethylenediamine with resin was complete after 15 h (5 equiv carbamate, 4.5 equiv DIEA).

As a result, the *p*-nitrophenyl carbamate method seemed to be the most effective for synthesis, because of the fast reaction times and because the *p*-nitrophenylcarbamate complex is a stable solid compound. However, in our hands, the *p*-nitrophenylcarbamate of mono-Boc piperazine showed no detectable reaction with amines, either on-resin or in solution. Although there have been reports of urea formation with *p*-nitrophenylcarbamate piperazine derivatives,[30,31] elevated temperatures are often required.[31] Presumably, this lack of reactivity is due to steric considerations, because the corresponding experiments with the chloroformamide of mono-Boc piperazine provided the desired product in good yields. As a result, the use of phosgene to generate the chloroformamide seemed to be the most generic synthetic route to urea formation, and this strategy was used for library synthesis.

Library Synthesis. In an attempt to illustrate the versatility of the "safety-catch" linker, a combinatorial library of peptidyl privileged structures was synthesized. A divergent synthesis was selected for this library, to maximize diversity in the minimum number of chemical steps.

After attachment of the "safety-catch" linker on aminomethylated polystyrene resin (**1**, Scheme 2), standard sequential solid-phase peptide synthesis was conducted (using Boc-protected amino acids) to add the first building block (Figure 4) (**4**). After removal of the *N*-terminal Boc-protecting group (**5**), the resin was dried down, divided, and then re-swollen in DMF. The addition of an isocyanate or a formamide chloride (**6**, building block 2, Figure 4) to the resin in the presence of a large excess of DIEA (11 equiv)

Scheme 2. Synthesis of Library Members[a]



[a] Reagents and conditions are as follows: (i) **4**{*3*} (BB1, Figure 4), synthesized using standard sequential Boc-protected SPPS; (ii) 3 equiv **6**{*7*} (BB2, Figure 4), 11 equiv DIEA, DMF, 45 min; (iii) 10 mL 9:0.5:0.5 HF/*p*-cresol/*p*-thiocresol for 1 h at 0 °C; and (iv) 8 equiv **8**{*1*} (BB3, Figure 4), DMF, 2d.

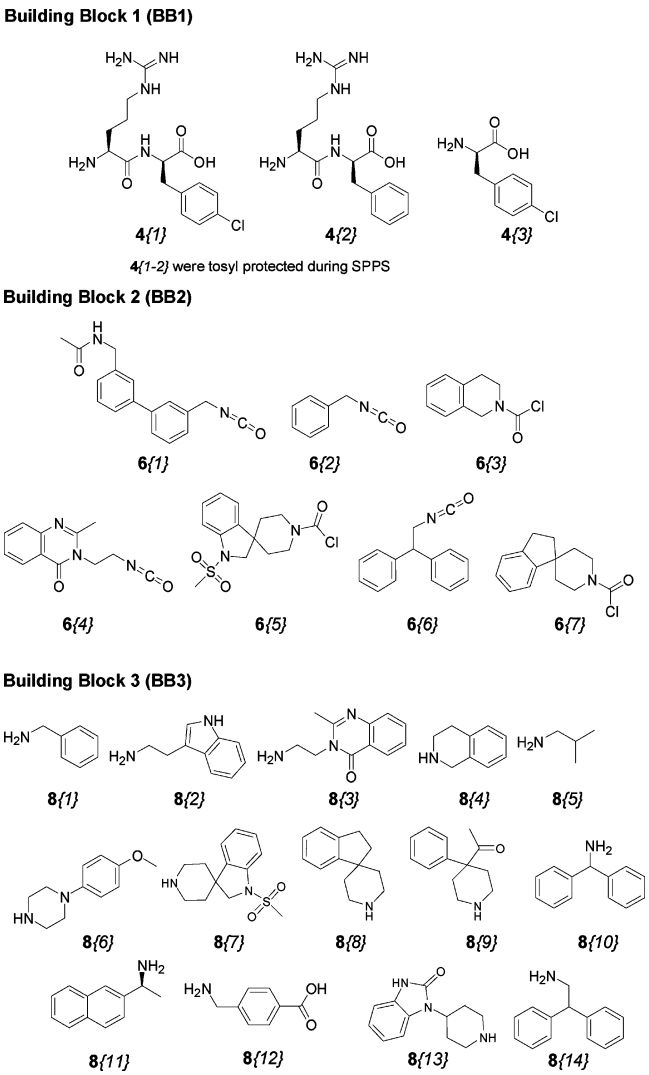
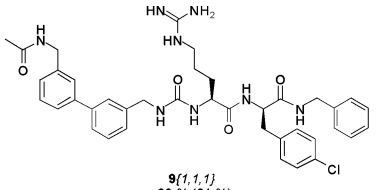


Figure 4. Library building blocks.

for 45 min yielded **7**. A shorter reaction time was necessary at this step, to minimize potential cleavage from resin, because of the basic conditions. The resin was then dried down and deprotected with 9:0.5:0.5 HF/*p*-cresol/*p*-thiocresol for 1 h at 0 °C. The more time-consuming resin treatment



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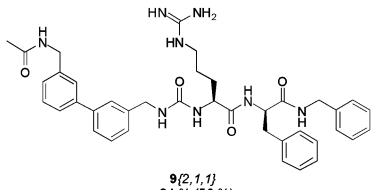

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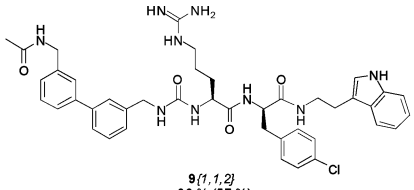
24 % (59 %)



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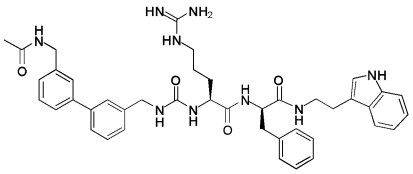

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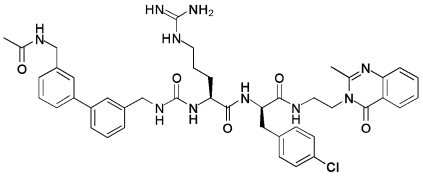

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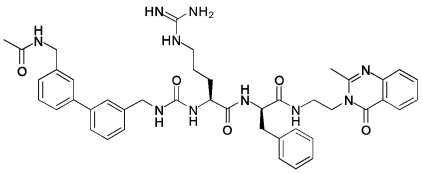

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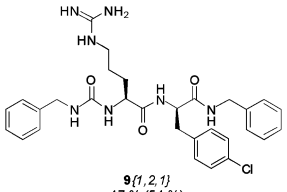

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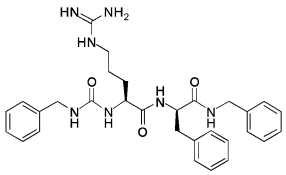

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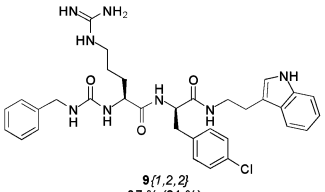

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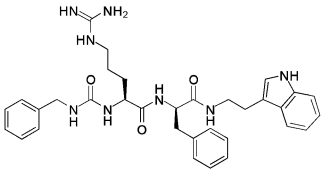

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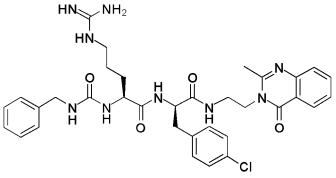
29 % (70 %)



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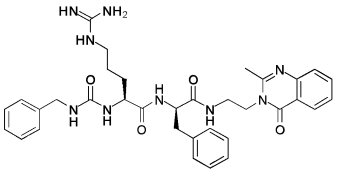
62 % (77 %)



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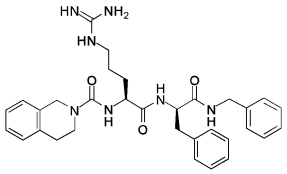
55 % (68 %)



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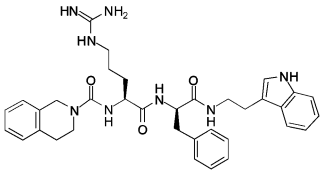

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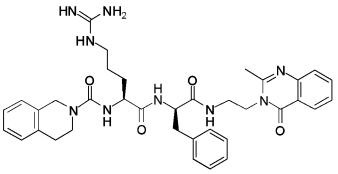

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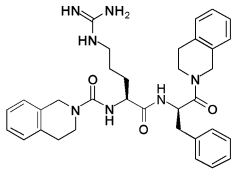

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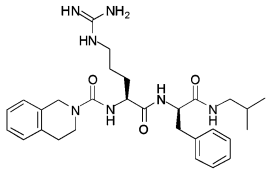

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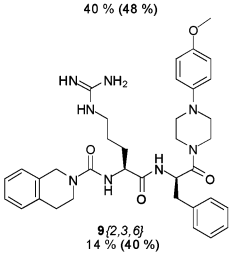
27 % (28 %)



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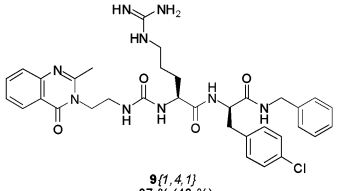

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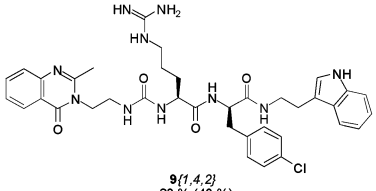
37 % (48 %)



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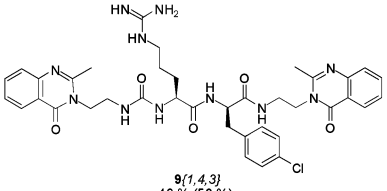

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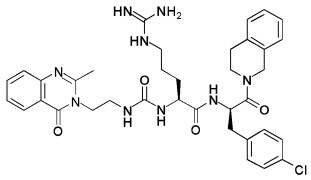

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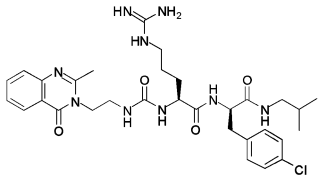

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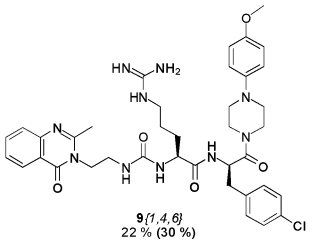

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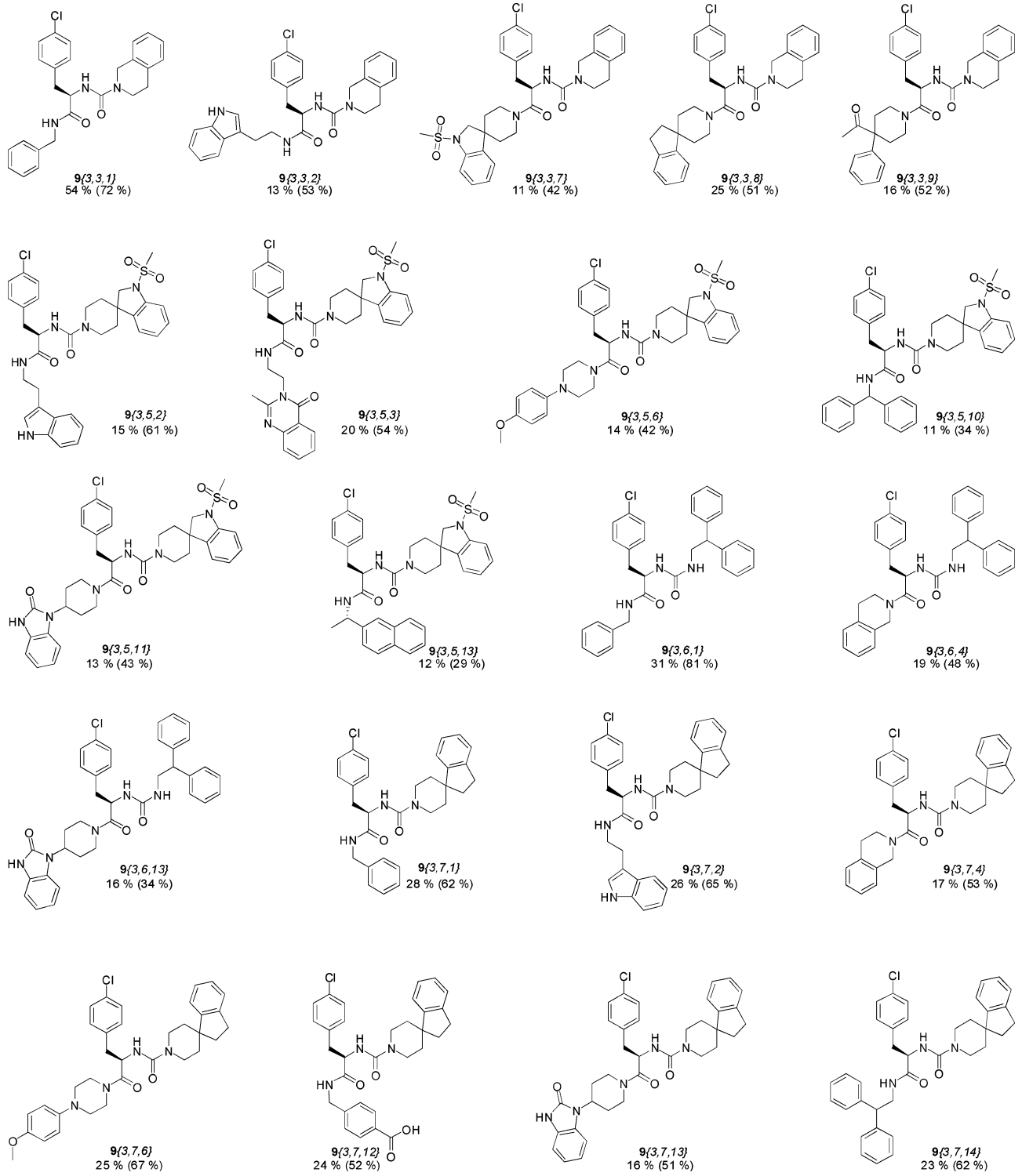

Figure 5. Library members. Purified yields are displayed below each compound, and the purity of the crude cleavage products are shown in brackets. Purity is calculated by analytical high-performance liquid chromatography (HPLC) at 214 nm.

with hydrofluoric acid (HF) was chosen for the activation of the "safety-catch" linker, rather than trifluoromethanesulfonic acid, to obtain better purity of the resultant compounds. After workup, the resin was then dried and divided further, prior to treatment with an excess of amine (**8**, building block 3, Figure 4) in DMF, to provide peptidyl privileged structures (see **9** in Figure 5) in moderate yield but with good purity. Each of these products was then purified by reversed-phase high-performance liquid chromatography (RP-HPLC). The best yields and purities obtained in the library were observed when primary amines were used for both cleavage and urea formation. Yields decreased considerably when secondary amines were used in either of these positions.

The amines selected for use in this library were biased toward known privileged substructures, including the bi-

phenyl, indole, quinazolinone, isoquinoline, spiropiperidine, and phenylpiperazine ring systems (Figure 4). The resulting products that were synthesized are displayed in Figure 5.

Conclusions

A synthetic approach has been developed on a "safety-catch" linker that allows rapid preparation of large libraries of peptidyl privileged structures. These molecules incorporate the urea moiety with amide bond formation/cleavage occurring as the final step, allowing significant diversification to be easily incorporated. Utilization of the urea amide bond isostere allows amines (based on privileged substructures or amino acid analogs) to be used at both the *N*- and *C*-termini of the molecule, allowing the potential of the same group of amines to be used at either end. This chemistry permits the rapid combinatorial synthesis of diverse arrays of a vast number of peptidyl privileged structures.

Experimental Section

Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck). The chromatograms were viewed under ultraviolet (UV) light or developed with iodine vapor or Ninhydrin stain (0.2% Ninhydrin, 1% H_2SO_4 in 2-propanol). Flash column chromatography was performed with flash silica gel 60 (0.063−0.200 mm, Merck). Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR), or 600 MHz (^{1}H NMR) on a Varian Gemini-300 instrument or a Bruker 600 Ultrashield instrument, respectively. ^{1}H and ^{13}C chemical shifts (δ) are given in parts per million (ppm), using residual protonated solvent as an internal standard. Coupling constants are given in units of Hz. The following abbreviations are used: s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet, dd = double of doublets, td = triplet of doublets, dt = doublet of triplets, ddd = doublet of doublets of doublets. Microanalyses were obtained using an elemental microanalyzer (Carlo Erba, model 1106). Low-resolution mass spectral data were recorded on a Micromass LCT (TOF MS ES+) instrument. High-resolution mass spectral data were obtained on a PE Sciex API QSTAR Pulsar (ES-QqTOF) instrument, using ACP (acyl carrier protein) (65−74) ($C_{47}H_{75}N_{12}O_{16}$ (M+H), 1063.5424) and reserpine ($C_{33}H_{40}N_2O_9$ (M+H), 609.2812) as internal references. The instrument resolution was set in the range of 10 000−12 000 for all standards. Infrared data were obtained on a FT-IR spectrometer (JASCO, model 460 Plus), using Nujol mull on CaF_2 disks. Melting points were determined on a hot stage (Bausch and Lomb). Analytical RP-HPLC tests were run on a Vydac C_{18} column (4.6 mm × 250 mm) or Phenomonex Luna 5 μ C_{18} column (50 mm × 2.0 mm), and preparative RP-HPLC tests were performed on a Vydac C_{18} column (22 mm × 250 mm) at 8 mL/min or on a Phenomonex Jupiter 10 μ Proteo 90 Å C_{18} column (100 mm × 21.2 mm). HPLC analyses were performed using an A:B solvent gradient (A: 99.5% H_2O, 0.5% TFA; B: 89.75% MeCN, 9.75% H_2O, 0.5% TFA). Abbreviations are as noted in Table 1. (2-Phenoxycarbonylamino-ethyl)-carbamic acid *tert*-butyl ester was synthesized in the same manner as the 4-methoxyphenyl carbamate that was synthesized by Saari et al.[32] [2-(4-Nitro-phenoxycarbonylamino)-ethyl]-carbamic acid *tert*-butyl ester and piperazine-1,4-dicarboxylic acid *tert*-butyl ester 4-nitro-phenyl ester were synthesized in an analogous manner to Boeijen and co-workers.[33,34] 3-(2-Amino-ethyl)-2-methyl-3H-quinazolin-4-one was synthesized as the hydrochloride salt from 2-methylbenzo[*d*][1,3]oxazin-4-one[35,36] in an analogous fashion to that reported by Dash et al.[37] The full experimental discussion for these compounds can be found in the Supporting Information. All spiropiperidine−indane substructures were provided as a gift from Novo Nordisk.

Table 1. List of Abbreviations Used in the Experimental Section

abbreviation	compound
Ac_2O	acetic anhydride
BOP	benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
DCM	dichloromethane
DIC	diisopropylcarbodiimide
DIEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
EtOAc	ethyl acetate
Et_2O	diethyl ether
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
MeCN	acetonitrile
MeOH	methanol
NDMBA	1,3-dimethylbarbituric acid
petrol	petroleum spirit (bp 40−60 °C)
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Materials. Boc-L-amino acids, synthesis-grade DMF, TFA, and DIEA were purchased from Auspep (Parkville, Australia). HBTU and BOP were purchased from Richelieu Biotechnologies (Montreal, Canada). AR-grade EtOAc, MeOH, CH_2Cl_2, $CHCl_3$, hexane, and acetone and HPLC-grade CH_3CN were all obtained from Laboratory Supply (Australia), and HF was purchased from CIG (Australia). Aminomethylpolystyrene resins with a substitution value of 0.41 mmol/g were purchased from Novabiochem. Trityl chloride polystyrene (TCP) resin with a substitution value of 0.96 mmol/g was purchased from PepChem (Germany). All other reagents were AR grade or better and were obtained from Aldrich or Fluka. The "safety-catch" linker (3-(3-benzyloxy-4-hydroxyphenyl)propionic acid and 3-(4-benzyloxy-3-hydroxyphenyl)propionic acid) was prepared as a mixture of monoprotected catechols, using the procedure of Bourne et al.[22] The following protected amino acids were used: Fmoc-Tyr(tBu)-OH, Fmoc-Arg(Pbf)-OH, Boc-Arg(Tos)-OH.

Peptide Synthesis and Urea Attachment. Fmoc-Solid-Phase Peptide Synthesis and Amino Acid Attachment to TCP Resin. *C*-terminal amino acid (1.5 equiv) was dissolved in DCM and DIEA (1.0 equiv) was added. This solution was then added to dry TCP resin (1 equiv). After shaking for 10 min, more DIEA (2.0 equiv) was added. The resin was then shaken for 1 h, MeOH (1 mL) was added, and the mixture shaken for an additional 20 min before draining the resin and washing with DCM (2 × 1 min), then DMF (2 × 1 min). Removal of the Fmoc-protecting group and extension

of the peptide chain was accomplished according to standard Fmoc-solid-phase peptide synthesis protocols.[38,39]

General Procedure for Rate Studies. Fmoc-Tyr(tBu)-Arg(Pbf)-Phe (70 mg or 100 mg) on TCP resin (0.034 or 0.049 mmol) was placed into a reaction vessel and swollen in DMF. The resin was then treated with 1:1 piperidine/DMF (2 × 1 min), then DMF (2 × 1 min). After resuspending in DMF (2 mL) 30 μL of the resin suspension was removed and dried down in 1:1 MeOH/DCM and then transferred to an Eppendorf tube. The resin was then treated in 1% TFA/DCM (100 μL) solution, which was immediately blown off with nitrogen. The residue was then dissolved in 9:1:0.005 MeCN/H_2O/TFA (125 μL), and centrifuged before an aliquot was removed for mass spectroscopy and analytical HPLC. The resin was then drained and either (i) isocyanate (3.8 equiv) was added in DMF (2 mL), followed by DIEA (36 equiv), or (ii) carbamate (5.2 equiv) was added in DMF (2 mL), followed by DIEA (4.4 equiv). Resin samples were removed during the course of the reaction, and worked up as done previously.

General Procedure for Isocyanate/Chloro Formamide Formation. The amine (1 equiv) was dissolved in a 1:1 biphasic mixture of DCM/saturated $NaHCO_3$ and cooled to 0 °C. Phosgene (1.8 M solution in toluene, 1.5 equiv) was then added to the DCM layer and the mixture stirred for 10 min at 0 °C. The organic layer was then separated, dried with $MgSO_4$, filtered, and concentrated under vacuum.

Library Synthesis. The library was synthesized according to Scheme 2. All library subunits are displayed in Figure 4.

Amino acid couplings were accomplished by established methods, using in situ neutralization/HBTU activation protocols for BOC chemistry.[40] When removing Boc-protecting groups on a solid-phase compounds attached to the "safety-catch" linker, an additional DCM washing step (2 × 1 min) was used between TFA and DMF washing steps.

C-Terminal Amino Acid Acylation to the "Safety-Catch" Linker. "Safety-catch" linker−Gly-Leu-Leu aminomethylated polystyrene resin (1 equiv) was swollen in DMF for 30 min, and then washed with DCM (2 × 1 min). In a separate vial, Boc-protected amino acid (8 equiv) was dissolved in DCM (10 mL) and DIC (4 equiv) was added. Two minutes after DIC addition, this solution was added to the drained resin, along with a catalytic amount of DMAP (∼50 mg). This mixture was left to couple for 9 h, after which time the resin was washed with DCM (2 × 1 min), DMF (2 × 1 min), DCM (1 × 1 min), TFA (2 × 1 min), DCM (1 × 1 min), and DMF (2 × 1 min).

Urea Formation for Library Synthesis. Isocyanate (3 equiv) was prepared and added to resin-bound free amine (1 equiv) swollen in DMF. Following isocyanate addition, DIEA (11 equiv) was added. After 45 min of shaking, the resin was drained, washed with DMF (2 × 1 min), then DCM (2 × 1 min), and dried under nitrogen. The ureas made from (3′-aminomethyl-biphenyl-3-ylmethyl)-carbamic acid *tert*-butyl ester were shaken for 45 min,and then the resin was drained and washed with DMF (2 × 1 min), DCM (1 × 1 min), TFA (2 × 1 min), DCM (1 × 1 min), and DMF (2 × 1 min) before treatment with 5 mL of 10% Ac_2O/DMF and DIEA (1.2 equiv) for 1 h. The resin was then drained and washed with DMF (2 × 1 min) and DCM (2 × 1 min) before drying under nitrogen.

Resin Deprotection/Activation and Cleavage from Resin. HF deprotection was accomplished using 9:0.5:0.5 HF/*p*-cresol/*p*-thiocresol for 1 h at 0 °C, according to the procedure given in the literature.[40] After resin deprotection/activation, the resin was washed with anhydrous ether and dried under nitrogen.

The resin was then dissolved in amine (4 equiv) in either DMF or DMSO and was left for 1 d, prior to filtration and washing with DMF or DMSO. For amines that were used as the acid salt, additional DIEA (1 equiv) was added for neutralization in the cleavage mixture. An additional amine (4 equiv) in DMF or DMSO was then added to the drained resin and left for an additional day. After the second filtration and washing, the combined filtrate was removed under reduced pressure and dissolved in 55:45:0.05 H_2O/MeCN/TFA and lyophilized before purification by preparative RP-HPLC.

2(S)-{3-[3′-(Acetylaminomethyl)biphenyl-3-ylmethyl]-ureido}-5-guanidinopentanoic Acid [1(R)-Benzylcarbamoyl-2-(4-chlorophenyl)ethyl]amide (9{*1,1,1*}). Yield after purification was 11.4 mg (38%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.60 (t, 1H, J = 6.0 Hz, −N*H*−CH_2−C_6H_5), 8.49 (d, 1H, J = 8.8 Hz, −CO−N*H*−CH(CH_2−C_6H_4Cl)−CO−), 8.38 (t, 1H, J = 5.8 Hz, −N*H*−CO−CH_3), 7.50−7.46 (m, 4H, Ar*H*), 7.41 (d, 1H, J = 7.45 Hz, Ar*H*), 7.38 (d, 1H, J = 7.45 Hz, Ar*H*), 7.34 (m, 1H, −CH_2−N*H*−C(═NH)NH_2), 7.31−7.28 (m, 2H, Ar*H*), 7.28−7.23 (m, 5H, Ar*H*), 7.22−7.19 (m, 2H, Ar*H*), 7.16−7.14 (m, 2H, Ar*H*), 6.64 (t, 1H, J = 6.0 Hz, −CH_2−N*H*−CO−NH−), 6.31 (d, 1H, J = 7.5 Hz, −CH_2−NH−CO−N*H*−), 4.51 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−), 4.31 (d, 2H, J = 5.9 Hz, Ac−NH−CH_2−), 4.23 (d, 2H, J = 5.5 Hz, −CH_2−NH−CO−NH−), 4.24 (dd, 1H, J = 15.1, 6.0 Hz, one of −CH_2−C_6H_5), 4.17 (dd, 1H, J = 15.1, 6.0 Hz, one of −CH_2−C_6H_5), 4.12 (m, 1H, −NH−C*H*((CH_2)$_3$−NH−C(═NH)NH_2)−CO−), 3.10 (dd, 1H, J = 13.7, 4.5 Hz, one of −CH_2−C_6H_4-Cl), 3.05−2.93 (m, 2H, −CH_2−NH−C(═NH)NH_2), 2.74 (dd, 1H, J = 13.7, 10.5 Hz, one of −CH_2−C_6H_4Cl), 1.88 (s, 3H, −NH−CO−CH_3), 1.39 (m, 1H, one of −CH_2−(CH_2)$_2$−NH−C(═NH)NH_2), 1.31 (m, 1H, one of −CH_2−(CH_2)$_2$−NH−C(═NH)NH_2), 1.18 (m, 1H, one of −CH_2−CH_2−NH−C(═NH)NH_2), 1.11 (m, 1H, one of −CH_2−CH_2−NH−C(═NH)NH_2). *m*/*z* (HR-ESI): 725.3336 (calc. for $C_{39}H_{46}ClN_8O_4$ [M+H], 725.3325).

2(S)-{3-[3′-(Acetylaminomethyl)biphenyl-3-ylmethyl]-ureido}-5-guanidinopentanoic Acid (1(R)-Benzylcarbamoyl-2-phenylethyl)amide (9{*2,1,1*}). Yield after purification was 6.8 mg (24%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.59 (t, 1H, J = 6.0 Hz, −N*H*−CH_2−C_6H_5), 8.49 (d, 1H, J = 8.8 Hz, −CO−N*H*−CH(CH_2−C_6H_5)−CO−), 8.36 (t, 1H, J = 5.8 Hz, −N*H*−CO−CH_3), 7.49−7.44 (m, 4H, Ar*H*), 7.39 (d, 1H, J = 7.8 Hz, Ar*H*), 7.37 (d, 1H, J = 7.8 Hz, Ar*H*), 7.29 (m, 1H, −CH_2−N*H*−C(═NH)NH_2), 7.28−7.22 (m, 7H, Ar*H*), 7.20−7.14 (m, 5H, Ar*H*), 6.61 (t, 1H, J = 6.0 Hz, −CH_2−N*H*−CO−NH−), 6.29 (d, 1H, J = 7.5 Hz, −CH_2−NH−CO−N*H*−), 4.50 (m, 1H, −NH−C*H*(CH_2−C_6H_5)−CO−), 4.30 (d, 2H, J = 5.8 Hz, Ac−NH−CH_2−),

4.24 (dd, 1H, J = 15.1, 6.0 Hz, one of −NH−CH_2−C_6H_5), 4.20 (d, 2H, J = 6.0 Hz, −CH_2−NH−CO−NH−), 4.13 (dd, 1H, J = 15.1, 6.0 Hz, one of −NH−CH_2−C_6H_5), 4.09 (m, 1H, −NH−CH($(CH_2)_3$−NH−C(=NH)NH_2)−CO−), 3.13 (dd, 1H, J = 13.6, 4.3 Hz, one of −CH−CH_2−C_6H_5), 2.99−2.87 (m, 2H, −CH_2−NH−C(=NH)NH_2), 2.72 (dd, 1H, J = 13.6, 11.0 Hz, one of −CH−CH_2−C_6H_5), 1.86 (s, 3H, −NH−CO−CH_3), 1.35 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.27 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.10 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2), 1.01 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 691.3741 (calc. for $C_{39}H_{47}N_8O_4$ [M+H], 691.3715).

2(S)-{3-[3′-(Acetylaminomethyl)biphenyl-3-ylmethyl]-ureido}-5-guanidinopentanoic Acid {1(R)-[2-(1*H*-Indol-3-yl)ethylcarbamoyl]-2-(4-chlorophenyl)ethyl}amide (9-{*1,1,2*}). Yield after purification was 12.1 mg (38%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.78 (s, 1H, ind N*H*), 8.44 (d, 1H, J = 8.9 Hz, −CO−N*H*−CH(CH_2−C_6H_4Cl)−CO−), 8.37 (t, 1H, J = 5.8 Hz, −CH_2−N*H*−Ac), 8.24 (t, 1H, J = 5.8 Hz, −CO−N*H*−$(CH_2)_2$−C_8H_6N), 7.50−7.45 (m, 6H, Ar*H*), 7.38 (d, 1H, J = 7.6 Hz, Ar*H*), 7.37 (d, 1H, J = 7.6 Hz, Ar*H*), 7.36 (m, 1H, −CH_2−N*H*−C(=NH)NH_2), 7.33−7.27 (m, 3H, Ar*H*), 7.24−7.21 (m, 4H, Ar*H*), 7.08 (s, 1H, ind 2-*H*), 7.04 (dd, 1H, J = 7.6, 6.7 Hz, ind 6-*H*), 6.93 (dd, 1H, J = 8.0, 6.7 Hz, ind 5-*H*), 6.65 (t, 1H, J = 6.0 Hz, −CH_2−N*H*−CO−NH−), 6.32 (d, 1H, J = 7.5 Hz, −CH_2−NH−CO−N*H*−), 4.46 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−), 4.35−4.26 (m, 4H, −NH−CH_2−$C_{12}H_8$−CH_2−NH−), 4.11 (m, 1H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−), 3.30 (m, 2H, −NH−CH_2−CH_2−C_8H_6N), 3.07 (dd, 1H, J = 13.7, 4.2 Hz, one of −CH_2−C_6H_4Cl), 3.05−2.93 (m, 2H, −CH_2−NH−C(=NH)NH_2), 2.83−2.75 (m, 2H, −NH−CH_2−CH_2−C_8H_6N), 2.70 (dd, 1H, J = 13.7, 10.6 Hz, one of −CH_2−C_6H_4Cl), 1.87 (s, 3H, −NH−CO−CH_3), 1.39 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.31 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.18 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2), 1.10 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 778.3599 (calc. for $C_{42}H_{49}ClN_9O_4$ [M+H], 778.3591).

2(S)-{3-[3′-(Acetylaminomethyl)biphenyl-3-ylmethyl]-ureido}-5-guanidinopentanoic Acid {1(R)-[2-(1*H*-Indol-3-yl)ethylcarbamoyl]-2-phenylethyl}amide (9{*2,1,2*}). Yield after purification was 9.4 mg (31%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.76 (s, 1H, ind N*H*), 8.45 (d, 1H, J = 8.8 Hz, −CO−N*H*−CH(CH_2−C_6H_5)−CO−), 8.35 (t, 1H, J = 5.8 Hz, −CH_2−N*H*−Ac), 8.22 (t, 1H, J = 5.7 Hz, −CO−N*H*−$(CH_2)_2$−C_8H_6N), 7.48−7.43 (m, 5H, Ar*H*), 7.37 (d, 1H, J = 7.6 Hz, Ar*H*), 7.36 (d, 1H, J = 7.6 Hz, Ar*H*), 7.32 (m, 1H, −CH_2−N*H*−C(=NH)NH_2), 7.30 (d, 1H, J = 8.1 Hz, ind 7-*H*), 7.24−7.19 (m, 6H, Ar*H*), 7.16 (m, 1H, Ar*H*), 7.07 (s, 1H, ind 2-*H*), 7.03 (dd, 1H, J = 7.6, 6.7 Hz, ind 6-*H*), 6.91 (dd, 1H, J = 8.0, 6.7 Hz, ind 5-*H*), 6.64 (t, 1H, J = 5.9 Hz, −CH_2−N*H*−CO−NH−), 6.30 (d, 1H, J = 7.2 Hz, −CH_2−NH−CO−N*H*−), 4.44 (m, 1H, −NH−C*H*(CH_2−C_6H_5)−CO−), 4.34−4.24 (m, 4H, −NH−CH_2−$C_{12}H_8$−CH_2−NH−), 4.08 (m, 1H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−), 3.33−3.22 (m, 2H, −NH−CH_2−CH_2−C_8H_6N), 3.10 (dd, 1H, J = 13.7, 4.1 Hz, one of −CH−CH_2−C_6H_5), 2.99−2.87 (m, 2H, −CH_2−NH−C(=NH)NH_2), 2.82−2.73 (m, 2H, −NH−CH_2−CH_2−C_8H_6N), 2.68 (dd, 1H, J = 13.7, 11.0 Hz, one of −CH−CH_2−C_6H_5), 1.86 (s, 3H, −NH−CO−CH_3), 1.34 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.28 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.12 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2), 1.01 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 744.3998 (calc. for $C_{42}H_{50}N_9O_4$ [M+H], 744.3981).

2(S)-{3-[3′-(Acetylaminomethyl)biphenyl-3-ylmethyl]-ureido}-5-guanidinopentanoic Acid {1(R)-[2-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)ethylcarbamoyl-2-(4-chlorophenyl)]-ethyl}amide (9{*1,1,3*}). Yield after purification was 19.0 mg (56%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.46−8.42 (m, 2H, −CO−N*H*−CH(CH_2−C_6H_4Cl)−CO−N*H*−), 8.37 (t, 1H, J = 5.8 Hz, −CH_2−N*H*−Ac), 8.08 (dd, 1H, J = 8.0, 1.5 Hz, quin 5-*H*), 7.77 (ddd, 1H, J = 8.1, 7.2, 1.5 Hz, quin 7-*H*), 7.56 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.49−7.44 (m, 5H, Ar*H*), 7.39−7.35 (m, 3H, Ar*H*, −CH_2−N*H*−C(=NH)NH_2), 7.31−7.28 (m, 2H, Ar*H*), 7.24−7.20 (m, 4H, Ar*H*), 6.67 (t, 1H, J = 6.0 Hz, −CH_2−N*H*−CO−NH−), 6.28 (d, 1H, J = 7.5 Hz, −CH_2−NH−CO−N*H*−), 4.39 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−), 4.31−4.26 (m, 4H, −NH−CH_2−$C_{12}H_8$−CH_2−NH−), 4.12−4.06 (m, 2H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−, one of −CH_2−$C_8H_7N_2O$), 4.00 (dt, 1H, J = 13.8, 7.1 Hz, one of −CH_2−$C_8H_7N_2O$), 3.43−3.30 (m, 2H, CH_2−CH_2−$C_8H_7N_2O$), 3.04−2.91 (m, 3H, one of −CH_2−C_6H_4Cl, −CH_2−NH−C(=NH)NH_2), 2.63 (dd, 1H, J = 13.7, 10.9 Hz, one of −CH_2−C_6H_4Cl), 2.56 (s, 3H, CH_3−C=N−), 1.87 (s, 3H, −NH−CO−CH_3), 1.36 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.27 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.19−1.05 (m, 2H, −CH_2−CH_2−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 821.3679 (calc. for $C_{43}H_{50}ClN_{10}O_5$ [M+H], 821.3649).

2(S)-{3-[3′-(Acetylaminomethyl)biphenyl-3-ylmethyl]-ureido}-5-guanidinopentanoic Acid {1(R)-[2-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)ethylcarbamoyl]-2-phenylethyl}-amide (9{*2,1,3*}). Yield after purification was 16.2 (50%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.45−8.40 (m, 2H, −CO−N*H*−CH(CH_2−C_6H_5)−CO−N*H*−), 8.35 (t, 1H, J = 5.7 Hz, −CH_2−N*H*−Ac), 8.07 (dd, 1H, J = 7.9, 1.2 Hz, quin 5-*H*), 7.76 (ddd, 1H, J = 8.1, 7.2, 1.4 Hz, quin 7-*H*), 7.56 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.48−7.43 (m, 5H, Ar*H*), 7.36 (d, 1H, J = 7.7 Hz, Ar*H*), 7.34 (d, 1H, J = 7.7 Hz, Ar*H*), 7.32 (m, 1H, −CH_2−N*H*−C(=NH)NH_2), 7.24−7.13 (m, 7H, Ar*H*), 6.65 (t, 1H, J = 5.9 Hz, −CH_2−N*H*−CO−NH−), 6.26 (d, 1H, J = 7.2 Hz, −CH_2−NH−CO−N*H*−), 4.38 (m, 1H, −NH−C*H*(CH_2−C_6H_5)−CO−), 4.29−4.24 (m, 4H, −NH−CH_2−$C_{12}H_8$−CH_2−NH−), 4.09−4.04 (m, 2H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−, one of −CH_2−$C_8H_7N_2O$), 3.91 (dt, 1H, J = 13.8, 7.0 Hz, one of −CH_2−$C_8H_7N_2O$), 3.40−3.28 (m, 2H, CH_2−CH_2−$C_8H_7N_2O$), 3.04 (dd, 1H, J = 13.7, 4.0 Hz, one of −CH−CH_2−C_6H_5), 2.98−2.86 (m, 2H, −CH_2−NH−C(=NH)NH_2), 2.62 (dd, 1H, J = 13.7, 11.3 Hz, one of −CH−CH_2−C_6H_5), 2.54 (s, 3H, CH_3−C=N−), 1.86 (s, 3H, −NH−CO−CH_3), 1.32 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.24

(m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.08 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$), 1.00 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$). *m/z* (HR-ESI): 787.4057 (calc. for $C_{43}H_{51}N_{10}O_5$ [M+H], 787.4039).

2(S)-(3-Benzylureido)-5-guanidinopentanoic Acid [1(R)-Benzylcarbamoyl-2-(4-chlorophenyl)ethyl]amide (9{*1,2,1*}). Yield after purification was 11.2 mg (47%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.62 (t, 1H, J = 5.9 Hz, $-CH-CO-NH-CH_2-C_6H_5$), 8.47 (d, 1H, J = 8.7 Hz, $-CO-NH-CH(CH_2-C_6H_4Cl)-CO-$), 7.37 (m, 1H, $-CH_2-NH-C(=NH)NH_2$), 7.31−7.15 (m, 14H, Ar*H*), 6.58 (t, 1H, J = 6.0 Hz, $-CH_2-NH-CO-NH-$), 6.27 (d, 1H, J = 7.6 Hz, $-CH_2-NH-CO-NH-$), 4.51 (m, 1H, $-NH-CH-(CH_2-C_6H_4Cl)-CO-$), 4.29−4.21 (m, 2H, $-CH-CO-NH-CH_2-C_6H_5$), 4.16−4.10 (m, 3H, $NH-CO-NH-CH_2-C_6H_5$, $-NH-CH((CH_2)_3-NH-C(=NH)NH_2)-CO-$), 3.09 (dd, 1H, J = 13.7, 4.5 Hz, one of $-CH_2-C_6H_4Cl$), 3.05−2.93 (m, 2H, $-CH_2-NH-C(=NH)NH_2$), 2.75 (dd, 1H, J = 13.7, 10.4 Hz, one of $-CH_2-C_6H_4Cl$), 1.39 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.29 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.21−1.07 (m, 2H, $-CH_2-CH_2-NH-C(=NH)NH_2$). *m/z* (HR-ESI): 578.2637 (calc. for $C_{30}H_{37}ClN_7O_3$ [M+H], 578.2641).

2(S)-(3-Benzylureido)-5-guanidinopentanoic Acid (1(R)-Benzylcarbamoyl-2-phenylethyl)amide (9{*2,2,1*}). Yield after purification was 7.7 mg (32%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.60 (t, 1H, J = 5.9 Hz, $-CH-CO-NH-CH_2-C_6H_5$), 8.46 (d, 1H, J = 8.7 Hz, $-CO-NH-CH(CH_2-C_6H_5)-CO-$), 7.31 (m, 1H, $-CH_2-NH-C(=NH)NH_2$), 7.29−7.14 (m, 15H, Ar*H*), 6.55 (t, 1H, J = 6.0 Hz, $-CH_2-NH-CO-NH-$), 6.24 (d, 1H, J = 7.3 Hz, $-CH_2-NH-CO-NH-$), 4.50 (m, 1H, $-NH-CH(CH_2-C_6H_5)-CO-$), 4.26 (dd, 1H, J = 15.1, 5.9 Hz, one of $-CH-CO-NH-CH_2-C_6H_5$), 4.20 (dd, 1H, J = 15.1, 5.9 Hz, one of $-CH-CO-NH-CH_2-C_6H_5$), 4.14−4.07 (m, 3H, $-NH-CH((CH_2)_3-NH-C(=NH)NH_2)-CO-$, $C_6H_5-CH_2-NH-CO-NH-$), 3.11 (dd, 1H, J = 13.6, 4.0 Hz, one of $-CH-CH_2-C_6H_5$), 2.99−2.88 (m, 2H, $-CH_2-NH-C(=NH)NH_2$), 2.73 (dd, 1H, J = 13.6, 10.4 Hz, one of $-CH-CH_2-C_6H_5$), 1.34 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.26 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.10 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$), 1.02 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$). *m/z* (HR-ESI): 544.3046 (calc. for $C_{30}H_{38}N_7O_3$ [M+H], 544.3031).

2(S)-(3-Benzylureido)-5-guanidinopentanoic Acid {1(R)-[2-(1*H*-Indol-3-yl)ethylcarbamoyl]-2-(4-chlorophenyl)-ethyl}amide (9{*1,2,2*}). Yield after purification was 9.6 mg (37%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.79 (s, 1H, ind N*H*), 8.41 (d, 1H, J = 8.8 Hz, $-CO-NH-CH(CH_2-C_6H_4Cl)-CO-$), 8.24 (t, 1H, J = 5.8 Hz, $-CO-NH-(CH_2)_2-C_8H_6N$), 7.50 (d, 1H, J = 7.9 Hz, ind 4-*H*), 7.38 (m, 1H, $-CH_2-NH-C(=NH)NH_2$), 7.32 (d, 1H, J = 8.0 Hz, ind 7-*H*), 7.30−7.26 (m, 4H, Ar*H*), 7.24−7.18 (m, 5H, Ar*H*), 7.11 (s, 1H, ind 2-*H*), 7.05 (dd, 1H, J = 8.0, 6.8 Hz, ind 6-*H*), 6.95 (dd, 1H, J = 7.9, 6.8 Hz, ind 5-*H*), 6.60 (t, 1H, J = 5.8 Hz, $-CH_2-NH-CO-NH-$), 6.28 (d, 1H, J = 7.3 Hz, $-CH_2-NH-CO-NH-$), 4.45 (m, 1H, $-NH-CH(CH_2-C_6H_4Cl)-CO-$), 4.22 (d, 2H, J = 5.8 Hz, $C_6H_5-CH_2-NH-$), 4.12 (m, 1H, $-NH-CH((CH_2)_3-NH-C(=NH)NH_2)-CO-$), 3.33 (m, 2H, $-NH-CH_2-CH_2-C_8H_6N$), 3.06 (dd, 1H, J = 13.7, 4.0 Hz, one of $-CH_2-C_6H_4Cl$), 3.04−2.94 (m, 2H, $-CH_2-NH-C(=NH)NH_2$), 2.83−2.77 (m, 2H, $-NH-CH_2-CH_2-C_8H_6N$), 2.70 (dd, 1H, J = 13.7, 10.6 Hz, one of $-CH_2-C_6H_4Cl$), 1.39 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.29 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.17 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$), 1.11 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$). *m/z* (HR-ESI): 631.2876 (calc. for $C_{33}H_{40}ClN_8O_3$ [M+H], 631.2907).

2(S)-(3-Benzylureido)-5-guanidinopentanoic Acid {1(R)-[2-(1*H*-Indol-3-yl)ethylcarbamoyl]-2-phenylethyl}amide (9{*2,2,2*}). Yield after purification was 7.2 mg (29%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.77 (s, 1H, ind N*H*), 8.42 (d, 1H, J = 8.8 Hz, $-CO-NH-CH(CH_2-C_6H_5)-CO-$), 8.22 (t, 1H, J = 5.6 Hz, $-CO-NH-(CH_2)_2-C_8H_6N$), 7.48 (d, 1H, J = 7.9 Hz, ind 4-*H*), 7.32 (m, 1H, $-CH_2-NH-C(=NH)NH_2$), 7.31 (d, 1H, J = 7.9 Hz, ind 7-*H*), 7.29−7.24 (m, 2H, Ar*H*), 7.24−7.18 (m, 8H, Ar*H*), 7.09 (s, 1H, ind 2-*H*), 7.04 (dd, 1H, J = 7.9, 6.7 Hz, ind 6-*H*), 6.93 (dd, 1H, J = 7.9, 6.7 Hz, ind 5-*H*), 6.57 (t, 1H, J = 6.0 Hz, $-CH_2-NH-CO-NH-$), 6.25 (d, 1H, J = 7.3 Hz, $-CH_2-NH-CO-NH-$), 4.44 (m, 1H, $-NH-CH(CH_2-C_6H_5)-CO-$), 4.21 (d, 2H, J = 5.8 Hz, $C_6H_5-CH_2-NH-$), 4.09 (m, 1H, $-NH-CH((CH_2)_3-NH-C(=NH)-NH_2)-CO-$), 3.34−3.28 (m, 2H, $-NH-CH_2-CH_2-C_8H_6N$), 3.08 (dd, 1H, J = 13.7, 4.2 Hz, one of $-CH-CH_2-C_6H_5$), 3.00−2.88 (m, 2H, $-CH_2-NH-C(=NH)NH_2$), 2.83−2.74 (m, 2H, $-NH-CH_2-CH_2-C_8H_6N$), 2.69 (dd, 1H, J = 13.7, 10.9 Hz, one of $-CH-CH_2-C_6H_5$), 1.34 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.26 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.11 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$), 1.01 (m, 1H, one of $-CH_2-CH_2-NH-C(=NH)NH_2$). *m/z* (HR-ESI): 597.3308 (calc. for $C_{33}H_{41}N_8O_3$ [M+H], 597.3296).

2(S)-(3-Benzylureido)-5-guanidinopentanoic Acid {1(R)-[2-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-ethylcarbamoyl]-2-(4-chlorophenyl)ethyl}amide (9{*1,2,3*}). Yield after purification was 17.1 mg (62%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.43 (t, 1H, J = 6.0 Hz, $-CO-NH-(CH_2)_2-$), 8.40 (d, 1H, J = 8.8 Hz, $-NH-CH(CH_2-C_6H_4Cl)-CO-$), 8.07 (d, 1H, J = 8.0 Hz, quin 5-*H*), 7.77 (dd, 1H, J = 8.1, 7.0 Hz, quin 7-*H*), 7.56 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.46 (dd, 1H, J = 8.0, 7.0 Hz, quin 6-*H*), 7.34 (m, 1H, $-CH_2-NH-C(=NH)NH_2$), 7.29−7.24 (m, 4H, Ar*H*), 7.21−7.16 (m, 5H, Ar*H*), 6.58 (t, 1H, J = 6.0 Hz, $-CH_2-NH-CO-NH-$), 6.22 (d, 1H, J = 7.3 Hz, $-CH_2-NH-CO-NH-$), 4.38 (m, 1H, $-NH-CH(CH_2-C_6H_4Cl)-CO-$), 4.18 (d, 2H, J = 5.9 Hz, $C_6H_5-CH_2-NH-CO-$), 4.11−4.06 (m, 2H, $-NH-CH((CH_2)_3-NH-C(=NH)NH_2)-CO-$, one of $-CH_2-C_8H_7N_2O$), 4.01 (dt, 1H, J = 13.7, 6.9 Hz, one of $-CH_2-C_8H_7N_2O$), 3.44−3.34 (m, 2H, $-CH_2-CH_2-C_8H_7N_2O$), 3.00 (dd, 1H, J = 13.8, 3.8 Hz, one of $-CH-CH_2-C_6H_4Cl$), 3.00−2.90 (m, 2H, $-CH_2-NH-C(=NH)NH_2$), 2.62 (dd, 1H, J = 13.8, 11.0 Hz, one of $-CH-CH_2-C_6H_4Cl$), 2.56 (s, 3H, $-CH_3$), 1.34 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.25 (m, 1H, one of $-CH_2-(CH_2)_2-NH-C(=NH)NH_2$), 1.16−1.05 (m, 2H,

−C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m/z* (HR-ESI): 674.2990 (calc. for $C_{34}H_{41}ClN_9O_4$ [M+H], 674.2965).

2(S)-(3-Benzylureido)-5-guanidinopentanoic Acid {1(R)-[2-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)ethylcarbamoyl]-2-phenylethyl}amide (9{*2,2,3*}). Yield after purification was 14.4 mg (55%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.43−8.40 (m, 2H, −CO−N*H*−CH(CH$_2$−C$_6$H$_5$)−CO−N*H*−), 8.08 (d, 1H, J = 7.9 Hz, quin 5-*H*), 7.77 (dd, 1H, J = 8.1, 7.2 Hz, quin 7-*H*), 7.56 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.45 (dd, 1H, J = 7.9, 7.2 Hz, quin 6-*H*), 7.30−7.13 (m, 11H, Ar*H*, −CH$_2$−N*H*−C(=NH)NH$_2$), 6.57 (t, 1H, J = 5.8 Hz, −CH$_2$−N*H*−CO−NH−), 6.20 (d, 1H, J = 7.3 Hz, −CH$_2$−NH−CO−N*H*−), 4.38 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−), 4.18 (d, 2H, J = 5.9 Hz, C$_6$H$_5$−C*H*$_2$−NH−CO−NH−), 4.11−4.06 (m, 2H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−, one of −C*H*$_2$−C$_8$H$_7$N$_2$O), 4.00 (dt, 1H, J = 13.7, 7.0 Hz, one of −C*H*$_2$−C$_8$H$_7$N$_2$O), 3.39 (m, 2H, −C*H*$_2$−CH$_2$−C$_8$H$_7$N$_2$O), 3.02 (dd, 1H, J = 13.7, 4.0 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 2.98−2.86 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.62 (dd, 1H, J = 13.7, 11.2 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 2.60 (s, 3H, −C*H*$_3$), 1.31 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.22 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.06 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.01 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m/z* (HR-ESI): 640.3365 (calc. for $C_{34}H_{42}N_9O_4$ [M+H], 640.3355).

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid [1(R)-(1-Benzylcarbamoyl-2-phenylethylcarbamoyl)-4-guanidino-(S)-butyl]amide (9{*2,3,1*}). Yield after purification was 5.8 mg (25%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.61 (t, 1H, J = 6.0 Hz, −CO−N*H*−CH$_2$−C$_6$H$_5$), 8.39 (d, 1H, J = 8.6 Hz, −N*H*−CH(CH$_2$−C$_6$H$_5$)−CO−), 7.34 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.27−7.11 (m, 13H, Ar*H*), 7.05 (m, 1H, Ar*H*), 6.63 (d, 1H, J = 6.8 Hz, −N−CO−N*H*−), 4.46−4.41 (m, 2H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−, one of isoquin 1-*H*), 4.36 (d, 1H, J = 16.6 Hz, one of isoquin 1-*H*), 4.29 (d, 2H, J = 5.9 Hz, −CO−NH−C*H*$_2$−C$_6$H$_5$), 3.96 (m, 1H, −N−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 3.46 (t, 2H, J = 5.9 Hz, isoquin 3-*H*), 3.18 (dd, 1H, J = 13.7, 3.8 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 3.00−2.90 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.74 (dd, 1H, J = 13.7, 11.0 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 2.72−2.62 (m, 2H, isoquin 4-*H*), 1.51−1.38 (m, 2H, −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.23 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.05 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m/z* (HR-ESI): 570.3191 (calc. for $C_{32}H_{40}N_7O_3$ [M+H], 570.3187).

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid (4-Guanidino-1(R)-{1-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-2-phenylethylcarbamoyl}-(S)-butyl)amide (9{*2,3,2*}). Yield after purification was 6.3 mg (25%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.80 (s, 1H, ind N*H*), 8.33 (d, 1H, J = 8.8 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_5$)−CO−), 8.23 (t, 1H, J = 5.5 Hz, −CO−N*H*−(CH$_2$)$_2$−C$_8$H$_6$N), 7.53 (d, 1H, J = 7.9 Hz, ind 4-*H*), 7.33 (d, 1H, J = 8.1 Hz, ind 7-*H*), 7.31 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.20−7.18 (m, 4H, Ar*H*), 7.16−7.13 (m, 5H, Ar*H*, ind 2-*H*), 7.06 (dd, 1H, J = 8.1, 6.9 Hz, ind 6-*H*), 7.04 (m, 1H, Ar*H*), 6.98 (dd, 1H, J = 7.9, 6.9 Hz, ind 5-*H*), 6.64 (d, 1H, J = 6.8 Hz, −N−CO−N*H*−), 4.54 (d, 1H, J = 16.4 Hz, one of isoquin 1-*H*), 4.49 (d, 1H, J = 16.4 Hz, one of isoquin 1-*H*), 4.38 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−), 3.97 (m, 1H, −NH−C*H*-((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 3.61−3.54 (m, 2H, isoquin 3-*H*), 3.39−3.31 (m, 2H, −NH−C*H*$_2$−CH$_2$−C$_8$H$_6$N), 3.15 (dd, 1H, J = 13.7, 3.8 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 3.01−2.91 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.88−2.80 (m, 2H, −NH−CH$_2$−C*H*$_2$−C$_8$H$_6$N), 2.77−2.72 (m, 2H, isoquin 4-*H*), 2.70 (dd, 1H, J = 13.7, 11.0 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 1.50−1.38 (m, 2H, −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.23 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.05 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m/z* (HR-ESI): 623.3473 (calc. for $C_{35}H_{43}N_8O_3$ [M+H], 623.3453).

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid (4-Guanidino-1(R)-{1-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-ethylcarbamoyl]-2-phenylethylcarbamoyl}-(S)-butyl)-amide (9{*2,3,3*}). Yield after purification was 11.0 mg (40%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.44 (t, 1H, J = 5.9 Hz, −CO−N*H*−(CH$_2$)$_2$−), 8.34 (d, 1H, J = 8.7 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_5$)−CO−), 8.10 (d, 1H, J = 8.0 Hz, quin 5-*H*), 7.77 (dd, 1H, J = 8.2, 7.0 Hz, quin 7-*H*), 7.55 (d, 1H, J = 8.2 Hz, quin 8-*H*), 7.47 (dd, 1H, J = 8.0, 7.0 Hz, quin 6-*H*), 7.33 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.21−7.17 (m, 5H, Ar*H*), 7.15−7.12 (m, 5H, Ar*H*), 6.59 (d, 1H, J = 6.7 Hz, −N−CO−N*H*−), 4.48 (s, 2H, isoquin 1-*H*), 4.33 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−), 4.11 (dt, 1H, J = 13.7, 6.4 Hz, one of −C*H*$_2$−C$_9$H$_7$N$_2$O), 4.02 (dt, 1H, J = 13.7, 7.0 Hz, one of −C*H*$_2$−C$_9$H$_7$N$_2$O), 3.94 (m, 1H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 3.57−3.49 (m, 2H, isoquin 3-*H*), 3.47−3.36 (m, 2H, −C*H*$_2$−CH$_2$−C$_9$H$_7$N$_2$O), 3.10 (dd, 1H, J = 13.7, 3.6 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 3.00−2.90 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.78−2.68 (m, 2H, isoquin 4-*H*), 2.65 (dd, 1H, J = 13.7, 11.2 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 2.58 (s, 3H, −C*H*$_3$), 1.48−1.36 (m, 2H, −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.22 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.04 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m/z* (HR-ESI): 666.3524 (calc. for $C_{36}H_{44}N_9O_4$ [M+H], 666.3511).

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid {1(R)-[1-Benzyl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxoethylcarbamoyl]-4-guanidino-(S)-butyl}amide (9{*2,3,4*}). Yield after purification was 3.5 mg (14%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.32 (d, 1H, J = 8.5 Hz, −CO−N*H*−CH-(CH$_2$−C$_6$H$_5$)−CO−, conf 1), 8.22 (d, 1H, J = 8.2 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_5$)−CO− conf 2), 7.35 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.21−7.00 (m, 13H, Ar*H*), 6.41 (m, 1H, −N−CO−N*H*−), 5.01 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−), 4.70 (d, 1H, J = 16.6 Hz, one of isoquin 1-*H*, conf 2), 4.68 (d, 1H, J = 16.7 Hz, one of isoquin 1-*H*, conf 1), 4.53 (1H, J = 16.6 Hz, one of isoquin 1-*H*, conf 2), 4.49−4.46 (m, 2H conf 1, 2H conf 2, isoquin 1-*H*), 4.45 (d, 1H, J = 16.7 Hz, one of isoquin 1-*H*, conf 1), 4.19 (m, 1H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 3.80−3.69 (m, 1H conf 1, 1H conf 2, isoquin 3-*H*), 3.59−3.50 (m, 3H conf 1, 3H conf 2, isoquin 3-*H*), 3.06−2.89 (m, 3H, one of −CH−C*H*$_2$−C$_6$H$_5$, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.81−2.53 (m, 5H, isoquin 4-*H*, one of −CH−C*H*$_2$−C$_6$H$_5$), 1.48 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.42−1.21 (m, 3H,

−C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$). *m*/*z* (HR-ESI): 596.3372 (calc. for $C_{34}H_{42}N_7O_3$ [M+H], 596.3344).

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid [4-Guanidino-1(R)-(1-isobutylcarbamoyl-2-phenylethylcarbamoyl)-(S)-butyl]amide (9{*2,3,5*}). Yield after purification was 6.0 mg (27%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.30 (d, 1H, J = 8.7 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_5$)−CO−), 7.97 (t, 1H, J = 5.8 Hz, −N*H*−C$_4$H$_9$), 7.32 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.21−7.08 (m, 9H, Ar*H*), 6.62 (d, 1H, J = 6.9 Hz, −N−CO−N*H*−), 4.49 (s, 2H, isoquin 1-*H*), 4.36 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−), 3.95 (m, 1H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 3.59−3.51 (m, 2H, isoquin 3-*H*), 3.13 (dd, 1H, J = 13.7, 4.0 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 3.00−2.81 (m, 4H, −C*H*$_2$−NH−C(=NH)NH$_2$, −NH−C*H*$_2$−CH(CH$_3$)$_2$), 2.79−2.70 (m, 2H, isoquin 4-*H*), 2.70 (dd, 1H, J = 13.7, 10.7 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 1.69 (m, 1H, −NH−CH$_2$−C*H*(CH$_3$)$_2$), 1.49−1.37 (m, 2H, −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.23 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.04 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 0.78 (d, 3H, J = 6.7 Hz, three of −NH−CH$_2$−CH(C*H*$_3$)$_2$), 0.78 (d, 3H, J = 6.7 Hz, three of −NH−CH$_2$−CH(C*H*$_3$)$_2$). *m*/*z* (HR-ESI): 536.3328 (calc. for $C_{29}H_{42}N_7O_3$ [M+H], 536.3344).

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid (1(R)-{1-Benzyl-2-[4-(4-methoxyphenyl)piperazin-1-yl]-2-oxoethylcarbamoyl}-4-guanidino-(S)-butyl)amide (9{*2,3,6*}). Yield after purification was 3.8 mg (14%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.29 (d, 1H, J = 8.7 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_5$)−CO−), 7.38 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.20−7.18 (m, 4H, Ar*H*), 7.16−7.07 (m, 5H, Ar*H*), 6.84 (d, 2H, J = 9.1 Hz, methoxyphenyl 3-*H* and 5-*H*), 6.78 (d, 2H, J = 9.1 Hz, methoxyphenyl 2-*H* and 6-*H*), 6.42 (d, 1H, J = 8.3 Hz, −N−CO−N*H*−), 4.97 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_5$)−CO−), 4.49−4.42 (m, 2H, isoquin 1-*H*), 4.18 (m, 1H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 3.65 (s, 3H, −C*H*$_3$), 3.66−3.60 (m, 2H, two of −N−(CH$_2$−C*H*$_2$)$_2$−N−C$_6$H$_4$OCH$_3$), 3.55−3.42 (m, 4H, isoquin 3-*H*, two of −N−(CH$_2$−C*H*$_2$)$_2$−N−C$_6$H$_4$OCH$_3$), 3.07−2.96 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.94 (dd, 1H, J = 13.6, 6.4 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 2.92 − 2.81 (m, 3H, three of −N−(C*H*$_2$−CH$_2$)$_2$−N−C$_6$H$_4$OCH$_3$), 2.79 (dd, 1H, J = 13.6, 8.0 Hz, one of −CH−C*H*$_2$−C$_6$H$_5$), 2.74−2.66 (m, 3H, isoquin 4-*H*, one of −N−(C*H*$_2$−CH$_2$)$_2$−N−C$_6$H$_4$OCH$_3$), 1.50 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.43−1.22 (m, 3H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$, −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m*/*z* (HR-ESI): 655.3735 (calc. for $C_{36}H_{47}N_8O_4$ [M+H], 655.3715).

5-Guanidino-2-{3-[2(S)-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethyl]ureido}pentanoic Acid [1(R)-Benzylcarbamoyl-2-(4-chlorophenyl)ethyl]amide (9{*1,4,1*}). Yield after purification was 10.2 mg (37%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.57 (t, 1H, J = 6.0 Hz, −N*H*−CH$_2$−C$_6$H$_5$), 8.41 (d, 1H, J = 8.7 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_4$Cl)−CO−), 8.07 (dd, 1H, J = 8.0, 1.3 Hz, quin 5-*H*), 7.77 (ddd, 1H, J = 8.0, 7.4, 1.3 Hz, quin 7-*H*), 7.55 (d, 1H, J = 8.0 Hz, quin 8-*H*), 7.46 (dd, 1H, J = 8.0, 7.4 Hz, quin 6-*H*), 7.33 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.30−7.14 (m, 9H, Ar*H*), 6.35 (t, 1H, J = 6.0 Hz, −(CH$_2$)$_2$−N*H*−CO−NH−), 6.27 (d, 1H, J = 7.6 Hz, −(CH$_2$)$_2$−NH−CO−N*H*−), 4.50 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_4$Cl)−CO−), 4.31 (dd, 1H, J = 15.2, 6.0 Hz, one of −NH−C*H*$_2$−C$_6$H$_5$), 4.25 (dd, 1H, J = 15.2, 6.0 Hz, one of −NH−C*H*$_2$−C$_6$H$_5$), 4.05 (m, 1H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−), 4.03−3.94 (m, 2H, C$_9$H$_7$N$_2$O−C*H*$_2$−), 3.29−3.16 (m, 2H, C$_9$H$_7$N$_2$O−CH$_2$−C*H*$_2$−), 3.07 (dd, 1H, J = 13.7, 4.5 Hz, one of −C*H*$_2$−C$_6$H$_4$Cl), 3.01−2.89 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.74 (dd, 1H, J = 13.7, 10.4 Hz, one of −C*H*$_2$−C$_6$H$_4$Cl), 2.52 (s, 3H, −C*H*$_3$), 1.35 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.25 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.13 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.07 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m*/*z* (HR-ESI): 674.2985 (calc. for $C_{34}H_{41}ClN_9O_4$ [M+H], 674.2965).

5-Guanidino-2-{3-[2(S)-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethyl]ureido}pentanoic Acid {2-(4-Chlorophenyl)-1(R)-[2-(1*H*-indol-3-yl)ethylcarbamoyl]ethyl}amide (9-{*1,4,2*}). Yield after purification was 8.4 mg (28%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.78 (s, 1H, ind N*H*), 8.33 (d, 1H, J = 8.7 Hz, −CO−N*H*−CH(CH$_2$−C$_6$H$_4$Cl)−CO−), 8.20 (t, 1H, J = 5.8 Hz, −CO−N*H*−(CH$_2$)$_2$−C$_8$H$_6$N), 8.07 (dd, 1H, J = 8.0, 1.3 Hz, quin 5-*H*), 7.76 (ddd, 1H, 7.9, 7.3, 1.3 Hz, quin 7-*H*), 7.54 (d, 1H, J = 7.9 Hz, quin 8-*H*), 7.52 (d, 1H, J = 8.0 Hz, ind 4-*H*), 7.45 (dd, 1H, J = 8.0, 7.3 Hz, quin 6-*H*), 7.34 (m, 1H, −CH$_2$−N*H*−C(=NH)-NH$_2$), 7.31 (d, 1H, J = 8.1 Hz, ind 7-*H*), 7.27 (d, 2H, J = 8.4 Hz, phenyl 3-*H* and 5-*H*), 7.20 (d, 2H, J = 8.4 Hz, phenyl 2-*H* and 6-*H*), 7.14 (s, 1H, ind 2-*H*), 7.03 (dd, 1H, J = 8.1, 6.9 Hz, ind 6-*H*), 6.94 (dd, 1H, J = 8.0, 6.9 Hz, ind 5-*H*), 6.37 (t, 1H, J = 6.0 Hz, −(CH$_2$)$_2$−N*H*−CO−NH−), 6.26 (d, 1H, J = 7.6 Hz, −(CH$_2$)$_2$−NH−CO−N*H*−), 4.44 (m, 1H, −NH−C*H*(CH$_2$−C$_6$H$_4$Cl)−CO−), 4.08−4.01 (m, 3H, −NH−C*H*((CH$_2$)$_3$−NH−C(=NH)NH$_2$)−CO−, C$_9$H$_7$N$_2$O−C*H*$_2$−), 3.39−3.24 (m, 4H, C$_9$H$_7$N$_2$O−CH$_2$−C*H*$_2$−, −NH−C*H*$_2$−CH$_2$−C$_8$H$_6$N), 3.02 (dd, 1H, J = 13.7, 4.4 Hz, one of −CH−C*H*$_2$−C$_6$H$_4$Cl), 3.00−2.90 (m, 2H, −C*H*$_2$−NH−C(=NH)NH$_2$), 2.80 (t, 2H, J = 7.6 Hz, −NH−CH$_2$−C*H*$_2$−C$_8$H$_6$N), 2.69 (dd, 1H, J = 13.7, 10.5 Hz, one of −CH−C*H*$_2$−C$_6$H$_4$Cl), 2.55 (s, 3H, −C*H*$_3$), 1.35 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.24 (m, 1H, one of −C*H*$_2$−(CH$_2$)$_2$−NH−C(=NH)NH$_2$), 1.13 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$), 1.07 (m, 1H, one of −C*H*$_2$−CH$_2$−NH−C(=NH)NH$_2$). *m*/*z* (HR-ESI): 727.3252 (calc. for $C_{37}H_{44}ClN_{10}O_4$ [M+H], 727.3230).

5-Guanidino-2(S)-{3-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethyl]ureido}pentanoic Acid {2-(4-Chlorophenyl)-1(R)-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethylcarbamoyl]-ethyl}amide (9{*1,4,3*}). Yield after purification was 15.6 mg (49%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.42 (t, 1H, J = 6.0 Hz, −CH−CO−N*H*−(CH$_2$)$_2$−C$_9$H$_7$N$_2$O), 8.38 (d, 1H, J = 8.7 Hz, −N*H*−CH(CH$_2$−C$_6$H$_4$Cl)−CO−), 8.05 (d, 1H, J = 8.0 Hz, quin 5-*H*), 7.99 (d, 1H, J = 8.0 Hz, quin 5-*H*), 7.77−7.73 (m, 2H, quin 7-*H*), 7.55 (d, 1H, J = 3.2 Hz, quin 8-*H*), 7.53 (d, 1H, J = 3.2 Hz, quin 8-*H*), 7.44 (dd, 1H, J = 8.0, 6.9 Hz, quin 6-*H*), 7.40 (dd, 1H, J = 8.0, 6.9 Hz, quin 6-*H*), 7.30 (m, 1H, −CH$_2$−N*H*−C(=NH)NH$_2$), 7.28 (d, 2H, J = 8.4 Hz, phenyl 3-*H* and 5-*H*), 7.20 (d, 2H, J = 8.4 Hz, phenyl 2-*H* and 6-*H*), 6.37 (t, 1H, J = 6.1 Hz,

−$(CH_2)_2$−N*H*−CO−NH−), 6.24 (d, 1H, J = 7.4 Hz, −$(CH_2)_2$−NH−CO−N*H*−), 4.38 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−), 4.10 (m, 1H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−), 4.09−3.99 (m, 4H, $C_9H_7N_2O$−CH_2−), 3.47 (m, 1H, one of −CH−CO−NH−CH_2−CH_2−$C_9H_7N_2O$), 3.35 (m, 1H, one of −CH−CO−NH−CH_2−CH_2−$C_9H_7N_2O$), 3.27−3.20 (m, 2H, $C_9H_7N_2O$−CH_2−CH_2−NH−CO−NH−), 3.01 (dd, 1H, J = 13.7, 3.8 Hz, one of −CH_2−C_6H_4Cl), 2.99−2.89 (m, 2H, −CH_2−NH−C(=NH)NH_2), 2.63 (dd, 1H, J = 13.7, 10.9 Hz, one of −CH_2−C_6H_4Cl), 2.58 (s, 3H, −CH_3), 2.56 (s, 3H, −CH_3), 1.32 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.22 (m, 1H, one of −CH_2-$(CH_2)_2$−NH−C(=NH)NH_2), 1.12−1.01 (m, 2H, −CH_2−CH_2−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 770.3299 (calc. for $C_{38}H_{45}ClN_{11}O_5$ [M+H], 770.3288).

5-Guanidino-2(S)-{3-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethyl]ureido}pentanoic Acid [1(R)-(4-Chlorobenzyl)-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxoethyl]amide (9-{*1,4,4*}). Yield after purification was 9.6 mg (33%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.55 (d, 1H, J = 8.6 Hz, −CO−N*H*−CH(CH_2−C_6H_4Cl)−CO−, conf 1), 8.46 (d, 1H, J = 8.6 Hz, −CO−N*H*−CH(CH_2−C_6H_4Cl)−CO−, conf 2), 8.07 (d, 1H, J = 8.0 Hz, quin 5-*H*), 7.75 (m, 1H, quin 7-*H*), 7.53 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.45 (m, 1H, quin 6-*H*), 7.36 (m, 1H, −CH_2−N*H*−C(=NH)NH_2), 7.26−7.09 (m, 8H, Ar*H*), 7.33 (m, 1H, −$(CH_2)_2$−N*H*−CO−NH−), 6.16 (m, 1H, −$(CH_2)_2$−NH−CO−N*H*−), 5.03 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−, conf 2), 4.98 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−, conf 2), 4.70 (d, 1H, J = 16.2 Hz, one of isoquin 1-*H*, conf 2), 4.69 (d, 1H, J = 16.9 Hz, one of isoquin 1-*H*, conf 1), 4.60 (d, 1H, J = 16.2, one of isoquin 1-*H*, conf 2), 4.49 (d, 1H, J = 16.9 Hz, one of isoquin 1-*H*, conf 1), 4.15 (m, 1H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−), 4.06−3.97 (m, 2H, $C_9H_7N_2O$−CH_2−), 3.78 (dt, 1H, J = 13.4, 5.6 Hz, one of isoquin 3-*H*, conf 1), 3.73 (dt, 1H, J = 12.9, 5.6 Hz, one of isoquin 3-*H*, conf 2), 3.62−3.52 (m, 1H one of isoquin 3-*H* conf 1, 1H one of isoquin 3-*H* conf 2), 3.33−3.22 (m, 2H, $C_9H_7N_2O$−CH_2−CH_2−), 3.05−2.90 (m, 3H, one of −CH_2−C_6H_4Cl, −CH_2−NH−C(=NH)NH_2), 2.83−2.64 (m, 3H, one of −CH_2−C_6H_4Cl, isoquin 4-*H*), 2.54 (s, 3H, −CH_3), 1.35 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.25−1.15 (m, 3H, −CH_2−CH_2−NH−C(=NH)NH_2, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 700.3142 (calc. for $C_{36}H_{43}ClN_9O_4$ [M+H], 700.3121).

5-Guanidino-2(S)-{3-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethyl]ureido}pentanoic Acid [2-(4-Chlorophenyl)-1(R)-isobutylcarbamoylethyl]amide (9{*1,4,5*}). Yield after purification was 10.6 mg (40%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.32 (d, 1H, J = 8.6 Hz, −N*H*−CH(CH_2−C_6H_4-Cl)−CO−), 8.08 (d, 1H, J = 8.1 Hz, quin 5-*H*), 8.00 (t, 1H, J = 5.6 Hz, −N*H*−C_4H_9), 7.77 (dd, 1H, J = 8.1 Hz, 6.9 Hz, quin 7-*H*), 7.55 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.46 (dd, 1H, J = 8.1, 6.9 Hz, quin 6-*H*), 7.33 (m, 1H, −CH_2−N*H*−C(=NH)NH_2), 7.29 (d, 2H, J = 8.2 Hz, phenyl 3-*H* and 5-*H*), 7.22 (d, 2H, J = 8.2 Hz, phenyl 2-*H* and 6-*H*), 6.34 (t, 1H, J = 5.9 Hz, −$(CH_2)_2$−N*H*−CO−NH−), 6.24 (d, 1H, J = 7.5 Hz, −$(CH_2)_2$−NH−CO−N*H*−), 4.44 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−), 4.06−4.00 (m, 3H, −NH−C*H*($(CH_2)_3$−NH−C(=NH)NH_2)−CO−, $C_9H_7N_2O$−CH_2−), 3.30−3.23 (m, 2H, $C_9H_7N_2O$−CH_2−CH_2−NH−), 3.01 (dd, 1H, J = 13.7, 4.4 Hz, one of −CH_2−C_6H_4Cl), 2.99−2.87 (m, 3H, −CH_2−NH−C(=NH)NH_2, one of NH−CH_2−$CH(CH_3)_2$), 2.82 (ddd, 1H, J = 13.4, 6.7, 5.6 Hz, one of NH−CH_2−$CH(CH_3)_2$), 2.70 (dd, 1H, J = 13.7, 10.6 Hz, one of −CH_2−C_6H_4Cl), 2.56 (s, 3H, −CH_3), 1.65 (m, 1H, NH−CH_2−C$H(CH_3)_2$), 1.33 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.23 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.13 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2), 1.06 (m, 1H, one of −CH_2−CH_2−NH−C(=NH)NH_2), 0.79 (d, 3H, J = 6.7 Hz, three of −NH−CH_2−$CH(CH_3)_2$), 0.77 (d, 3H, J = 6.7 Hz, −NH−CH_2−$CH(CH_3)_2$). *m*/*z* (HR-ESI): 640.3142 (calc. for $C_{31}H_{43}ClN_9O_4$ [M+H], 640.3121).

5-Guanidino-2(S)-{3-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)ethyl]ureido}pentanoic Acid {1(R)-(4-Chlorobenzyl)-2-[4-(4-methoxyphenyl)-piperazin-1-yl]-2-oxoethyl}-amide (9{*1,4,6*}). Yield after purification was 6.8 mg (22%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.53 (d, 1H, J = 8.7 Hz, −N*H*−CH(CH_2−C_6H_4Cl)−CO−), 8.07 (d, 1H, J = 8.1 Hz, quin 5-*H*), 7.76 (dd, 1H, J = 8.1, 7.0 Hz, quin 7-*H*), 7.53 (d, 1H, J = 8.1 Hz, quin 8-*H*), 7.45 (dd, 1H, J = 8.1, 7.0 Hz, quin 6-*H*), 7.37 (m, 1H, −CH_2−N*H*−C(=NH)NH_2), 7.29 (d, 2H, J = 8.4 Hz, chlorophenyl 3-*H* and 5-*H*), 7.25 (d, 2H, J = 8.2 Hz, chlorophenyl 2-*H* and 6-*H*), 6.86 (d, 2H, J = 9.1 Hz, methoxyphenyl 3-*H* and 5-*H*), 6.76 (d, 2H, J = 9.1 Hz, methoxyphenyl 2-*H* and 6-*H*), 6.32 (t, 1H, J = 6.0 Hz, −$(CH_2)_2$−N*H*-CO−NH−), 6.16 (d, 1H, J = 8.6 Hz, −$(CH_2)_2$−NH−CO−N*H*−), 4.96 (m, 1H, −NH−C*H*(CH_2−C_6H_4Cl)−CO−), 4.15 (m, 1H, −NH−C*H*-($(CH_2)_3$−NH−C(=NH)NH_2)−CO−), 4.01−3.91 (m, 2H, $C_9H_7N_2O$−CH_2−), 3.71−3.64 (m, 2H, two of −N−(CH_2−CH_2)$_2$−N−$C_6H_4OCH_3$), 3.59 (s, 3H, −O−CH_3), 3.52−3.45 (m, 2H, two of −N−(CH_2−CH_2)$_2$−N−$C_6H_4OCH_3$), 3.28−3.17 (m, 2H, $C_9H_7N_2O$−CH_2−CH_2−NH−), 3.05−2.90 (m, 4H, −CH_2−NH−C(=NH)NH_2, one of −CH−CH_2−C_6H_4Cl, one of −N−(CH_2−CH_2)$_2$−N−$C_6H_4OCH_3$), 2.89−2.75 (m, 4H, one of −CH−CH_2−C_6H_4Cl, three of −N−(CH_2−CH_2)$_2$−N−$C_6H_4OCH_3$), 2.53 (s, 3H, −C−CH_3), 1.35 (m, 1H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2), 1.26−1.15 (m, 3H, one of −CH_2−$(CH_2)_2$−NH−C(=NH)NH_2, −CH_2−CH_2−NH−C(=NH)NH_2). *m*/*z* (HR-ESI): 759.3522 (calc. for $C_{38}H_{48}ClN_{10}O_5$ [M+H], 759.3492).

Spiro(1-methanesulfonyl-3′-piperidine-2,3-dihydro-1*H*-indole-1-carboxylic Acid {2-(4-Chlorophenyl)-1-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-ethyl}-amide (9{*3,5,2*}). Yield after purification was 2.4 mg (14%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.44 (m, 1H, $NCH_2CH_2CH_2CCH_2$−), 1.54 (m, 3H, $NCH_2CH_2CH_2CCH_2$−), 2.80 (m, 5H, $NCH_2CH_2CH_2$-CCH_2−, N*H*CON, CH_2CH_2NHCO), 2.94 (m, 2H, CH_2CH_2-NCO), 3.02 (s, 3H, SO_2CH_3), 3.33 (m, 2H, $NCH_2CH_2CH_2$-CCH_2−), 3.84 (s, 2H, $CH_2NSO_2CH_3$), 3.92 (m, 2H, $NCH_2CH_2CH_2CCH_2$−), 4.43 (m, 1H, CH_2CH), 6.61 (d, J = 8.3 Hz, 2H, Ar*H*), 7.04 (m, 4H, Ar*H*), 7.14 (d, J = 2.3 Hz, 1H, Ar*H*), 7.28 (m, 6H, Ar*H*), 7.54 (d, J = 7.9 Hz, 1H, Ar*H*), 7.71 (br s, 1H, CH_2CH_2N*H*CO), 8.00 (t, J = 5.7 Hz, 1H, Ar*H*), 10.81 (s, N*H* indole).

Spiro(1-methanesulfonyl-3′-piperidine-1-carboxylic Acid [2-(4-Chlorophenyl)-1-(1-naphthalen-2-yl-ethylcarbamoyl)-ethyl]-amide (9{*3,5,11*}). Yield after purification was 2.3 mg (13%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.40 (d, J = 6.6 Hz, 3H, CHCH_3), 1.44−1.57 (m, 4H, NCH$_2$CH_2CCH_2-CH$_2$−), 2.78 (m, 2H, SO$_2$NCH_2), 2.93 (m, 2H, ClC$_6$H$_4$CH_2), 3.02 (s, 3H, SO$_2$CH_3), 3.83 (dd, J_1 = 5.5 Hz, J_2 = 16.5 Hz, 2H, NCH_2CH$_2$CCH$_2$CH_2−), 3.96 (t, J = 17.1 Hz, 2H, NCH_2-CH$_2$CCH$_2$CH_2−), 4.46 (m, 1H, CH$_2$CH), 5.51 (m, 1H, CH$_3$-CH), 6.64 (d, J = 8.8 Hz, 1H, NCONH), 6.97 (m, 2H, ArH), 7.21 m, 2H, ArH), 7.35 (m, 4H, ArH), 7.48 (m, 3H, ArH), 7.87 (m, 4H, ArH), 8.45 (d, J = 7.7 Hz, 1H, CHCONH).

Spiro(1-methanesulfonyl-3′-piperidine-1-carboxylic Acid {2-(4-Chlorophenyl)-1-[2-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-ethylcarbamoyl]-ethyl}-amide (9{*3,5,12*}). Yield after purification was 3.6 mg (20%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.43−1.57 (m, 4H, NCH$_2$CH_2CCH_2CH$_2$−), 2.64 (s, 3H, CCH_3), 2.76 (m, 3H, NCH_2CH$_2$CCH$_2$CH_2− and ClC$_6$H$_4$CH_2), 2.92 (dd, J_1 = 4.4 Hz, J_2 = 13.2 Hz, 1H, ClC$_6$H$_4$CH_2), 3.04 (s, 3H, SO$_2$CH_3), 3.45 (m, 2H, CONHCH$_2$-CH_2), 3.85 (s, 2H, SO$_2$NCH_2), 3.92 (m, 2H, NCH_2CH$_2$CCH$_2$-CH_2−), 4.11 (t, J = 6.5 Hz, 2H, CONHCH$_2$CH_2), 4.29 (m, 1H, CH$_2$CH), 6.63 (d, J = 8.8 Hz, 1H, NCONH), 7.06 (t, J = 7.7 Hz, 1H, ArH), 7.10 (d, J = 7.7 Hz, 1H, ArH), 7.23 (t, J = 7.7 Hz, 1H, ArH), 7.28 (m, 3H, ArH), 7.32 (m, 2H, ArH), 7.49 (t, J = 7.7 Hz, 1H, ArH), 7.58 (d, J = 7.7 Hz, 1H, ArH), 7.80 (d, J = 8.8 Hz, 1H, ArH), 8.11 (d, J = 7.7 Hz, 1H, ArH), 8.45 (d, J = 6.5 Hz, 1H, CHCONH).

***N*-Benzyl-3-(4-chlorophenyl)-2-[3-(2,2-diphenylethyl)-ureido]-propionamide (9{*3,6,1*}).** Yield after purification was 4.3 mg (31%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 2.72 (m, 1H, ClC$_6$H$_4$CH_2), 2.83 (m, 1H, ClC$_6$H$_4$CH_2), 3.60 (m, 2H, CH_2CH(Ph)$_2$), 4.04 (m, 1H, CH$_2$CH(Ph)$_2$), 4.19 (m, 1H, ClC$_6$H$_4$CH$_2$CH), 4.24 (m, 1H, ClC$_6$H$_4$CH$_2$CH), 4.39 (m, 1H, NHCH_2Ph), 6.00 (t, J = 5.7 Hz, NHCONHCH$_2$), 6.18 (d, J = 8.4 Hz, NHCONHCH), 7.05−7.29 (m, 19 H, ArH), 8.41 (t, J = 5.7 Hz, 1H, CONHCH$_2$).

1-[1-(4-Chlorobenzyl)-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxoethyl]-3-(2,2-diphenylethyl)-urea (9{*3,6,4*}). Yield after purification was 2.7 mg (19%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 2.72 (m, 4H, ClC$_6$H$_4$CH_2, *isoquin* 4-H), 3.61 (m, 3H, *isoquin* 3-H and NHCONHCH_2), 3.75 (m, 1H, NHCONHCH_2), 4.04 (m, 1H, CH$_2$CH(Ph)$_2$), 4.45 (m, 1H, *isoquin* 1-H), 4.65 (m, 1H, *isoquin* 1-H), 4.89 (m, 1H, ClC$_6$H$_4$CH$_2$CH), 5.97 (m, 1H, NHCONH), 6.36 (d, J = 8.8 Hz, 1H, NHCONH), 7.08−7.31 (m, 9 H, ArH), 7.25 (m, 9H, ArH), 8.41 (t, J = 5.7 Hz, 1H, CONHCH$_2$).

1-{1-(4-Chlorobenzyl)-2-oxo-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-ethyl}-3-(2,2-diphenylethyl)-urea (9{*3,6,15*}). Yield after purification was 2.7 mg (16%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.67 (m, 2H, CON(CH$_2$CH_2)$_2$CH), 2.05 (m, 2H, CON(CH$_2$CH_2)$_2$CH), 2.69 (m, 2H, ClC$_6$H$_4$CH_2), 2.87 (m, 1H, CON(CH_2CH$_2$)$_2$CH), 3.01 (m, 1H, CON(CH_2CH$_2$)$_2$C), 3.66 (m, 2H, CON(CH_2CH$_2$)$_2$C), 4.02 (m, 2H, NHCONHCH_2), 4.41 (m, 1H, CON(CH$_2$CH$_2$)$_2$-CH), 4.49 (m, 1H, CONHCH$_2$CH), 4.85 (m, 1H, ClC$_6$H$_4$-CH$_2$CH), 6.02 (s, 1H, NHCONH), 6.30 (d, J = 9.8 Hz, 1H, NHCONH), 6.96 (m, 3H, ArH), 7.25 (m, 15H, ArH), 10.83 (s, 1H, *benzoimidazole* NH).

Spiro(indan-1,4′-piperidine)-1-carboxylic Acid [1-Benzylcarbamoyl-2-(4-chlorophenyl)-ethyl]-amide (9{*3,7,1*}). Yield after purification was 3.8 mg (28%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.35 (t, J = 10.9 Hz, 2H, CON(CH$_2$-CH_2)$_2$C), 1.49 (m, 2H, CON(CH$_2$CH_2)$_2$C), 1.99 (m, 2H, *indane* CCH_2CH$_2$), 2.85 (m, 5H, CONHCH_2CH$_2$, *indane* CCH_2CH$_2$, ClC$_6$H$_4$CH_2), 3.01 (dd, J_1 = 14.3 Hz, J_2 = 5.5 Hz, 1H, *indane* CCH_2CH$_2$), 3.92 (dd, 2H, CON(CH_2-CH$_2$)$_2$C), 3.92 (m, 2H, CON(CH_2CH$_2$)$_2$C), 4.31 (m, 2H, CONHCH_2), 4.42 (m, 1H, ClC$_6$H$_4$CH$_2$CH), 6.62 (d, J = 7.7 Hz, 1H, NHCON), 7.00 (d, J = 6.6 Hz, 1H, ArH), 7.11−7.25 (m, 6H, ArH), 7.32 (m, 6H, ArH), 8.41 (t, J = 6.6 Hz, 1H, CONHCH$_2$).

Spiro(indan-1,4′-piperidine)-1-carboxylic Acid {2-(4-chlorophenyl)-1-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-ethyl}-amide (9{*3,7,2*}). Yield after purification was 3.9 mg (26%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.35 (t, J = 11.0 Hz, 2H, CON(CH$_2$CH_2)$_2$C), 1.49 (m, 2H, CON(CH$_2$-CH_2)$_2$C), 2.00 (m, 2H, *indane* CCH_2CH$_2$), 2.85 (m, 7H, CONHCH_2CH_2, *indane* CCH_2CH$_2$, ClC$_6$H$_4$CH_2), 2.96 (dd, J_1 = 13.2 Hz, J_2 = 4.4 Hz, 1H, *indane* CCH_2CH$_2$), 3.35 (m, 2H, CON(CH_2CH$_2$)$_2$C), 3.92 (m, 2H, CON(CH_2CH$_2$)$_2$C), 4.35 (m, 1H, ClC$_6$H$_4$CH$_2$CH), 6.55 (d, J = 8.8 Hz, 1H, NHCON), 6.95−7.23 (m, 7H, ArH), 7.28−7.35 (m, 4H, ArH), 7.56 (d, J = 7.7 Hz, 1H, ArH), 8.01 (t, J = 7.7 Hz, 1H, CONHCH$_2$), 10.82 (s, 1H, *tryptamine* NH).

Spiro(indan-1,4′-piperidine)-1-carboxylic Acid [1-(4-Chlorobenzyl)-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxo-ethyl]-amide (9{*3,7,4*}). Yield after purification was 2.0 mg (14%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.34 (m, 2H, CON(CH$_2$CH_2)$_2$C), 1.49 (m, 2H, CON(CH$_2$CH_2)$_2$C), 2.00 (m, 2H, *indane* CCH$_2$CH_2), 2.83 (m, 8H, *isoquin* 3-H and 4-H, *indane* CCH_2CH$_2$, ClC$_6$H$_4$CH_2), 3.60 (m, 2H, CON(CH_2-CH$_2$)$_2$C), 3.94 (m, 2H, CON(CH_2CH$_2$)$_2$C), 4.48 (m, 1H, *isoquin* 1-H), 4.80 (m, 2H, *isoquin* 1-H and ClC$_6$H$_4$CH$_2$CH), 6.80 (m, 1H, NHCON), 7.03 (m, 1H, ArH), 7.11−7.33 (m, 11H, ArH).

Spiro(indan-1,4′-piperidine)-1-carboxylic Acid [2-(4-Chlorophenyl)-1-(2,2-diphenylethylcarbamoyl)-ethyl]-amide (9{*3,7,7*}). Yield after purification was 3.6 mg (23%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.32 (t, J = 12.1 Hz, 2H, CON(CH$_2$CH_2)$_2$C), 1.45 (m, 2H, CON(CH$_2$CH_2)$_2$C), 1.96 (m, 2H, *indane* CCH_2CH$_2$), 2.62 (m, 2H, ClC$_6$H$_4$CH_2), 2.75 (m, 2H, *indane* CCH$_2$CH_2), 2.83 (t, J = 6.6 Hz, 2H, CONHCH_2), 3.65 (m, 1H, CON(CH_2CH$_2$)$_2$C), 3.84 (m, 3H, CON(CH_2CH$_2$)$_2$C), 4.18 (t, J = 7.7 Hz, 1H, CONHCH$_2$CH), 4.24 (m, 1H, ClC$_6$H$_4$CH$_2$CH), 6.45 (d, J = 8.7 Hz, 1H, NHCON), 7.00 (d, 1H, ArH), 7.15 (m, 7H, ArH), 7.28 (m, 10H, ArH), 7.95 (t, J = 5.5 Hz, 1H, CONH).

Spiro(indan-1,4′-piperidine)-1-carboxylic Acid {1-(4-Chlorobenzyl)-2-[4-(4-methoxyphenyl)-piperazin-1-yl]-2-oxoethyl}-amide (9{*3,7,14*}). Yield after purification was 4.0 mg (26%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.37 (m, 2H, CON(CH_2CH$_2$)$_2$C), 1.52 (m, 2H, CON(CH_2CH$_2$)$_2$C), 2.01 (m, 2H, *indane* CCH$_2$CH_2), 2.85 (m, 10H, *indane* CCH_2-CH_2, ClC$_6$H$_4$CH_2, CON(CH_2CH$_2$)$_2$N, CON(CH_2CH$_2$)$_2$C),

3.23 (m, 2H, CON(CH_2CH_2)$_2$CH), 3.57 (m, 2H, CON(CH_2-CH_2)$_2$N), 3.70 (s, 3H, OCH_3), 3.97 (m, 2H, CON(CH_2-CH_2)$_2$N), 4.85 (m, 1H, $ClC_6H_4CH_2CH$), 6.84 (m, 5H, NHCON and ArH), 7.03 (m, 1H, ArH), 7.11 (m, 2H, ArH), 7.18 (m, 1H, ArH), 7.32 (m, 4H, ArH).

Spiro(indan-1,4′-piperidine)-1-carboxylic Acid {1-(4-Chlorobenzyl)-2-oxo-2-[4-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)-piperidin-1-yl]-ethyl}-amide (9{*3,7,15*}). Yield after purification was 2.6 mg (16%). ^{1}H NMR (600 MHz, d_6-DMSO): δ 1.37 (m, 2H, CON(CH_2CH_2)$_2$C), 1.49 (m, 2H, CON(CH_2CH_2)$_2$C), 1.67 (m, CON(CH_2CH_2)$_2$CH), 2.01 (m, 2H, *indane* CCH_2CH_2 and CON(CH_2CH_2)$_2$CH), 2.68 (m, 1H, *indane* CCH_2CH_2), 2.83 (m, 5H, *indane* CCH_2CH_2, ClC_6H_4-CH_2, CON(CH_2CH_2)$_2$CH), 2.98 (m, 2H, CON(CH_2CH_2)$_2$-CH), 4.04 (m, 3H, CON(CH_2CH_2)$_2$C), 4.53 (m, 2H, CON-(CH_2CH_2)$_2$C and CON(CH_2CH_2)$_2$CH), 4.84 (m, 1H, ClC_6H_4-CH_2CH), 6.71 (m, 1H, NHCON), 6.85−7.25 (m, 7H, ArH), 7.30−7.45 (m, 5H, ArH), 10.85 (s, 1H, *benzoimidazole*-2-*one* NH).

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Supporting Information Available. Description of the synthesis of some of the amines used in the library, as well as spectral data for the library members (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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