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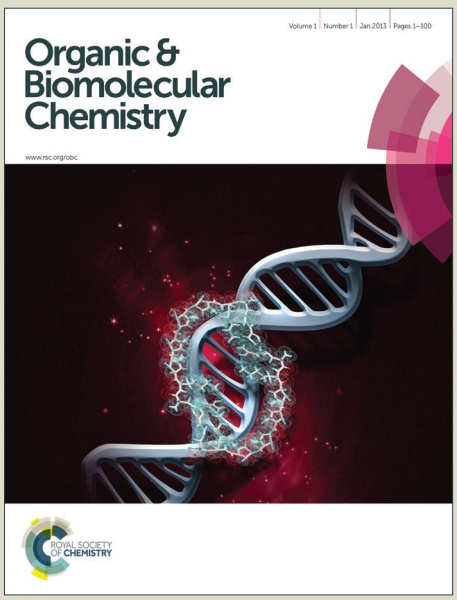

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A facile one pot route for the synthesis of imide tethered peptidomimetics

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A simple and efficient method for the synthesis of *N, N'*-orthogonally protected imide tethered peptidomimetics is presented. The imide peptidomimetics were synthesized by coupling *in situ* generated selenocarboxylate of N^{α}-protected amino acids with N^{α}-protected amino acid azides in good yields. The protocol was also successfully applied for the synthesis of hybrid tripeptidomimetics bearing both amide and imide functionalities. In addition, coumarinic imide conjugates of amino acids have been accomplished employing this protocol. The present method provides a convenient and easy access to imide tethered peptidomimetics and compatible with common protecting groups employed in peptide chemistry.

Introduction

As the central biological role of peptides has become more explicit, the replacement of the peptide bond by surrogates to enhance metabolic stability and/or probe receptor specificity has become a central theme of research.[1] Modification of an amide backbone with isosteres having specific amide conformational constraints and beneficial biological activities is often necessary for enhancing enzymatic stability of a peptide lead in drug development.[1a] In this direction, several classes of peptidomimetics possessing non-native bonds including ureas, carbamates, oligosulfonamides, thioxopeptides, hydrazino peptides, aminoxy peptides, reduced amide (methylene), heterocycles and peptoids have been successfully explored for therapeutic applications.[1,2] Our group has demonstrated the synthesis of ureido, thioureido, selenoureido peptides, selenoxopeptides as well as various heterocyclic tethered peptidomimetics in recent period.[3]

Imide functionality possesses two carbonyl groups bound to nitrogen and has complementary hydrogen bonding propensity similar to that of urea. In addition to being valuable intermediates in synthesis, they are widespread in pharmaceuticals such as ethosuximide, thalidomide, antiracetam and fungisides such as captan.[4] Also their significance is evident by their presence in naturally occurring compounds such as thymine, uracil, antibiotic fumaramidmycin,[5a,b] coniothyriomycin,[5c] SB-311009,[5d,e] palauimide,[5f] immunosuppressants microlin A and B,[5g] dolstatin 15,[5h] cytotoxic anticancer agent althiomycin.[5i] On the other hand, imide dipeptides were shown to adopt β-folding conformations in non-H-bonding solvents, exhibit strong hydrogen-bonding propensity, and form much stronger and more stable β-sheet-like interactions than those of the natural peptide sequences.[6] The recent interesting developments of imide chemistry in peptides include the use of imide ligation for assembly and controlled disassembly of peptide-drug conjugates[7] and the activation of backbone amide in a peptide via a pyroglutamyl imide, which then leads to a peptide thioester upon displacement by a thiol.[8] In another report, peptide imides were generated by Ag(I)-promoted coupling of amino acids and peptides with amino ester thioamides which undergo regioselective hydrolysis to native peptides.[9]

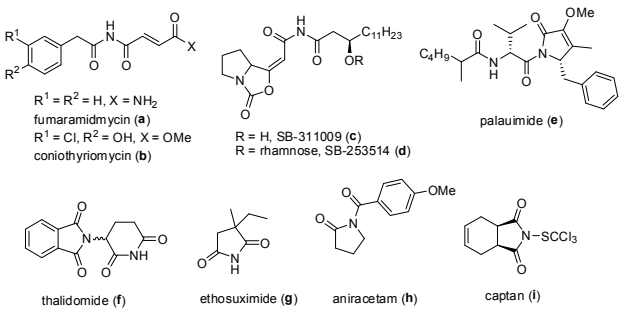

Figure 1. Structures of some naturally occurring imides (**a**-**e**) and pharmaceutically active compounds (**f**-**h**) and a fungicide (**i**) with imide functionality

Imides were generally prepared by the acylation of aromatic amides with excess of acylating reagents such as acyl chloride or anhydride under strong basic or acidic conditions.[10] Imides were also prepared by the Pd catalysed coupling reaction of

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organoborons with methyl-*N*-[methoxy(methylthio)]methylene carbamate in the presence of excess of Cu(I) thiophene-2-carboxylate.[11] Wang et al. reported a copper catalysed amidation of aldehydes in presence of *N*-bromosuccinimide for the synthesis of imides.[12] Nicolaou and Mathison reported the oxidation of secondary amides to corresponding imides in presence of Dess-Martin periodinane.[13] The ceric ammonium nitrate promoted oxidation of substituted oxazoles yields the imide derivatives.[14] In another report, arylamino imides were synthesized from tertiary amines in a copper-catalysed Ugi type reaction.[15] Most of these approaches though efficient for the synthesis of imide derivatives, they are largely limited to aromatic imide derivatives.

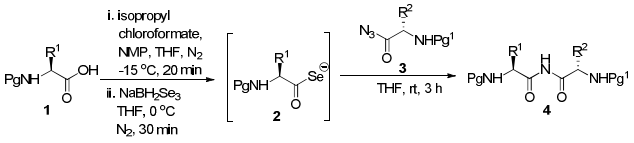
Imides have also been employed as intermediates in the synthesis of α-aminodicarboxylic acids starting from cyclic amino acids such as acylated L-proline derivatives[16a,b] as well as in the synthesis of L-ω-carbamoyl-α-amino acids[16c,d] and (*S*)-6-hydroxynorleucine[16e] from acyclic acyl amines.[16] Also few examples of oxidation of glycine residues to imides in a peptide ester has been reported.[17] All these methods were based on oxidation of amide framework using ruthenium based oxidizing agents.

Though imide derivatives of amino acids have been reported, imide as a peptide bond isostere is limited to few reports. This can be ascribed to difficult synthetic accessibility to imide as a peptide bond replacement by existing methods as well as harsh and tedious conditions that are not compatible with sensitive functionalities in peptides which can lead to racemization and other side reactions. Andrus et al. reported the synthesis of microlin precursor mixed acyclic imides by reacting amide anion of a lactam (generated using *n*-BuLi at -78 ^{o}C) with pentafluorophenyl ester of proline derivatives at -78 ^{o}C.[18] Ke et al. used similar strategy for the synthesis of imide dipeptides by coupling protected amino acid amide anions with 4-nitrophenyl esters of amino acids using *n*-BuLi at -78 ^{o}C.[19] Thus the method involves difficulty of handling *n*-BuLi and the yields of imide-dipeptides reported were moderate (54-68%). In another report, Mhidia et al.[7] employed reaction of peptide thioacids with azidoformates for the assembly of drug conjugates via imide ligation. Several other groups have also explored the Williams amidation reaction of thioacids with electron-poor azides such as sulfonyl azides for peptide or protein conjugate synthesis.[20] However, for electon rich and sterically hindered azides, the thioacid/azide amidation leads to low yields and often requires high reactant concentration and temperature to achieve satisfactory conversions.[21]

Considering the greater reactivity of selenocarboxylates as compared to thioacids, Knapp and Darout reacted selenocarboxylates with azides such as *N*-glycosyl azide and hindered 2-azidopiperidine derivative leading to amidation at room temperature.[22a] Hu and coworkers[22b,d] have improvised this methodology for the generation of selenocarboxylates which are then coupled with azides to form the amide bond. Few examples of electron deficient azides such as phosphoryl azide, sulfonyl azide and benzoyl azide have also been explored. However benzoyl azide gave poor yield on reaction with two equivalents of benzoic acid selenocarboxylate at 55 ^{o}C in THF. We envisioned that the enhanced reactivity of selenocarboxylates can be tapped for a useful imide bond formation via its coupling with an acid azide. Thus we envisaged to prepare imide tethered-dipeptides in a straight forward route involving in situ formation of selenocarboxylate intermediate of N^{α}-protected amino acids and the subsequent non-nucleophilic imidation with N^{α}-protected amino acid azides in a single pot.

Results and discussion

Initially N^{α}-protected amino acids were converted into corresponding selenocarboxylates using Lalancette reagent. The selenating reagent, $NaBH_2Se_3$ was freshly prepared by a slight modification of the literature procedure i.e., by the treatment of $NaBH_4$ with selenium powder in THF at 0 ^{o}C under N_2 atmosphere.[23] The reagent was less explored as a selenium transfer agent and recently employed by us for the synthesis of N^{β}-amino diselenides.[24] The precursor amino acid **1a** was first activated with isopropyl chloroformate (^{i}PCF) and N-methylpiperidine (NMP) in THF at -15 ^{o}C for 20 min to the corresponding mixed anhydride. The mixed anhydride was in situ treated with $NaBH_2Se_3$ under N_2 atmosphere for 30 min to generate the corresponding selenocarboxylate **2a**. Thus formed selenocarboxylate was reacted immediately with the N^{α}-protected amino acid azide[25] **3a** to form the corresponding imide derivative **4a** (Scheme 1). The reaction was monitored by TLC for the disappearance of starting acid azide, which was then subjected to aqueous work up and purification.



Scheme 1 One pot synthesis of imide peptidomimetics from Nα-protected amino acid selenocarboxylates and amino acid derived acid azides

Next we set out to optimize the coupling conditions for the selenocarboxylate/acid azide imidation using model substrates Fmoc-Ala-N_3 **3a** and selenocarboxylate derived from Boc-Phe-OH **1a**. Different solvents *viz* THF, acetonitrile, toluene, CH_2Cl_2 and ethanol were screened for the selenocarboxylate/acid azide imidation reaction in parallel reactions (Table 1). THF was found to be the solvent of choice with 1.5 equiv of requisite selenocarboxylate for an optimum yield of 92% of the desired imide. An increase of the selenocarboxylate equivalent and change of solvents had no significant effect on the overall yields. Further increase of temperature to 55 ^{o}C resulted in lower yield of imide, presumably due to the instability of acyl azide leading Curtius rearrangement (Table 1, entry 3). The optimized conditions were then employed with a variety of acid azides and amino acids for the preparation of imide tethered dipeptidomimetics in good yields (Table 2, entries **a**-**f**). It is noteworthy that the mild reaction conditions are compatible with commonly employed protecting groups

(Fmoc, Boc, Cbz) in peptide chemistry. To further check the efficiency and scope of the protocol, the reaction invloving selenocarboxyalte of amino acid **1a** and amino acid azide **3a** was carried out on 20 mmol scale. To our gratification, a satisfactory yield of 85% was obtained under the aforementioned optimized conditions. In a separare experiment, the coupling of selenocarboxylate of Fmoc-Leu-OH with benzoyl azide was carried out to find out the possibility of the acyl scrambling which was observed in the analogous coupling of thioacids.[7b] However, only the unsymmetrical imide Fmoc-Leu-ψ[CONHCO]Ph was isolated in 88 % yield. The advantage of the present method over the thioacid coupling with azides is the superior reactivity of selenocarboxylates which accelerates coupling with the acid azides. The scrambling of acyl groups leading to mixture of symmetrical and unsymmetrical imides in case of thioacid coupling can be attributed to the lower reactivity and long reaction duration. The coupling conditions employed in the present protocol was found to be racemization free as evidenced by RP-HPLC analysis of diastereomeric imide peptidyl adducts Fmoc-L-Phg-ψ[CONHCO]-Ala-Boc 4d and Fmoc-D-Phg-ψ[CONHCO]-Ala-Boc 4d*. The compounds 4d and 4d* showed the retention times of 19.56 min and 17.75 min respectively. Further, the mixture prepared by coupling Boc-Ala-N_3 with racemic Fmoc-L,D-Phg-OH showed distinct retention times 17.60 min and 19.09 min indicating the presence of two isomers and confirming that the protocol is free from racemization.

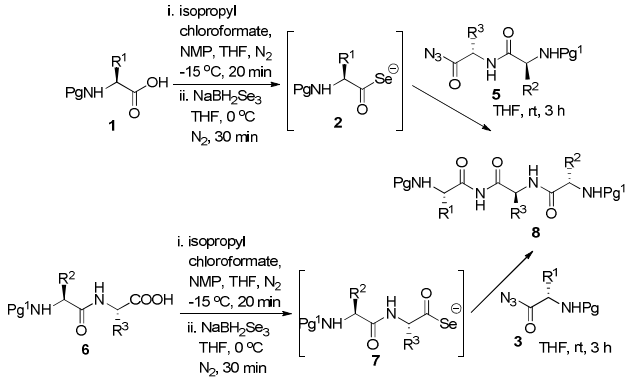
Table 1 Optimization of coupling conditions for the imidation reaction

Entry	Solvent	Equivalents of selenocarboxylate	Yield[a] (%)
1	THF	1.2	88
2	THF	1.5	92
3	THF	1.5	68[b]
4	THF	2.0	92
5	acetonitrile	1.5	82
6	toluene	1.5	68
7	CH_2Cl_2	1.5	70
8	ethanol	1.5	75

Reaction condition: Boc-Phe-OH, isopropyl chloroformate, NMP, THF, -15 °C, 20 min; Then add freshly prepared $NaBH_2Se_3$ to the mixture under N_2 at 0 °C; After 20 min of stirring add Fmoc-Ala-N_3 to the mixture. [a] Isolated yield after silica gel column chromatography, [b] coupiling carried out at 55 °C.

In the next part of the study, synthesis of hybrid tripeptidomimetics containing both amide and imide functionalities in the peptide backbone was explored. In this direction, the *in situ* generated selenocarboxylate of Boc-Ala-OH was reacted with the dipeptide acid azide[25b] Fmoc-Ala-Phe-N_3. The resultant peptide imide hybrid Fmoc-Ala-Phe-ψ[CONHCO]-Ala-Boc was obtained in poorer yield of 20% even after 4 h. The starting azide was recovered from the reaction mixture quantitatively. The lower yield is largely due to the lesser solubility of Fmoc-protected peptide azide leading to heterogeneity of the reaction mixture. However, when Cbz-Ala-Phe-N_3 was coupled with selenocarboxylate of Fmoc-Ala-OH, the reaction mixture was homogeneous and gratifyingly the yield of the imide product **8a** (Table 2 entry h) was improved to 82 %. As an alternate strategy, we carried out reverse coupling of *in situ* generated peptide acid derived selenocarboxylates and N^{α}-protected amino acid azides. At first, N^{α}-protected peptide acids (obtained by the standard procedure)[26] was treated with isopropyl chloroformate (1.5 eq) and *N*-methylpiperidine (1.5 eq) followed by treatment with $NaBH_2Se_3$ (1.5 eq) to generate corresponding peptide selenocarboxylates in situ. The peptide selenocarboxylates were then reacted with N^{α}-protected amino acid azide (1.0 eq). To our gratification the resultant hybrid tripeptidomimetic **8b-8e** bearing amide and imide units in the peptide backbone were isolated in 76-84% yield after workup and purification by column chromatography (Scheme 2, Table 2 entries i-l). Inspired by these results, next we coupled the peptide azide Cbz-Ala-Phe-N_3 with peptide selenocarboxylate of Boc-Ala-Phe-OH. A satisfactory yield (74%) of **8f** (Table 2 entry m) was obtained proving the efficacy of the method for the insertion of imide tether in the middle of desired peptides.

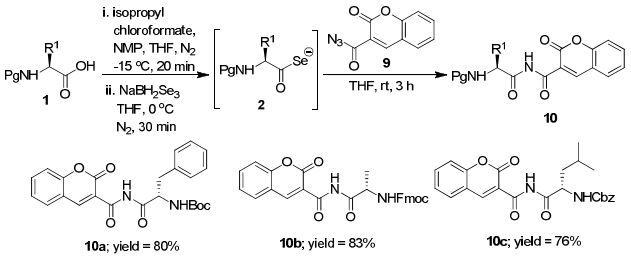
The possibility of racemization in case of activated dipeptide selenocarboxylates was determined by the RP-HPLC analyses of imide adducts obtained by coupling selenocarboxylate of Boc-Ala-Phe-OH with Fmoc-D/L-Ala-N_3. The compounds Boc-Ala-Phe-ψ[CONHCO]-L-Ala-Fmoc **8b** and Boc-Ala-Phe-ψ[CONHCO]-D-Ala-Fmoc **8b*** showed the retention times of 17.04 min and 14.20 min respectively, whereas their equimolar mixture indicated distinct retention times at 17.29 min and 14.63 min thereby confirming the absence of racemization.



Scheme 2 Synthesis of hybrid tripeptidomimetics containing both amide and imide functionalities from peptide acid derived selenocarboxylates (Pg, Pg^1 = Boc, Cbz or Fmoc; R^1, R^2, R^3 = amino acid side chains)

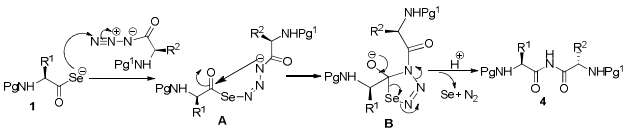
Coumarin and its derivatives have broad applicability in medicinal chemistry and have been extensively used in fluorescent dyes,[27a] organic light-emitting diodes[27b-d] and fluorescent labels as well as probes to study complex biological systems.[27] Also 3-substituted coumarinic systems were shown to induce specific activities[28] and thus coumarin 3-carboxylic acid is converted to corresponding acid azide **9** through the reported procedure.[25c] The resulting acid azide was then coupled with the *in situ* generated selenocarboxylates **2**, under the optimized reaction conditions to afford the corresponding

coumarinic imide conjugates of amino acids **10** in reasonably good yields (Scheme 3).



Scheme 3 One pot synthesis of coumarin conjugates of imide derivatives from N^{α}-protected amino acid selenocarboxylates

Based on literature precedents[22] and our observations, a plausible mechanism for the imide formation has been postulated in scheme 4. The selenocarboxylates have been shown to be stable in solvents such as THF and acetonitrile with a half life 11-16 h.[22b] The longer half life has been ascribed the presence of traces of reducing agents in the reaction mixture, which might delay the oxidative decomposition of selenocarboxylates. The linear coupling of selenocarboxylate ion **2** with the acid azide initially forms an intermediate (**A**). This intermediate (**A**) then undergoes intramolecular cyclization to form a five membered selenatriazoline intermediate (**B**). The selenatriazoline intermediate on aqueous workup undergoes a retro-[3+2] cycloaddition generating the target imide **4** as a stable molecule with the release of N_2 and elemental selenium as byproducts.



Scheme 4 Possible reaction pathway for imide formation

Conclusion

A simple, mild and facile route for the preparation of *N, N'*-orthogonally protected imide tethered peptidomimetics in good yields has been described. The protocol employs in situ generated selenocarboxylates of N^{α}-protected amino acids and N^{α}-protected amino acid azides as precursor elements to incorporate imide moiety into the peptide backbone. The scale-up of the reaction up to 20 mmol has been accomplished smoothly. The same protocol was then extended to prepare hybrid tripeptidomimetics bearing both amide and imide units in the peptide backbone employing selenocarboxylates of N^{α}-protected peptide acids and N^{α}-protected amino acid azides. Further coumarinic imide conjugates of amino acids were accessed using the similar strategy. The facile incorporation of imide motif in the dipeptide and tripeptide backbone will be significant considering their potential to generate different possible backbone H-bonding patterns.

Table 2 Imidation of amino acid derived selenocarboxylates with amino acid azides

Entry	Amino acid 1/ peptide acid 7	Acid azide 3	Imide peptidomimetics	Yield (%)[a]
a	Boc-Phe-OH	Fmoc-Ala-N_3	Fmoc-Ala-ψ[CONHCO]-Phe-Boc (**4a**)	92
b	Boc-Val-OH	Fmoc-Phe-N_3	Fmoc-Phe-ψ[CONHCO]-Val-Boc (**4b**)	90
c	Cbz-Gly-OH	Fmoc-Phe-N_3	Fmoc-Phe-ψ[CONHCO]-Gly-Cbz (**4c**)	88
d	Boc-Ala-OH	Fmoc-Phg-N_3	Fmoc-Phg-ψ[CONHCO]-Ala-Boc (**4d**)	89
e	Cbz-Leu-OH	Fmoc-Val-N_3	Fmoc-Val-ψ[CONHCO]-Leu-Cbz (**4e**)	85
f	Cbz-Val-OH	Boc-Gly-N_3	Boc-Gly-ψ[CONHCO]-Val-Cbz (**4f**)	87
g	Fmoc-Leu-OH	$PhCON_3$	Fmoc-Leu-ψ[CONHCO]-Ph (**4g**)	88
h	Fmoc-Ala-OH	Cbz-Ala-Phe-N_3	Cbz-Ala-Phe-ψ[CONHCO]-Ala-Fmoc (**8a**)	82
i	Boc-Ala-Phe-OH	Fmoc-Ala-N_3	Boc-Ala-Phe-ψ[CONHCO]-Ala-Fmoc (**8b**)	84
j	Boc-Phe-Val-OH	Fmoc-Ile-N_3	Boc-Phe-Val-ψ[CONHCO]-Ile-Fmoc (**8c**)	78
k	Cbz-Ala-Leu-OH	Fmoc-Phe-N_3	Cbz-Ala-Leu-ψ[CONHCO]-Phe-Fmoc (**8d**)	80
l	Boc-Ala-Leu-OH	Cbz-Gly-N_3	Boc-Ala-Leu-ψ[CONHCO]-Gly-Cbz (**8e**)	76
m	Boc-Ala-Phe-OH	Cbz-Ala-Phe-N_3	Boc-Ala-Phe-ψ[CONHCO]-Phe-Ala-Cbz (**8f**)	74

[a] Isolated yield after silica gel column chromatography

Experimental

General experimental details

All chemicals were used as obtained from Sigma Aldrich Company, USA. All the solvents were dried and purified using recommended procedures in the literature whenever necessary. High resolution mass spectra were recorded on a Micromass Q-TOF micromass spectrometer and ESMS on LCQ Deca XP MAX using electron spray ionization mode. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 300 MHz and 100 MHz spectrometer, respectively, at the Indian Institute of Science, Bangalore. RP-HPLC analysis of epimers was carried out by LCQ Deca XP MAX VWD at λ = 272nm; flow

rate: 1.0 mL/min; column: Thermoscientific C18 syncronis, pore size-5 µm, diameter x length = 4.6 x 250 nm; method: gradient 0.1% TFA water-acetonitrile; acetonitrile 30-100% in 30 min. Melting points were determined in an open capillary and are uncorrected. TLC experiments were done using MERCK TLC aluminum sheets (silica gel 60 F254) and chromatograms were visualized by exposing in iodine chamber or UV-lamp. Column chromatography was performed on silica gel (100-200 mesh) using ethyl acetate and hexane mixtures as eluent.

Preparation of $NaBH_2Se_3$. To a solution of sodium borohydride (1.5 mmol) in anhydrous THF (5 mL), black selenium powder (4.5 mmol) was added at room temperature under N_2 atmosphere. Immediate gas evolution is observed and the reaction is exothermic. The consumption of the selenium powder in less than 10 min indicated the formation of $NaBH_2Se_3$. The reagent is ready to be used.

General Imidation Procedure. To a solution of N^{α}-protected amino acid (1.5 mmol) and *N*-methylpiperidine (0.182 mL, 1.5 mmol) in THF (10 mL) was added a 1.0 M solution of isopropylchloroformate (1.5 mmol) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 20 min at 0 °C. Then, the obtained mixed anhydride solution was slowly added into the prepared $NaBH_2Se_3$ solution over a period of 5 min. The reaction mixture was stirred for an additional 30 min below 5 °C under a nitrogen atmosphere. Then, a solution of azide (1.0 mmol) in THF (1 mL) was added into the above N^{α}-protected amino selenocarboxylate solution via a syringe. the imidation reaction was carried out at 0 °C to room temperature for 3 h. The reaction mixture was filtered through a Celite pad that was then rinsed with EtOAc (3 × 25 mL). The combined organic phase was washed with 5% $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 through filtration, the filtrate was treated with activated charcoal. The activated charcoal was filtered off, and the filtrate was then concentrated to dryness. The crude product was purified by flash column chromatography (FCC) on silica gel.

Fmoc-Ala-ψ[CONHCO]-Phe-Boc, 4a. White solid (0.51 g, 92%). Mp 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.55 (br s, 1H), 7.80-7.00 (m, 13H), 5.80 (br s, 1H), 5.43 (br s, 1H), 4.63 (s, 1H), 4.27 (t, *J* = 6 Hz, 1H), 4.24 (d, *J* = 8 Hz, 2H), 4.18-4.10 (m, 1H), 3.33 (d, *J* = 4 Hz, 1H), 3.18 (d, *J* = 8 Hz, 1H), 1.40 (s, 9H) 1.25 (d, *J* = 4 Hz, 3H); : ^{13}C NMR (75 MHz, $CDCl_3$, δ): 174.98, 174.05, 156.39, 154.03, 143.26, 141.01, 136.67, 131.58, 130.72, 128.28, 126.05, 125.40, 125.16, 119.12, 79.95, 67.26, 62.61, 53.12, 47.45, 37.93, 28.20, 19.07; HRMS calcd for $C_{32}H_{35}N_3O_6$ $(M+H)^+$ 558.2604; found: 558.2607.

Fmoc-Phe-ψ[CONHCO]-Val-Boc, 4b. White solid (0.52 g, 90%). Mp 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.95 (br s, 1H), 7.77-7.21 (m, 13H), 4.99 (br s, 1H), 4.40 (m, 3H), 4.18 (t, *J* = 4 Hz, 2H), 3.93 (br s, 1H), 2.85 (d, *J* = 4 Hz, 2H), 2.20 (m , 1H) 1.45 (s, 9H) 1.26 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 174.08, 171.40, 155.60, 155.27, 143.95, 141.46, 137.69, 129.38, 128.76, 127.83, 127.19, 126.79, 125.15,120.11, 79.69, 66.83, 64.08, 54.25, 47.37, 37.43, 31.11, 29.82, 17.60; HRMS calcd for $C_{34}H_{39}N_3O_6$ $(M+H)^+$ 586.2917; found: 586.2935.

Fmoc-Phe-ψ[CONHCO]-Gly-Cbz, 4c. White solid (0.53 g, 92%). Mp 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.63 (br s, 1H), 7.95-7.14 (m, 19H), 5.03 (d, *J* = 7.2 Hz, 2H), 4.41 (t, *J* = 5.6 Hz, 1H), 4.29 (t, *J* = 5.6 Hz, 2H), 4.27 (d, *J* = 3.2 Hz, 1H), 3.35 (s, 2H), 2.94 (d, *J* = 8 Hz, 2H), 2.72 (d, *J* = 12 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 174.26, 171.49, 155.10,154.32, 143.81, 143.64, 141.26, 136.89, 129.04, 128.72, 128.14, 127.75, 127.42, 127.10, 126.84, 125.81, 125.04, 119.95, 66.98, 65.88, 57.79, 47.02, 45.09, 38.67; HRMS calcd for $C_{34}H_{31}N_3O_6$ $(M+H)^+$ 578.2291; found: 578.2297.

Fmoc-Phg-ψ[CONHCO]-Ala-Boc, 4d. White solid (0.48 g, 89%). Mp 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.67 (br s, 1H), 7.73-7.23 (m, 13H), 5.78(br s, 1H), 5.27 (br s, 1H), 4.34(t, *J* = 12 Hz, 1H), 4.22-4.16 (m, 2H), 4.10 (d, *J* = 7.2 Hz, 2H), 1.37 (s, 9H) 1.35 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 174.88, 171.33, 156.34, 155.81, 143,54, 140.91, 139.49, 133.89, 129.54, 127.44, 126.81, 124.88, 123.48, 119.66, 80.48, 66.37, 60.88, 50.91, 46.85, 29.35, 18.60; HRMS calcd for $C_{31}H_{33}N_3O_6$ $(M+H)^+$ 544.2448; found: 544.2443.

Fmoc-Val-ψ[CONHCO]-Leu-Cbz, 4e. White solid (0.49 g, 85%). Mp 184-186 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.51 (br s, 1H), 7.77-7.26 (m, 14H), 6.31 (br s, 1H), 5.12 (s, 2H), 4.88-4.78 (m, 1H), 4.71-4.62 (m, 1H), 4.43 (d, J= 12.4 Hz, 2H), 4.26 (t, J = 5.2 Hz, 1H), 2.82-2.78 (m, 1H), 1.70-1.58 (m, 3H), 0.98 (d, J = 7.2 Hz, 6H), 0.86 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.50, 171.06, 156.64, 155.87, 143.58, 140.94, 138.13, 134.28, 128.52, 127.45, 126.83, 125.01, 123.73, 119.67, 66.95, 66.80, 60.68, 50.94, 46.88, 40.28, 30.90, 26.87, 22.05, 18.70; HRMS calcd for $C_{34}H_{39}N_3O_6$ $(M+H)^+$ 586.2917; found: 586.2912.

Boc-Gly-ψ[CONHCO]-Val-Cbz, 4f. White solid (0.35 g, 87%). Mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.46 (br s, 1H), 7.36-7.24 (m, 5H), 6.45 (d, *J* = 8 Hz, 1H), 5.29 (br s, 1H), 5.13 (s, 2H), 4.52-4.50 (m, 1H), 3.82 (d, 2H *J* = 8Hz), 2.18-2.12 (m, 1H), 1.46 (s, 9H) 0.93-0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 171.76, 171.39, 156.06, 155.36, 136.56, 129.28, 128.59, 126.85, 80.16, 67.18, 65.79, 50.05, 31.21, 28.19, 19.39; ESMS m/z: calcd for $C_{20}H_{29}N_3O_6$ $(M+H)^+$ 408.20; found: 408.20.

Fmoc-Leu-ψ[CONHCO]-Ph, 4g. White solid (0.40 g, 88%). Mp 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.38 (br s, 1H), 7.84-7.26 (m, 13H), 5.55 (d, J = 8.2 Hz, 1H), 4.92 (br s, 1H), 4.42 (t, J = 7.2 Hz, 2H), 4.22 (d, J = 6.8 Hz, 1H), 1.82-1.62 (m, 3H) 0.92 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 172.09, 167.31, 156.56, 151.16, 143.90, 143.71, 141.42, 127.85, 127.20, 125.17, 124.59, 124.10, 120.11, 67.31, 53.53, 47.25, 41.14, 23.53, 22.15; HRMS calcd for $C_{28}H_{28}N_2NaO_4$ $(M+Na)^+$ 479.1947; found: 479.1943.

Cbz-Ala-Phe-ψ[CONHCO]-Ala-Fmoc, 8a. White solid (0.54 g, 82%). Mp 165-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.93 (br s,

1H), 7.77-7.14 (m, 18H), 6.98 (d, J = 7.2 Hz, 1H), 5.39 (br s, 1H), 5.29 (s, 2H), 4.42 (t, J = 7.2 Hz, 2H), 4.20 (d, J = 6.8 Hz, 1H), 4.12-4.05 (m, 1H), 3.97-3.82 (m, 2H), 2.86 (d, J = 7.2 Hz, 2H), 1.32-1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.58, 173.29, 156.96, 156.72, 144.01, 141.45, 129.38, 128.69, 127.90, 127.81, 127.17, 126.70, 125.11, 124.59, 124.48, 124.10, 123.59, 120.09, 67.84, 62.53, 60.06, 59.69, 47.21, 38.10, 22.81, 22.66: HRMS calcd for $C_{38}H_{38}N_4NaO_7$ $(M+Na)^+$ 685.3638; found: 685.3724.

Boc-Ala-Phe-ψ[CONHCO]-Ala-Fmoc, 8b. White solid (0.35 g, 84%). Mp 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.23 (br s, 1H), 7.77-7.20 (m, 14H), 7.12 (d, J = 6.8 Hz, 1H), 5.55 (br s, 1H), 5.28 (br s, 2H), 4.87 (br s, 1H), 4.41 (t, J = 6.8 Hz, 1H), 4.23 (d, J = 6.8 Hz, 2H), 3.06 (d, J = 8.0 Hz, 1H), 2.90 (d, J = 8.8 Hz, 1H), 1.48 (d, J = 7.8 Hz, 3H), 1.38 (d, J = 8.2 Hz, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 171.86, 171.73, 168.67, 155.58, 154.02, 143.96, 141.97, 136.36, 129.36, 128.80, 127.82, 127.20, 127.15, 125.10, 120.08, 79.44, 67.22, 62.15, 53.85, 52.49, 47.16, 37.82, 29.33, 17.86, 17.73; ESMS calcd for $C_{35}H_{40}N_4O_7$ $(M+H)^+$ 629.29; found: 629.40.

Boc-Phe-Val-ψ[CONHCO]-Ile-Fmoc, 8c. White solid (0.35 g, 78%). Mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.55 (br s, 1H), 7.73-7.16 (m, 13H), 6.78 (s, 1H), 5.66-5.58 (m, 1H), 5.49 (br s, 1H), 4.85-4.73 (m, 2H), 4.40 (t, *J* = 12 Hz, 1H), 4.20-4.12 (m, 3H), 3.18-2.96 (m, 2H), 1.48-1.41 (m, 2H), 1.38 (s, 9H), 1.11 (d, 6H), 0.93-0.87 (m, 8H): ^{13}C NMR (75 MHz, $CDCl_3$, δ): 172.88, 172.59, 168.20, 155.99, 155.31, 143.75, 143.59, 141.22, 136.13, 129.12, 128.64, 127.67, 127.02, 125.02, 119.93, 80.09, 67.23, 66.72, 59.02, 54.40, 46.04, 36.36, 36.23, 31.88, 29.65, 27.31, 24.17, 19.04, 18.78; HRMS calcd for $C_{40}H_{50}N_4O_7$ $(M+H)^+$ 699.3758; found: 699.3763.

Cbz-Ala-Leu-ψ[CONHCO]-Phe-Fmoc, 8d. White solid (0.35 g, 80%). Mp 181-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.99 (br s, 1H), 8.081-8.067 (d, *J* = 7.6 Hz, 1H), 7.88-7.20 (m, 18H), 5.00 (s, 2H), 4.75 (br s, 1H), 4.55-4.38 (m, 3H), 4.20-4.08 (m, 4H), 2.95 (d, *J* = 10.8 Hz, 1H), 2.78 (d, *J* = 11.2 Hz, 1H), 2.65 (t, *J* = 4 Hz, 2H), 1.69-1.55 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 0.89-0.84 (m, 6H): ^{13}C NMR (75 MHz, $CDCl_3$, δ): 171.94, 171.32, 168.35, 156.87, 155.76, 143.41, 141.26, 141.22, 138.77, 138.45, 128.57, 127.79, 127.64, 127.16, 125.17, 125.02, 124.13, 120.73, 120.01, 68.51, 66.29, 60.51, 55.96, 47.22, 35.48, 25.00, 22.94, 14.24; HRMS calcd for $C_{41}H_{44}N_4O_7$ $(M+Na)^+$ 727.3108; found: 727.3204.

Boc-Ala-Leu-ψ[CONHCO]-Gly-Cbz, 8e. White solid (0.37 g, 76%). Mp 181-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.10 (br s, 1H), 7.47-7.34 (m, 6H), 6.66 (d, J = 4.2 Hz, 1H), 5.27 (br s, 1H), 5.11 (s, 2H), 4.30-4.22 (m, 1H), 4.05-3.94 (m, 1H), 3.73 (d, J = 7.8 Hz, 2H), 1.75-1.66 (m, 2H), 1.60-1.52 (m, 1H), 1.33 (s, 9H), 1.14 (d, J = 8.0 Hz, 3H), 0.88-0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 170.44, 170.06, 169.14, 156.70, 156.20, 135.04, 128.64, 128.61, 128.29, 79.10, 67.18, 59.85, 53.05, 44.21, 38.25, 29.05, 25.65, 22.80, 18.05; ESMS calcd for $C_{24}H_{36}N_4O_7$ $(M+H)^+$ 493.26; found: 493.26.

Boc-Ala-Phe-ψ[CONHCO]-Phe-Ala-Cbz, 8f. White solid (0.51 g, 74%). Mp 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.62 (br s, 1H), 7.77-7.11 (m, 15H), 6.83 (d, J = 7.2 Hz, 2H), 5.88 (br s, 1H), 5.29 (s, 2H), 5.12 (d, J = 6.8 Hz, 1H), 5.05-4.91 (m, 2H), 4.89-4.82 (m, 2H), 3.19-3.08 (m, 4H), 1.48-1.41 (m, 6H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.83, 173.25, 156.26, 156.02, 129.41, 128.68, 128.22, 127.70, 127.51, 127.25, 125.96, 125.82, 125.05, 124.59, 124.10, 119.23, 81.37, 66.00, 58.53, 52.44, 38.62, 29.83, 22.82. HRMS calcd for $C_{37}H_{45}N_5NaO_8$ $(M+Na)^+$ 710.3166; found: 710.3166.

(S)-tert-butyl(1-oxo-1-(2-oxo-2H-chromene-3-carboxamido)-3-phenylpropan-2-yl)carbamate, 10a. Yellow Gum (0.34 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.62 (s, 1H), 8.50 (s, 1H), 7.69-7.52 (m, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.42-7.28 (m, 5H), 4.82 (d, *J* = 6.2 Hz, 1H), 4.69-4.65 (m, 1H), 3.19-3.14 (m, 2H), 1.36 (s, 9H): ^{13}C NMR (75 MHz, $CDCl_3$, δ): 176.30, 169.83, 153.65, 152.63, 136.65, 131.13, 129.40, 128.53, 128.34, 126.99, 126.48, 120.32, 119.11, 117.86, 117.51, 79.33, 62.28, 38.56, 28.37; HRMS calcd for $C_{24}H_{24}N_2O_6$ $(M+H)^+$ 437.1713; found: 437.1710.

(S)-(9H-fluoren-9-yl)methyl(1-oxo-1-(2-oxo-2H-chromene-3-carboxamido)propan-2-yl)carbamate, 10b. White solid (0.41 g, 84%). Mp 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.56 (br s, 1H), 8.98 (s, 1H), 7.76-7.26 (m, 12H), 5.58 (br s, 1H), 4.47-4.38 (m, 3H), 4.25-4.22 (t, *J* = 12 Hz, 1H), 1.26 (d, *J* = 12 Hz, 3H): ^{13}C NMR (75 MHz, $CDCl_3$, δ):176.71, 169.86, 154.93, 151.44, 143.99, 143.86, 141.41, 135.62, 130.51, 127.80, 127.19, 127.16, 125.88, 125.10, 120.07, 118.41, 117.24, 116.99, 66.75, 51.05, 49.04, 17.36 ; HRMS calcd for $C_{28}H_{22}N_2O_6$ $(M+Na)^+$ 505.1376; found: 505.1375.

(S)-benzyl(4-methyl-1-oxo-1-(2-oxo-2H-chromene-3-carboxamido)pentan-2-yl)carbamate, 10c. Yellow Gum (0.33 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.52 (br s, 1H), 8.63 (s, 1H), 7.68-7.53 (m, 2H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.37-7.25 (m 5H), 5.01 (s, 2H), 4.75 (d, *J* = 8 Hz, 1H), 4.56-4.52 (m, 1H), 1.61-1.52 (m, 1H), 1.28-1.14 (m, 2H), 0.89-0.72 (d, *J* = 4 Hz, 6H): ^{13}C NMR (75 MHz, $CDCl_3$, δ): 175.13, 169.40, 153.49, 151.03, 136.32, 130.03, 128.81, 128.70, 128.44, 128.31, 128.20, 125.20, 125.13, 117.48, 116.13, 67.44, 56.02, 40.03, 24.05, 22.94; HRMS calcd for $C_{24}H_{24}N_2O_6$ $(M+H)^+$ 437.1713; found: 437.1710.

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