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2,4,5-Trichlorophenyl-(9*H*-fluoren-9-ylmethoxycarbonylamino)methylcarbamates: Synthesis, isolation, characterization and utility in the synthesis of dipeptidyl ureas

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An efficient synthesis of 2,4,5-trichlorophenyl-(9*H*-fluoren-9-ylmethoxycarbonylamino)methylcarbamates employing isocyanates derived from several Fmoc-amino acids has been described. All the carbamates made have been obtained as crystalline solids and are fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. They have been used as building blocks for the synthesis of several dipeptidyl urea esters. The coupling of carbamates with *N,O*-bis[trimethylsilyl]amino acids resulted in Fmoc-protected dipeptide urea acids in good yield as well as purity. All the dipeptidyl urea esters and acids made have been well characterized.

IPC: **Int.Cl.**[7] **C 07 K**

The modification of peptide backbone for forming or stabilizing well defined structures, i.e., turns[1], helices[2,3] or sheets[4,5] *via* non-covalent interactions has been gaining much attention in obtaining peptidomimetics[6,7]. In this context, unsymmetrical ureas has recently emerged as a promising class of compounds[8-11]. Further, it has been found that dipeptidyl ureas inhibit aspartic peptidases[12]. The insertion of a urea bond (-HNCONH-) in place of a peptide bond (-CONH-) generally involves the reaction of an isocyanate and an amine. Either amino or carboxyl group of an amino acid can be converted into an isocyanate moiety. The first route involves the conversion of α-amino group of amino acid ester hydrochloride[13] and peptide ester hydrochloride salts[14] by treatment with a solution of phosgene in toluene and pyridine in CH_2Cl_2 at 0 °C or saturated aqueous sodium bicarbonate solution at 0 °C. Amino acid ester isocyanates have been found to be volatile and have been purified by Kugelrohr distillation. In the case of peptide ester isocyanates, they could be neither purified nor isolated[14]. The second approach for the synthesis of isocyanates involves the conversion of carboxyl group of N^{α}-protected amino acids *via* acid azides and their Curtius rearrangement. Recently, our group has demonstrated the synthesis, isolation as well as characterization of various isocyanates[15] derived from Fmoc-amino acids *via* azides[16] through their rearrangement. Liskamp group demonstrated the utility of active carbamates as monomer building blocks for the synthesis of oligoureas peptidomimetics[17]. Their synthetic strategy involves the conversion of Boc-amino acid to C-terminal amide and then to the corresponding nitrile, followed by its reduction to amine. And, the reaction with 4-nitrophenyl chloroformate in the presence of diisopropylethylamine (DIEA) resulted in active 4-nitrophenyl carbamates. Alternatively, Guichard group converted Boc- as well as Fmoc-β-amino acids *via* acid azides to isocyanates, which have been trapped by *N*-hydroxy succinimide leading to the formation of *O*-succinimidyl carbamates[18]. Several other routes like generation of monoprotected diamines to isocyanates[19], azido 4-nitrophenyl carbamates[20,21], pentafluorophenyl methylcarbamates[22] were also available for the introduction of a urea moiety in the peptide backbone.

The preparation, properties and profits in the use of 2,4,5-trichlorophenyl esters of Boc- as well as Fmoc-protected amino acids for the synthesis of biologically active peptides [Leu]enkephalinamide[23], dermorphin[24] and oxytocin[25] by the solid phase method has been well documented. The present paper describes the synthesis of 2,4,5-trichlorophenyl-(9*H*-fluoren-9-ylmethoxycarbonylamino)methylcarbamates and their utility for the synthesis of various dipeptidyl urea esters as well as urea acids.

Fmoc-amino acid azides, prepared either from the corresponding acid chlorides or the *in situ* generated mixed anhydrides using ethyl chloroformate, have been converted to the corresponding isocyanates employing a microwave-accelerated rearrangement[15]. The resulting isocyanates **2** can be used directly without isolation. Also, they can be isolated and then reacted with 2,4,5-trichlorophenol in which case they have to be stored at 4°C. The reaction of isocyanates **2** in toluene with 2,4,5-trichlorophenol in CH_2Cl_2 and an equimolar quantity of *N*-methylmorpholine (NMM) at r.t. results in the formation of the carbamates **3 (Scheme I**, **Table I)**. The reaction was found to be complete in 30 min. In all the cases, the carbamates separated out as solids at r.t. They have been isolated by filtration and are recrystallized from DMF-CH_2Cl_2.The carbamates **3** can also be prepared using DMF as a solvent. As both the reactants as well as products are completely soluble in DMF, the completion of the course of the reaction can be easily monitored by TLC. In such crops, the reaction mixture was diluted by the addition of CH_2Cl_2 or petroleum ether, which resulted in the separation of the analytically pure carbamates **3**. All the carbamates **3a-n** made have been fully characterrized by IR, ^{1}H NMR and ^{13}C NMR spectra. Employing this method, the amino acids containing *tert*-butyl, Boc, trityl and benzyl groups for side chain protection have been converted to the corresponding carbamates. We found that reaction of carbamates **3** with amino acid esters in DMF in the presence of NMM at r.t. resulted in the separation of the urea esters **5a-h** as solids (**Scheme II**). The reaction was found to be rapid and completed in about 30 min. A simple recrystallization using DMSO-water mixture gave all dipeptidyl urea esters in about 85-90% yield as well as analytically pure compounds **5a-h** (**Table II**).

Table I — Physical constants of 2,4,5-trichlorophenyl-(9*H*-fluoren-9-ylmethoxycarbonyl amino)methylcarbamates

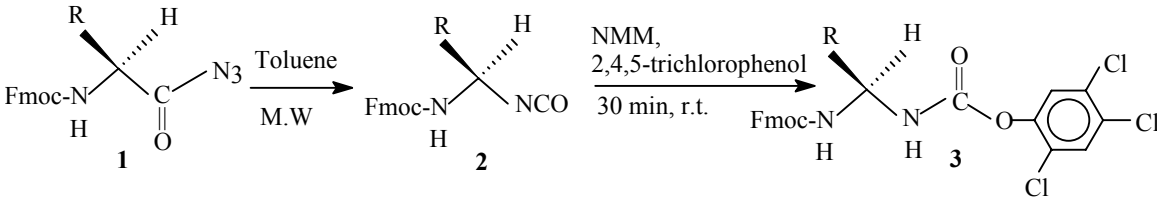
Compd **3**	R	m.p. °C	$[\alpha]_D^{25}$ (c 1, DMF)	Yield (%)
a	$CH(CH_3)C_2H_5$	116	-4.0	85
b	C_6H_5	164	-2.2	89
c*	C_6H_5	162	+2.1	88
d	$(CH_2)_2COO^tBu$	165	-4.2	89
e	$CH(CH_3)_2$	119	-8.1	88
f	$(CH_2)_4NHBoc$	151	-3.5	87
g	$CH_2CONH(Trt)$	153	-2.8	86
h	$CH(O^tBu)CH_3$	173	-6,2	88
i	CH_2OBn	150	-3.7	90
j	H	171	-	89
k	$CH_2CH(CH_3)_2$	140	-2.5	88
l	CH_3	159	-5.9	87
m	$CH_2C_6H_5$	143	-3.4	86
n	$CH_2C_6H_4(O^tBu)$	136	-5.6	89

* D-configuration

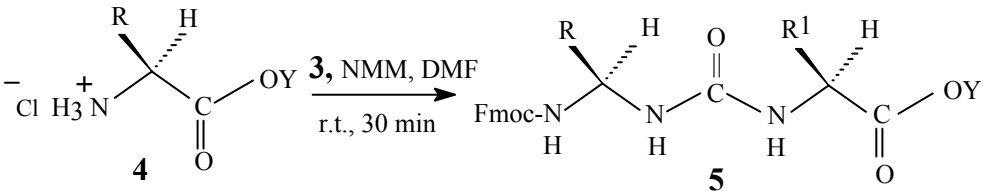
Further, the reaction of carbamates **3** with the *in situ* generated *N,O*-bis[trimethylsilyl]amino acids **7** in CH_2Cl_2 at r.t. resulted in the dipeptidyl urea acids **8** (**Scheme III**). A simple work-up of the reaction mixture followed by recrystallization gave analytically pure dipeptidyl urea acids in 84-90% yield (**Table III**). All the dipeptidyl urea esters and urea acids made have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Experimental Section

Melting points were determined using capillary method and are uncorrected. IR spectra were recorded



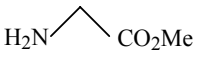
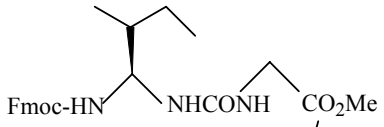
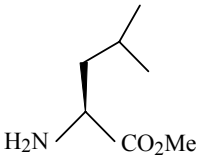
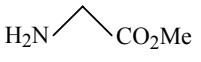
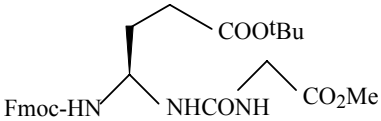
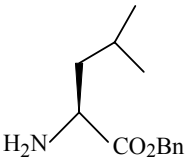
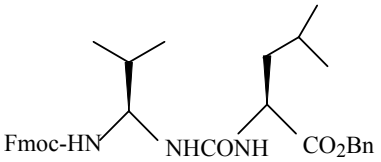
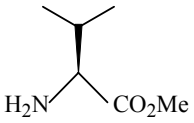
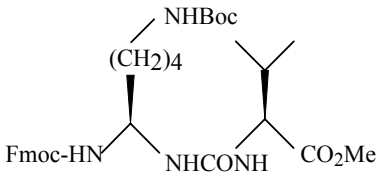
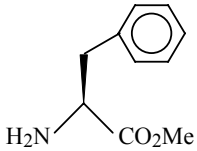
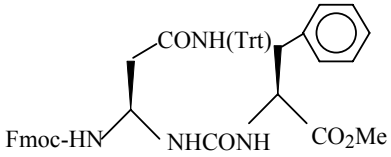
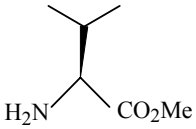
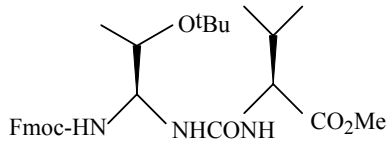
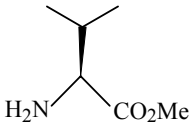
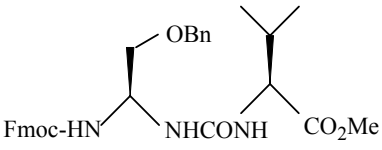
Scheme I

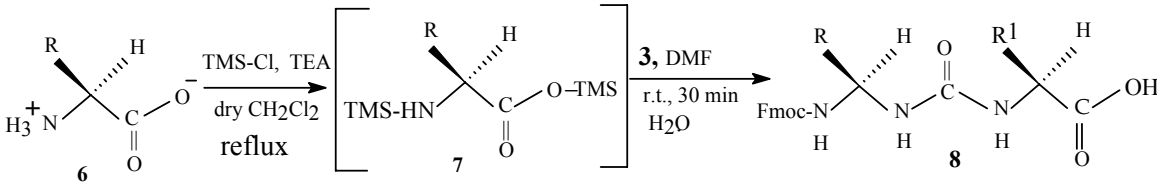


Y= CH_3, $CH_2C_6H_5$

Scheme II

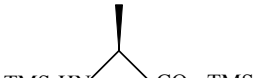
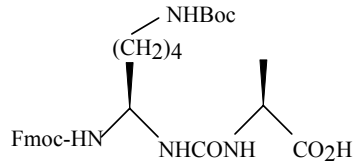
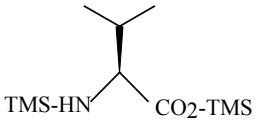
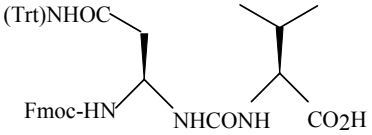
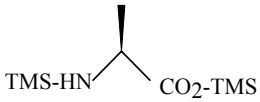
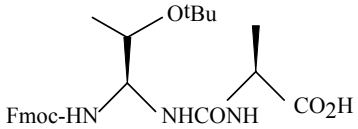
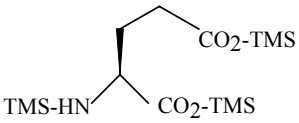
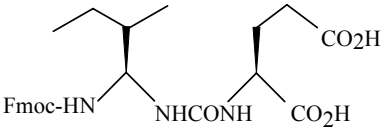
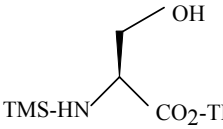
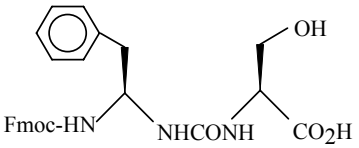
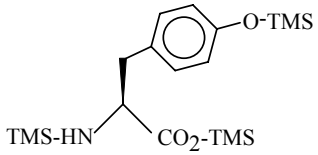
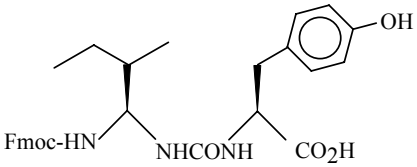
Table II— Formation of substituted ureas **5** from carbamates **3** and various amino acid ester

Compd	Carbamate	Amino acid ester	Time (min)	Urea esters	m.p. °C	Yield (%)
5a	**3a**		45		143	85
5b	**3m**		45		165	84
5c	**3e**		40		156	88
5d	**3f**		35		184	85
5e	**3g**		35		179	85
5f	**3h**		30		196	88
5g	**3i**		35		154	85
5h	**3j**		35		168	88



Scheme III

Table III — Formation of substituted urea acids **8** from charbamates **3** and various bis-[trimethylsilyl] amino acids

Compd	Carbamate	bis-TMS [Amino acid]	Time (min)	Urea acid	m.p. °C	Yield (%)
8a	**3f**		30		118	85
8b	**3g**		35		172	86
8c	**3h**		30		135	84
8d	**3a**		35		184	87
8e	**3m**		30		176	89
8f	**3a**		35		170	87

on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). Specific rotations were recorded on Rudolf Research Autopol IV automatic polarimeter. Elemental analyses were carried out using Perkin-Elmer Analyser and the samples were dried for 24 hr under vacuum before analysis. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Mass spectra were recorded on MALDI-TOF (KRATOS) and PE-SCIEX 150 EX LC-MS. All solvents were freshly distilled prior to use. Amino acid methyl ester hydrochlorides were prepared by using methanol and thionyl chloride. Fmoc-amino acid azides were prepared by the procedures reported by us[16].

General procedure for the preparation of 2,4,5-trichlorophenyl-(9*H*-fluoren-9-ylmethoxycarbonyl-amino)methylcarbamates 3a-n. The Fmoc-amino acid azide **1** (1 mmole) in toluene was converted to the respective isocyanate **2** by the Curtius rearrangement by exposure to microwave irradiation at its 60% power until the rearrangement was complete. The solution was cooled to r.t. and 2,4,5-trichlorophenol (1.2 mmoles) and NMM (1.2 mmoles) were added. It was stirred at r.t. till the completion of the reaction. The separated solid was filtered and washed with CH_2Cl_2 and toluene (1:1) to get the product as a solid. They were recrystallized from DMF-CH_2Cl_2 in good yield (**Table I**).

DMF can also been used as a solvent for the above reaction. In such crops, after the completion of the reaction, the addition of CH_2Cl_2 or petroleum ether results in the separation of the carbamate as an analytically pure sample.

2, 4, 5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-methylbutyl}carbamate 3a: ^{1}H NMR (DMSO): δ 0.95 (6H, m), 1.25-1.4 (3H, m), 3.8 (1H, m), 4.2 (1H, t), 4.35 (2H, m), 6.45 (1H, d), 7.25-8.12 (10H, m); ^{13}C NMR (DMSO): δ 11.5, 15.7, 26.0,37.8, 48.4, 56.6, 120.0, 124.5, 125.1, 127.1, 127.9, 129.7, 132.0, 141.3, 143.7, 151.2, 153.7, 155.5; MS (MALDI-TOF): m/z 570.6 $[M+Na]^+$, 586.7 $[M+K]^+$; Anal. Calcd for $C_{27}H_{25}N_2O_4Cl_3$: C, 59.19; H, 4.59; N, 5.11. Found: C, 59.12; H, 4.62; N, 5.24%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-1-phenylmethyl}carbamate 3b: ^{1}H NMR (DMSO): δ 4.2 (1H, t), 4.3-4.45 (3H, m), 6.6 (1H, d), 7.1-8.16 (15H, m); ^{13}C NMR (DMSO): δ 47.2, 54.1, 66.6, 120.0, 124.2, 125.1, 126.9, 127.0, 127.3, 127.8, 128.7, 129.0, 129.3, 132.0, 136.8, 141.2, 143.9, 151.1, 155.9, 156.6; MS (MALDI-TOF): m/z 590.6 $[M+Na]^+$, 606.9 $[M+K]^+$; Anal. Calcd for $C_{29}H_{21}N_2O_4Cl_3$: C, 61.33; H, 3.73; N, 4.93. Found: C, 61.24; H, 3.48; N, 4.78%.

2, 4,5-Trichlorophenyl{(1*R*)-1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-1-phenylmethyl}carbamate 3c**: ^{1}H NMR (DMSO): δ 4.1 (1H, t), 4.25-4.35 (3H, m), 6.65 (1H, d), 7.15-8.1 (15H, m); ^{13}C NMR (DMSO): δ 47.3, 54.1, 66.5, 120.0, 124.2, 125.1, 126.9, 127.0, 127.4, 127.8, 128.7, 129.0, 129.3, 132.0, 136.8, 141.2, 143.9, 151.1, 155.9, 156.6; MS (MALDI-TOF): m/z 590.5 $[M+Na]^+$, 606.7 $[M+K]^+$; Anal. Calcd for $C_{29}H_{21}N_2O_4Cl_3$: C, 61.33; H, 3.73; N, 4.93. Found: C, 61.24; H, 3.48; N, 4.78%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-3-[4-(*tert*-butoxy)carbonyl]propyl}carbamate 3d: ^{1}H NMR (DMSO): δ 1.5 (9H, s), 2.2-2.6 (4H, m), 4.2-4.4 (4H, m), 6.6-6.8 (2H, m), 7.1-8.1 (10H, m); ^{13}C NMR (DMSO): δ 19.1, 28.0, 37.8, 47.3, 48.7, 66.7, 81.6, 120.1, 124.4, 125.1, 127.0, 127.9, 129.7, 132.0, 141.4, 151.2, 155.6, 156.8; MS (MALDI-TOF): m/z 642.8 $[M+Na]^+$, 659.0 $[M+K]^+$; Anal. Calcd for $C_{30}H_{29}N_2O_6Cl_3$: C, 58.12; H, 4.71; N, 4.52. Found: C, 58.34; H, 4.54; N, 4.68%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-methyl propyl}carbamate 3e: ^{1}H NMR (DMSO): δ 0.95 (7H, m), 3.8 (1H, m), 4.2 (1H, t), 4.4 (2H, m), 6.4 (1H, d), 7.3-8.15 (10H, m); ^{13}C NMR (DMSO): δ 18.2, 19.5, 30.6, 47.4, 56.8, 66.9, 120.2, 124.5, 125.3, 127.2, 127.9, 132.0, 141.5, 143.8, 151.4, 155.9, 157.5; MS (MALDI-TOF): m/z 554.2 $[M+Na]^+$, 572.8 $[M+K]^+$; Anal. Calcd for $C_{26}H_{23}N_2O_4Cl_3$: C, 58.49; H, 4.34; N, 5.24. Found: C, 58.28; H, 4.25; N, 5.10%.

2, 4, 5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-{[(*tert*-butoxy)carbonyl]-amino}pentyl}carbamate 3f: ^{1}H NMR (DMSO): δ 1.2-1.5 (15H, m), 3.1 (2H, m), 3.6 (1H, m), 4.2 (1H, t), 4.4 (2H, m), 4.7 (1H, m), 6.0 (1H, br), 6.4 (1H, br), 7.3-8.1 (10H, m); ^{13}C NMR (DMSO): δ 22.4, 28.3, 29.8, 30.6, 39.64, 47.0, 51.4, 66.9, 79.3, 120.1, 124.5, 125.0, 127.2, 127.9, 129.8, 132.2, 141.5, 143.8, 150.9, 155.9, 156.6, 157.0; MS (MALDI-TOF): m/z 685.7 $[M+Na]^+$, 702.0 $[M+K]^+$; Anal. Calcd for $C_{32}H_{34}N_3O_6Cl_3$: C, 57.97; H, 5.17; N, 6.34. Found: C, 58.18; H, 5.32; N, 6.1%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-3-{(N-trityl)propanamidyl}carbamate 3g: ^{1}H NMR (DMSO): δ 2.4(2H, m), 4.2 (4H, m), 6.0 (1H, br), 6.4 (1H, br), 7.2-8.1 (25H, m); ^{13}C NMR (DMSO): δ 38.24, 47.1, 51.4, 66.9, 120.1, 122.4, 124.6, 125.0, 126.4, 126.9, 127.2, 127.9, 128.7, 129.1,129.8, 132.0, 136.9, 141.5, 143.8, 151.6, 155.8, 157.2; MS (MALDI-TOF): m/z 814.0 $[M+Na]^+$, 830.1 $[M+K]^+$; Anal. Calcd for $C_{44}H_{34}N_3O_5Cl_3$: C, 66.8; H, 4.33; N, 5.31. Found: C, 66.28; H, 4.25; N, 5.10%.

2, 4, 5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-{[2-(*tert*-butoxy)propyl}-carbamate 3h: ^{1}H NMR (DMSO): δ 1.2 (9H, s), 3.1 (2H, m), 3.6 (1H, m), 4.2 (1H, t), 4.4 (2H, m), 6.0 (2H, br), 7.3-8.1 (10H, m); ^{13}C NMR (DMSO): δ 22.4, 28.3, 29.8, 30.6, 39.64, 47.0, 51.4, 66.9, 79.3, 120.1, 124.2, 125.0, 127.2, 127.9, 129.4, 132.6, 141.5, 143.8, 151.4, 155.6, 156.5; MS (MALDI-TOF): m/z 614.7 $[M+Na]^+$, 631.0 $[M+K]^+$; Anal. Calcd for $C_{29}H_{29}N_2O_5Cl_3$: C, 58.85; H, 4.94; N, 4.73. Found: C, 58.58; H, 4.65; N, 4.40%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-benzyloxy)}ethyl carbamate 3i: ^{1}H NMR (DMSO): δ 3.85 (1H, m), 4.2 (1H, t), 4.35 (2H, m), 5.14 (2H, br), 7.15-8.12 (15H, m); ^{13}C NMR (DMSO): δ 38.6, 47.2, 50.7, 61.5, 66.8, 120.0, 122.6, 124.2, 125.0, 126.4, 127.0, 127.2, 127.7,128.8, 129.1, 129.4, 132.7, 136.9, 141.3, 143.8, 155.6, 156.8; MS (MALDI-TOF): m/z 634.7 $[M+Na]^+$, 650.9 $[M+K]^+$; Anal. Calcd for $C_{31}H_{25}N_2O_5Cl_3$: C, 63.46; H, 4.29; N, 4.77. Found: C, 63.62; H, 4.50; N, 4.82%.

2, 4, 5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}methyl carbamate 3j: ^{1}H NMR (DMSO): δ 3.2 (2H, br), 4.2 (1H, t), 4.4 (2H, d), 6.5 (2H, s), 7.25-8.16 (10H, m); ^{13}C NMR

(* D-configuration)

(DMSO): δ 41.5, 48.5, 66.6, 120.2, 124.6, 125.2, 127.6, 128.0, 129.5, 132.5, 141.5, 143.4, 151.8, 154.2, 157.5; MS (MALDI-TOF): m/z 514.5 $[M+Na]^+$, 530.6 $[M+K]^+$; Anal. Calcd for $C_{23}H_{17}N_2O_4Cl_3$: C, 56.18; H, 3.48; N, 5.69. Found: C, 56.28; H, 3.4; N, 5.54%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-3-methylbutyl} carbamate 3k: ^{1}H NMR (DMSO): δ 0.95 (6H, m), 1.25-1.4 (3H, m), 3.8 (1H, m), 4.12 (1H, t), 4.35 (2H, m), 6.45 (1H, d), 7.25-8.12 (10H, m); ^{13}C NMR (DMSO): δ 22.0, 23.2, 24.8, 41.9, 47.4, 66.6, 120.0, 124.4, 125.2, 127.0, 129.1, 132.1, 132.5, 141.4, 143.6, 153.7, 155.9; MS (MALDI-TOF): m/z 570.6 $[M+Na]^+$, 586.7 $[M+K]^+$; Anal. Calcd for $C_{27}H_{25}N_2O_4Cl_3$: C, 59.19; H, 4.59; N, 5.11. Found: C, 59.14; H, 4.42; N, 5.14%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}ethyl carbamate 3l: ^{1}H NMR (DMSO): δ 1.14 (3H, d), 3.85 (1H, m), 4.2 (1H, t), 4.35 (2H, m), 6.6 (1H, d), 7.2-8.1 (10H, m); ^{13}C NMR (DMSO): δ 18.3, 48.0, 48.5, 66.6, 120.2, 124.2, 125.2, 127.3, 128.1, 129.8, 132.6, 141.9, 144.1, 151.4, 156.1, 157.2; MS (MALDI-TOF): m/z 528.5 $[M+Na]^+$, 544.8 $[M+K]^+$; Anal. Calcd for $C_{24}H_{19}N_2O_4Cl_3$: C, 56.99; H, 3.78; N, 5.54. Found: C, 56.89; H, 3.86; N, 5.46%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-phenyl ethyl}carbamate 3m: ^{1}H NMR (DMSO): δ 2.85 (2H, d), 4.1 (1H, t), 4.25-4.45 (3H, m), 6.58 (1H, d), 7.1-8.15 (15H, m); ^{13}C NMR (DMSO): δ 38.8, 47.2, 52.6, 66.6, 120.1, 122.6, 124.6, 125.0, 127.1, 127.2, 127.8, 128.7, 129.1, 129.8, 132.0, 136.9, 141.2, 143.5, 151.4, 155.8, 156.4; MS (MALDI-TOF): m/z 604.6 $[M+Na]^+$, 620.7 $[M+K]^+$; Anal. Calcd for $C_{30}H_{23}N_2O_4Cl_3$: C, 61.92; H, 3.98; N, 4.81. Found: C, 61.78; H, 3.88; N, 4.8%.

2,4,5-Trichlorophenyl{1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-[4-(*tert*-butoxy)phenyl]-ethyl}carbamate 3n: ^{1}H NMR (DMSO): δ 1.3 (9H, s), 2.8 (2H, d), 3.95 (1H, t), 4.3-4.5 (3H, m), 6.4 (1H, d), 7.1-8.1 (14H, m); ^{13}C NMR (DMSO): δ 28.8, 38.2, 47.3, 54.5, 66.6, 78.6, 120.0, 122.0, 124.5, 125.0, 125.1, 127.2, 127.7, 128.8, 129.1, 129.6, 131.8, 136.9, 141.5, 143.6, 153.8, 154.5, 156.8, 158.3; MS (MALDI-TOF): m/z 676.7 $[M+Na]^+$, 692.8 $[M+K]^+$; Anal. Calcd for $C_{34}H_{31}N_2O_5Cl_3$: C, 62.44; H, 4.78; N, 4.28. Found: C, 62.0; H, 4.52; N, 4.08%.

General procedure for the synthesis of dipeptidyl urea esters 5a-h. To a stirred solution of amino acid methyl ester hydrochloride salt (1 mmole) in DMF (5 mL) and NMM (2 mmoles), carbamate **3** (1 mmole) was added and stirred at r.t. till the completion of the reaction. The separated solid was filtered and crystallized from DMSO-water (70:30) to get the dipeptidyl urea ester as a crystalline off-white solid.

Fmoc-Ile^u-Gly-OMe 5a: ^{1}H NMR (DMSO): δ 0.8 (6H, m), 1.1 - 1.65 (3H, m), 2.5 (2H, m), 3.6 (3H, s), 3.8 (1H, m), 4.2 - 4.4 (3H, m), 5.0 (1H, d), 6.3 -6.5 (2H, m), 7.3 - 7.9 (8H, m); ^{13}C NMR (DMSO): δ 11.0, 14.3, 25.0, 40.4, 41.2, 46.7, 51.5, 61.5, 65.1, 120.0, 125.2, 127.0, 127.6, 140.7, 143.8, 155.0, 156.8, 171.5; ESMS: m/z 440.2; Anal. Calcd for $C_{24}H_{29}N_3O_5$: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.38; H, 6.52; N, 9.38%.

Fmoc-Phe^u-Leu-OMe 5b: ^{1}H NMR (DMSO): δ 0.95 (6H, d), 1.35 (2H, s), 1.6 (1H, m), 2.82 (2H, d), 3.65 (3H, m), 3.8 (1H, m), 4.1- 4.4 (4H, m), 5.1 (1H, d), 6.5 - 6.7 (2H, m), 7.2 - 7.85 (13H, m); ^{13}C NMR (DMSO): δ 22.0, 23.0, 24.5, 37.2, 47.3, 51.4, 54.2, 61.3, 66.6, 120.1, 125.0, 126.5, 127.0, 127.5, 128.5, 129.2, 137.5, 141.3, 144.0, 155.8, 156.5, 171.6; MS (MALDI-TOF): m/z 552.6 $[M+Na]^+$, 568.7 $[M+K]^+$; Anal. Calcd for $C_{31}H_{35}N_3O_5$: C, 70.30; H, 6.66; N, 7.93. Found: C, 70.18; H, 6.57; N, 7.81%.

Fmoc-Asp(O^{t}Bu)^u-Gly-OMe 5c: ^{1}H NMR (DMSO): δ 1.45 (9H, s), 1.9 (2H, d), 2.6 (2H, d), 3.65 (3H, s), 4.1 (1H, t), 4.3 - 4.4 (3H, m), 5.8 (1H, d), 6.5 - 6.7 (2H, m), 7.3 - 7.75 (8H, m); ^{13}C NMR (DMSO): δ 27.9, 37.5, 41.5, 47.1, 50.0, 61.3, 66.8, 81.5, 120.0, 125.0, 127.5, 128.0, 141.0, 144.1, 155.5, 156.5, 170.8, 171.1; MS (MALDI-TOF): m/z 519.8 $[M+Na]^+$, 536.0 $[M+K]^+$; Anal. Calcd for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.66; H, 6.07; N, 8.29%.

Fmoc-Val^u-Leu-OBn 5d: ^{1}H NMR (DMSO): δ 0.92 (12H, m), 1.32 - 1.85 (4H, m), 3.1 (2H, s), 3.7 - 3.8 (2H, m), 4.2 (1H, t), 4.42 (2H, m), 5.1 (1H, d), 6.6 - 6.7 (2H, m), 7.2 - 7.85 (13H, m); ^{13}C NMR (DMSO): δ 18.5, 19.5, 22.0, 23.1, 24.5, 29.2, 37.2, 40.2, 47.2, 51.5, 59.0, 66.6, 120.0, 125.0, 126.5, 127.0, 127.2, 128.0, 128.4, 129.3, 137.6, 141.2, 144.0, 155.4, 156.8, 176.4; MS (MALDI-TOF): m/z 580.0 $[M+Na]^+$, 596.1 $[M+K]^+$; Anal. Calcd for $C_{33}H_{39}N_3O_5$: C, 71.07; H, 7.05; N, 7.53. Found: C, 70.96; H, 6.89; N, 7.41%.

Fmoc-Lys(ε-Boc)^u-Val-OMe 5e: ^{1}H NMR (DMSO): δ 0.96 (7H, m), 1.4 (9H, m), 1.8-2.2 (8H, m), 3.65 (3H, s), 4.1 (1H, t), 4.3 - 4.4 (3H, m), 5.8 (1H, d), 6.1 (1H, br), 6.5 - 6.7 (2H, m), 7.3 - 7.75 (8H, m); ^{13}C NMR (DMSO): δ 18.1, 19.2, 22.5, 28,2, 29,9,30.5, 31.5, 39.5, 47.1, 51.0, 66.8, 79.2, 81.5, 120.0, 125.0, 127.5, 128.0, 141.0, 144.1, 155.5, 156.5, 170.8; MS (MALDI-TOF):

m/z 519.8 $[M+Na]^+$, 536.0 $[M+K]^+$; Anal. Calcd for $C_{32}H_{44}N_3O_7$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.66; H, 6.07; N, 8.29%.

Fmoc-Asn(Trt)^u-Phe-OMe 5f: ^{1}H NMR (DMSO): δ 2.4 (2H, d), 2.8 (2H, d), 3.65 (3H, s), 4.1 (1H, t), 4.3-4.4 (3H, m), 5.8 (1H, d), 6.5 - 6.7 (3H, m), 7.2-7.9 (28H, m); ^{13}C NMR (DMSO): δ 37.8, 38.9, 48.1, 67.8, 120.0, 125.0, 127.0, 127.5, 128.0, 128.8, 129.1, 136.9, 141.2, 144.1, 155.5, 156.5, 170.8, 171.1; MS (MALDI-TOF): m/z 723.68 $[M+Na]^+$, 739.8 $[M+K]^+$; Anal. Calcd for $C_{42}H_{44}N_4O_6$: C, 71.98; H, 6.33; N, 8.4. Found: C, 71.86; H, 6.27; N, 8.29%.

Fmoc-Thr(OtBu)u-Val-OMe 5g: ^{1}H NMR (DMSO): δ 0.94-1.2 (16H, m), 1.9 (3H, d), 3.2 (1H, m), 3.6 (3H, s), 3.86 (2H, m), 4.1 (1H, t), 4.4 (2H, m), 5.8 (1H, d), 6.5 - 6.7 (2H, m), 7.3 - 7.75 (8H, m); ^{13}C NMR (DMSO): δ 18.1, 19.3, 27.9, 30.6, 47.1, 50.4, 61.3, 66.8, 73.5, 120.0, 125.0, 127.5, 128.0, 141.0, 144.1, 155.5, 158.5, 171.1; MS (MALDI-TOF): m/z 548.5 $[M+Na]^+$, 564.6 $[M+K]^+$; Anal. Calcd for $C_{29}H_{39}N_3O_6$: C, 66.65; H, 7.5; N, 8.4. Found: C, 66.56; H, 7.47; N, 8.29%.

Fmoc-Ser(OBn)^u-Val-OMe 5h: ^{1}H NMR (DMSO): δ 0.95 (7H, m), 3.6 (5H, m), 3.8 (2H, m), 4.1 (1H, t), 4.4 (3H, m), 5.8 (1H, br), 6.5 - 6.7 (2H, m), 7.3 - 7.75 (13H, m); ^{13}C NMR (DMSO): δ 18.1, 19.3, 30.5, 47.1, 50.2, 62.3, 66.8, 120.0, 125.0, 127.0, 127.5, 127.9, 128.8, 129.1, 136.9, 141.0, 144.1, 155.5, 156.5, 171.1; MS (MALDI-TOF): m/z 568.4 $[M+Na]^+$, 584.5 $[M+K]^+$; Anal. Calcd for $C_{31}H_{35}N_3O_6$: C, 68.24; H, 6.47; N, 7.7. Found: C, 68.26; H, 6.37; N, 7.39%.

General procedure for the preparation of *N*$^{\alpha}$-Fmoc protected dipeptidyl urea acids 8a-f. To a stirred suspension of amino acid (1 mmole) in CH_2Cl_2 (5 mL) was added freshly distilled TMS-Cl (1.2 mmoles) and TEA (1.2 mmoles) and refluxed for 1 hr. The reaction mixture was cooled to r.t. and carbamate **3** (1 mmole) was added. It was stirred at r.t. until the completion of the reaction. The solvent was evaporated and water (10 mL) was added to the residue. The separated solid was filtered and recrystallized from DMSO-water to obtain the dipeptidyl urea acids.

In the case of Glu, Ser and Tyr, 2.4 mmoles of TMS-Cl and TEA were used.

Fmoc-Lys(ε-Boc)^u-Ala-OH 8a: ^{1}H NMR (DMSO): δ 1.18 (3H, d), 1.45 (15H, s), 3.03 (2H, m), 3.82 (2H, m), 4.2 (1H, t), 4.4 (2H, m), 6.01 (1H, br), 6.5 - 6.7 (3H, m), 7.3 - 7.75 (8H, m); ^{13}C NMR (DMSO): δ 18.4, 22.5, 28.4 29.9, 31.6, 39.5, 46.8, 48.4, 51.6, 66.8, 79.3, 120.0, 125.0, 127, 127.5, 128.0, 141.0, 144.0, 155.5, 156.5, 158.2, 178.4, 171.1; MS (MALDI-TOF): m/z 577.4 $[M+Na]^+$, 593.5 $[M+K]^+$; Anal. Calcd for $C_{29}H_{38}N_4O_7$: C, 62.80; H, 6.90; N, 10.10. Found: C, 62.66; H, 6.57; N, 10.20%.

Fmoc-Asn(Trt)^u-Val-OH 8b: ^{1}H NMR (DMSO): δ 0.96 (7H, s), 2.5 (2H, m), 3.9-4.2 (5H, m), 6.2 (2H, m), 6.5 - 6.7 (2H, m), 7.2 - 7.8 (23H, m); ^{13}C NMR (DMSO): δ 18.1, 19.3, 30.5, 37.8, 47.1, 48.5, 67.0, 71.2, 120.0, 125.0, 127,127.5, 127.9, 128.8, 129.1, 136.9, 141.0, 143.8, 155.5, 174.0, 170.8, 178.1; MS (MALDI-TOF): m/z 733.8 $[M+Na]^+$, 749.8 $[M+K]^+$; Anal. Calcd for $C_{43}H_{42}N_4O_6$: C, 72.66; H, 5.96; N, 7.88. Found: C, 72.80; H, 5.74; N, 8.09%.

Fmoc-Thr(O^{t}Bu)^u-Ala-OH 8c: ^{1}H NMR (DMSO): δ 1.17-1.2 (15H, s), 3.5 (1H, m), 3.85 (2H, m), 4.1 (1H, t), 4.4 (2H, m), 5.8 (1H, d), 6.5 - 6.7 (2H, m), 7.2- 7.8 (8H, m); ^{13}C NMR (DMSO): δ 18.4, 27.5, 47.1, 50.6, 61.8, 66.8, 73.6, 120.0, 125.0, 127, 127.5, 141.2, 143.9, 155.5, 158.5, 178.1; MS (MALDI-TOF): m/z 506.5 $[M+Na]^+$, 522.0 $[M+K]^+$; Anal. Calcd for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88; N, 8.69. Found: C, 62.26; H, 6.87; N, 8.49%.

Fmoc-Ile^u-Glu-OH 8d: ^{1}H NMR (DMSO): δ 0.91 (6H, d), 1.12 (3H, m), 1.52 (1H, m), 2.1 - 2.45 (4H, m), 3.6 (1H, m), 4.05 (1H, m), 4.21 (1H, t), 4.43 (2H, m), 4.95 (1H, d), 6.65 - 6.85 (2H, m), 7.25 - 7.76 (8H, m); ^{13}C NMR (DMSO): δ 11.3, 15.6, 25.5, 32.1, 35.7, 38.3, 47.3, 49.9, 57.3, 66.5, 119.9, 125.0, 127.0, 127.6, 141.2, 143.9, 156.3, 158.3, 177.9, 178.2; MS (MALDI-TOF): m/z 553.9 $[M+Na]^+$, 570.0 $[M+K]^+$: Anal. Calcd for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.56; H, 6.12; N, 8.30%.

Fmoc-Phe^u-Ser-OH 8e: ^{1}H NMR (DMSO): δ 2.9 (2H, d), 3.8 (4H, m), 4.1-4.5 (4H, m), 6.1 (1H, d), 6.8 -7.0 (2H, m), 7.1 - 7.85 (13H, m); ^{13}C NMR (DMSO): δ 37.5, 47.2, 51.9, 54.5, 62.5, 66.5, 120.0, 125.3, 126.8, 127.1, 127.6, 128.5, 129.1, 137.6, 141.4, 144.0, 157.6, 158.4, 177.9; MS (MALDI-TOF): m/z 511.8 $[M+Na]^+$, 527.9 $[M+K]^+$; Anal. Calcd for $C_{27}H_{27}N_3O_6$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.50; N, 8.44%.

Fmoc-Ile^u-Tyr-OH 8f: ^{1}H NMR (DMSO): δ 0.9 (6H, m), 1.1 (1H, m), 1.52 (2H, m), 2.25 (1H, br), 2.85 (2H, d), 3.6 (1H, m), 4.2 (1H, t), 4.42 (2H, m), 4.95 (1H, d), 6.65 - 6.85 (2H, m), 7.1 - 7.8 (12H, m); ^{13}C NMR (DMSO): δ 11.3, 15.4, 25.5, 35.9, 36.6, 47.5, 54.3, 57.5, 66.7, 119.9, 124.2, 124.8, 127.1, 127.6, 129.6, 132.8, 141.2, 144.1, 154.5, 156.8, 158.2, 178.4; MS (MALDI-TOF): m/z 554.0 $[M+Na]^+$, 570.1 $[M+K]^+$; Anal. Calcd for $C_{30}H_{33}N_3O_6$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.66; H, 6.13; N, 7.79%.

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