Scientia Iranica C (2018) 25(6), 3311–3321

Sharif University of Technology
Scientia Iranica
Transactions C: Chemistry and Chemical Engineering
http://scientiairanica.sharif.edu

Bromodimethylsulfonium bromide: A novel reagent for the one-pot synthesis of potent N^a-ureido peptides and study of molecular docking and antibacterial activities

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Received 14 August 2017; received in revised form 25 November 2017; accepted 14 May 2018

KEYWORDS
N^a-ureidopeptides;
BDMS;
Curtius rearrangement;
Molecular docking;
Antibacterial activity.

Abstract. N^a-protected ureidopeptides were efficiently synthesized using bromodimethylsulfonium bromide mediated Curtius rearrangement through the *in-situ* generation of carboxylated sulfonium intermediate. Conversion of carboxylic acids to ureidopeptides in good yield was achieved in one pot under mild reaction conditions through a simple workup. To check the binding modes and binding affinity of urea functional group with target protein, the synthesized compounds were subjected to docking studies. Docking scores confirmed that the Boc-Leu-ψ[NHCONH]-Ala-OMe and Leu-ψ[NHCONH]-Ala-OMe molecules had the lowest energy and good agreement with the results of antibacterial studies against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeroginosa* in comparison with streptomycin sulphate as a standard. The synthesized compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies.

1. Introduction

Urea moiety is the chief nitrogenous product of protein metabolism acting as a critical structural element in many biologically active molecules [1,2]. Chemically modified peptides with urea backbone have received considerable interest in the field of pharmaceuticals, medicinals, agrochemicals, and biology [3-6]. As drugs, ureas were used for the development of HIV-protease inhibitors in the treatment of AIDS [7]. The urea functionality has been utilized to create highly organized structures such as xanthine [8], antiglycating agent [9], FKBP12-urea complex [10], neutral anion receptors [11], combretastatin A-4 [12], FAAH inhibitor [13], and transporter UT-B [14]. It has been used in DNA gyrase and topoisomerase IV [15], epoxidehydrolase [16], and several other classes of enzyme inhibitor [17] and subjected to biological screening. Urea linkage has the ability to create systematically arranged 6- or 8-member rings with organic anions [18] and this group act as a hydrogen bond donor through their two NH protons. Also, the urea moiety acts as acceptor due to the presence of lone pairs of the C=O group [19], which helps in the synthesis of crystalline organic solids.

Currently, ureidopeptides have been synthesized through the following methods. The Curtius rearrangement basically involved the conversion of an

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doi: 10.24200/sci.2018.5013.1043

acyl azide into the corresponding isocyanate intermediate under thermal conditions. Trapping of the isocyanate with suitable amino acid ester yielded urea [20]. Alternatively, few more coupling agents like *N*-ethyl-*N* dimethylaminopropylcarbodiimide (EDC) [21], *O*-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) [22], *N,N*-disuccinimido carbonate (DSC) [23], Deoxo-Fluor, and $TMSN_3$ [24] were used. Ureidopeptides were also synthesized using methyl carbamates as starting materials by reacting amino acid esters and *N*, *O*-bis-TMS (amino acids) [25]. However, these approaches involved lengthy procedures. Moreover, some of the reagents and products sometimes formed may be unstable and converted into harmful by-products, hence requiring special care. Therefore, it is necessary to use a convenient, inexpensive reagent [26] to yield contamination-free stable target products.

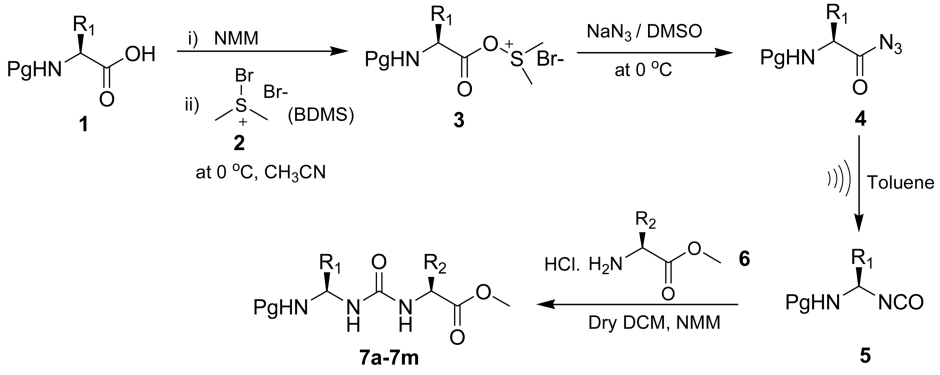
BDMS (bromodimethylsulfonium bromide) was discovered by Meerwein et al. [27] and acts as a catalyst as well as effective brominating agent in a variety of organic transformations [28-37]. Because of the advantages such as low cost, easy accessibility, minimal side products, and low time duration for the activation of desired functional groups, BDMS found a wide range of applications in the synthetic chemistry. The combination of BDMS-$ZnCl_2$ was used in converting ketoximes to amides [38] and condensation reaction of three components to α-amino amidine [39]. BDMS was used efficiently in the synthesis of methyl 2-deoxy-4, 6-*O*-benzylidene galactopyranoside [40] and dithioacetal derivatives of sugar [41]. Yadav et al. reported the *in situ* generation of DMSO during the formation of unsymmetrical ureas from hydroxamic acids using BDMS [42]. The application of BDMS in the synthesis of N^a-protected ureidopeptides is not established according to the literature survey. Hence, herein, we report a mild and efficient route for the synthesis of biologically active peptidylureas employing BDMS in one pot. Furthermore, the synthesized compounds are screened for *in-silico* molecular docking and in-vivo anti-bacterial studies.

2. Results and discussion

2.1. Chemistry

N^a-protected amino acid (**1**) was dissolved in CH_3CN (acetonitrile) at 0°C and its carboxyl group was activated by the addition of BDMS (**2**) as one of the organometallic solids in the formation of *in-situ* generated carboxylated sulfonium intermediate (**3**) in the presence of NMM (/it N-methyl morpholine) as a base. The reaction mixture was stirred for 15 minutes at the same temperature. The carboxylated sulfonium intermediate reacted with NaN_3 dissolved in DMSO; then, the carbonyl group attacked the negative part of azide to get acyl azide (**4**) and DMSO. Sodium bromide was the by-product. Progress of the reaction was monitored through TLC (thin layer chromatography). Then, acyl azide was subjected to Curtius rearrangement under sonication for 45 minutes. The isocyanate (**5**) formed was coupled with amino acid ester (**6**) in dry DCM (dichloromethane) to form the final product of ureidopeptides (**7a**-**7m**) (Scheme 1). The resulting mixture was stirred at 0°C for 4-5 hours until the completion of the reaction (as monitored by TLC). Through this procedure, several peptidylureas were synthesized from N^a-protected Fmoc/Cbz/Boc amino acids (Table 1) and the protocol was free from racemization.

Studies on the reaction were initiated with Fmoc-alanine as starting material. For this isocyanate, the precursor was prepared through the Curtius rearrangement of the corresponding acid azide. The isocyanate was then treated with equivalent amount of ValOMe with DCM as solvent in the presence of a base at 0°C to yield the urea derivative (7**i**). The reaction was run in the presence of BDMS. As expected, there was a tremendous surge up to 90% in the yield. This observation was consistent with



Pg = Fmoc, Boc and Cbz protecting group; $\mathbf{R_1}$ = Amino acid side chain

Scheme 1. Synthesis of N^{α}-protected ureas (**7a-7m**) using BDMS.

Table 1. List of N^a-protected ureas prepared via Scheme 1.

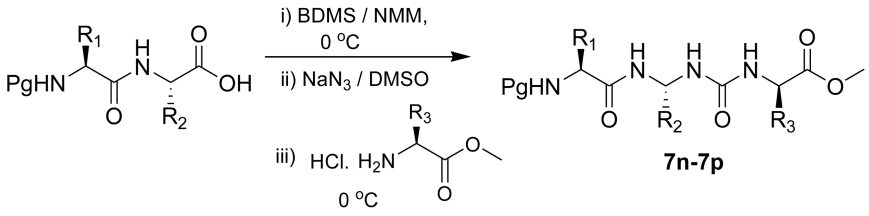
Entry	Compound	Yield (%)	M.p./°C
7a	N^a-Fmoc-Ala-ψ[NHCONH]-Val-OMe	90	180
7b	N^a-Fmoc-Phe-ψ[NHCONH]-Ser-OMe	81	170
7c	N^a-Cbz-Val-ψ[NHCONH]-Gly-OMe	85	165
7d	N^a-Cbz-Met-ψ[NHCONH]-Phe-OMe	89	170
7e	N^a-Boc-Ala-ψ[NHCONH]-Ser-OMe	80	205
7f	N^a-Boc-Leu-ψ[NHCONH]-Ala-OMe	90	Gum
7g	N^a-Fmoc-Phe-ψ[NHCONH]-Ala-OMe	83	185
7h	N^a-Fmoc-Leu-ψ[NHCONH]-Ile-OMe	84	91
7i	N^a-Fmoc-Val-ψ[NHCONH]-Ala-OMe	80	174
7j	N^a-Fmoc-Try-ψ[NHCONH]-Ala-OMe	87	205
7k	N^a-Boc-Val-ψ[NHCONH]-Ala-OMe	75	Gum
7l	N^a-Fmoc-Ile-ψ[NHCONH]-Val-OMe	86	159
7m	N^a-Cbz-Thr-ψ[NHCONH]-Val-OMe	90	165

Table 2. Yield of N^a-Fmoc-Ala-ψ[NHCONH]-Val-OMe (**7i**) over different reagents via Scheme 1.

Entry	Compound	Coupling agents/activating agent	Yield (%)
1	**7i**	TBTU	80
2	**7i**	EDC	79
3	**7i**	DSC	82
4	**7i**	BDMS	90

Table 3. List of N^a-protected urea-peptide hybrids prepared via Scheme 2.

Entry	Compound	Yield (%)	M.p./°C
7n	N^a-Fmoc-Ile-Gly-ψ[NHCONH]-Leu-OMe	75	161
7o	N^a-Cbz-Phe-Leu-ψ[NHCONH]-Ile-OMe	72	Gum
7p	N^a-Cbz-Leu-Phe-ψ[NHCONH]-Ala-OMe	73	187



Pg = Fmoc and Cbz protecting group; **R_1, R_2** and **R_3** = Amino acid side chains

Scheme 2. Synthesis of N^{α}-protected urea-peptide hybrids (**7n-7p**) using BDMS.

the proven mechanism of activation of isocyanates towards nucleophillic attack. Parallel reactions were also run with coupling agents like *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), *N*-ethyl-*N* dimethylaminopropylcarbodiimide (EDC), and *N,N*-disuccinimido carbonate (DSC) as replacements for BDMS. However, the yields in these cases were only up to 79-82% even with higher equivalents (Table 2). The overall course of the BDMS activated reaction starting from the corresponding protected amino acid was completed within 6 h.

Furthermore, the protocol was extended to the preparation of a series of N^a-protected urea-peptide hybrids (Table 3) starting from Fmoc-dipeptide acids via Scheme 2. The dipeptides were converted into their respective acyl azide derivatives in the presence of BDMS subjected to the Curtius rearrangement and reacted with amino acid methyl esters to afford the

ureido bond linked peptide esters (**7n**-**7p**) in about 75% yield. Then, the final reaction mixture of all urea derivatives was washed with water to get crude product and purified through recrystallization using DMSO-H_2O. The final compounds were confirmed by their FTIR, ^{1}H NMR, ^{13}C NMR, and MS spectral studies.

A common problem in peptide synthesis is that racemization of amino acids may occur through side reactions. The enantiomeric purities were determined by the ^{1}H NMR analysis of urea adducts made by the coupling of Boc-Phe-OH with optically pure (*R*)-(+)-1-phenylethylamine and (*S*)-(-)-1-phenylethylamine, containing the methyl group doublets at $\delta = 1.29$, 1.31 and 1.26, 1.28, respectively, in separate experiments via Scheme 1. The equimolar mixture of these compounds obtained by reacting racemic 1-phenylethylamine with Boc-Phe-OH had methyl peaks at 1.26, 1.28, 1.29, and 1.31 ppm corresponding to the presence of two epimers. Thus, the present study revealed that the protocol was free from racemization in the preparation of ureas.

2.2. Molecular docking study of urea derivatives

Three target proteins from different organisms, namely, *Escherichia coli* (1C14) [43], *Staphylococcus aureus* (2UVO) [44], and *Pseudomonas aeroginosa* (2ZCP) [45], were selected to assess the binding efficacy and inhibitory effects of synthesized compounds against them in the *in-silico* method. The protein structures were downloaded from Protein Data Bank [46] and cleaned by deleting water molecules and any other heterogeneous molecules that came from crystallographic preparations [47]. Energy minimization of the targets was performed with the help of standard dynamics cascade protocol of Discovery Studio 3.5 (DS 3.5) by 20,000 steps of steepest descent minimization protocol and a standard relaxation procedure using restrained molecular dynamics [48]. The active sites were identified by receptor cavity method using DS 3.5 [49]. 2D structure of all the ligands was drawn in Chemdraw ultra 8.0 and exported as mol file for further processing in DS 3.5 [50]. Using 'Prepare Ligand' tool in the DS, all possible 3D conformers were generated based on the flexibility of bonds in the molecules. The generated conformers were optimized using CHARMm force field and, then, minimized through 500 steps of steepest descent minimization algorithm with RMS gradient kept at 0.1. The lowest energy ligand conformations selected among the generated conformations were then grouped into one library file and subjected to docking. Molecular docking provides preliminary information about the binding modes of ligand molecules in and around receptor cavities as well as predicts possible intermolecular non-covalent bonding. Binding modes may then be used to predict the strength of association between the ligands and receptors using certain scoring functions that include number and types of bonds, hysteric clashes, and electronic repulsions as parameters. The flex docking score correlates with the binding affinity of the molecules with the target [51]. Docking results for all the three compounds against three different target proteins are tabulated in Tables 4 and 5. Docking results confirm that the compounds **P-1** and **DP-1** have very low lead IT scores against all the targets, indicating their effective binding mode. Pictorial representations of the binding modes of the top two lead molecules against each target are shown in Figure 1.

2.3. Antibacterial activity

The urea derivative showed significantly improved antibacterial activity against tested macrolide-susceptible

Table 4. Docking results of protected ureas.

Entry	Molecule	Bacterial pathogens		
		Escherichia coli	*Staphylococcus aureus*	*Pseudomonas aeroginosa*
P-1	Boc-Leu-ψ[NHCONH]-Ala-OMe	−13.43	−13.80	−13.13
P-3	Fmoc-Phe-ψ[NHCONH]-Ser-OMe	−5.98	−4.66	−3.76
P-5	Cbz-Val-ψ[NHCONH]-Gly-OMe	−9.98	−8.40	−10.77

Table 5. Docking results of deprotected ureas.

Entry	Molecule	Bacterial pathogens		
		Escherichia coli	*Staphylococcus aureus*	*Pseudomonas aeroginosa*
DP-1	Leu-ψ[NHCONH]-Ala-OMe	−16.30	−17.87	−15.11
DP-3	Phe-ψ[NHCONH]-Ser-OMe	−16.64	−12.37	−18.98
DP-5	Val-ψ[NHCONH]-Gly-OMe	−19.82	−11.31	−18.88

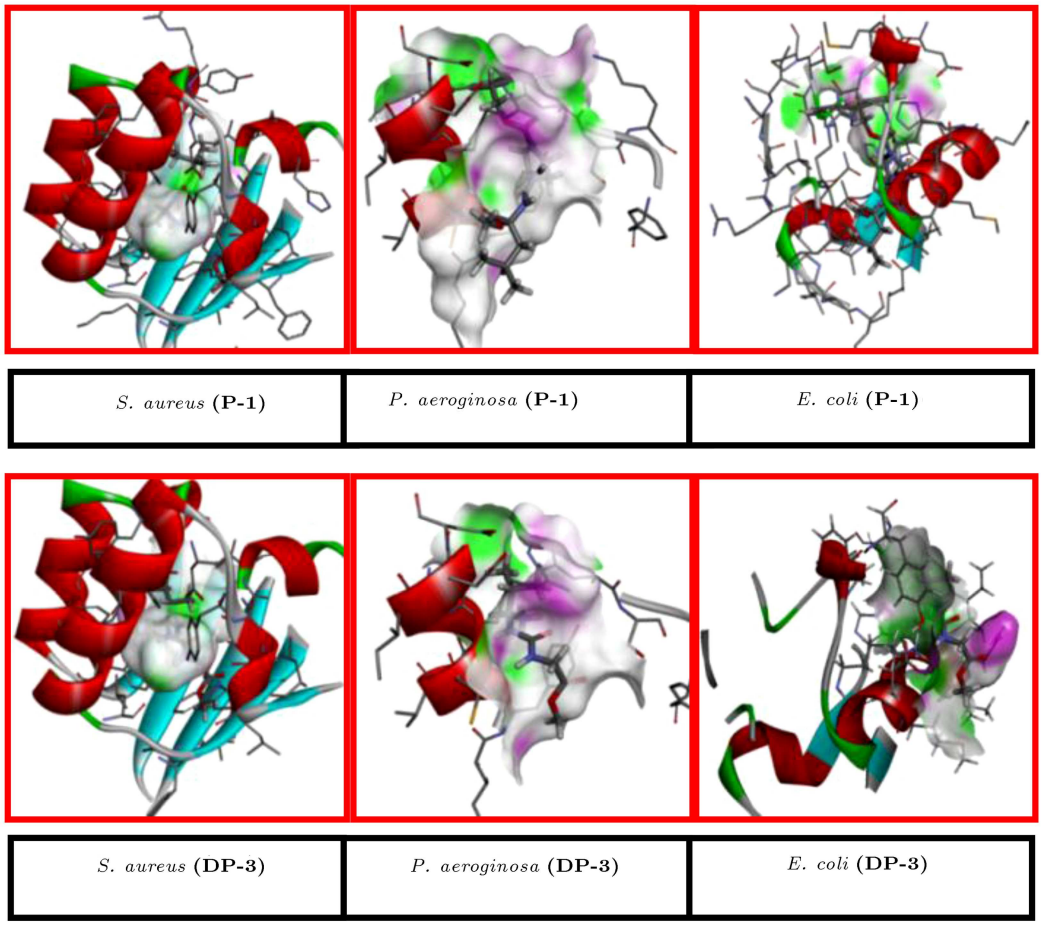


Figure 1. Pictorial representations of the binding modes of protected (P) and deprotected (DP) ureidopeptides with target proteins.

and resistant strain [52]. In the present work, antibacterial activity of Boc-Leu-ψ[NHCONH]-Ala-OMe (**P-1**) and Leu-ψ[NHCONH]-Ala-OMe (**DP-3**) was screened by agar well diffusion method [53] against three pathogenic bacterial strains (two gram +ve and one gram −ve), namely, *Escherichia Coli* (MTCC1692), *Staphylococcus aureus* (MTCC 3160), and *Pseudomonas aeroginosa* (MTCC1688). Preliminary screening was done to check antibacterial activity against bacterial strains. Mueller-Hinton agar plates were inoculated by 24 h culture of bacteria. The synthesized compounds were dissolved in DMSO and placed on the surface of the inoculated plates at concentration of 10 mg/1 mL. Streptomycin sulphate was used as standard antibiotic. After incubation at 37°C for 24 h, the diameter of inhibition zone was measured (mm). The inhibition zones of **P-1** and **DP-1** values were determined.

The antibacterial activity results of the compounds **P-1** and **DP-3** exhibited significant activity against two gram −ve and one gram +ve pathogens. Wells of approximately 6 mm diameter were made on MH agar plates using gel puncture. All the synthesized compounds were dissolved in DMSO (10 mg/1 mL) separately and varied concentrations of compounds were used to assess the activity. In each well, a volume of 50 μl streptomycin sulphate standard (2 mg/1 mL) and 50 μl, 100 μl, and 200 μl of respective compounds were added to individual plates. Each set of plates was prepared in triplicates and the plates were incubated at 37°C for 24 h; then, the inhibition zones obtained were measured. The samples of protected and deprotected ureas were subjected to antibacterial studies using streptomycin sulphate. It was observed that derivatives of compounds **P-1** and **DP-1** had inhibitory activity against all the three pathogens, as reported in Table 6. The compounds were shown to have moderate activities against all the three organisms in 50 μl, as in standard streptomycin sulphate. The compound **P-1** showed 25 mm, 26 mm, and 28 mm zone sizes against *Escherichia Coli*; 20 mm, 21 mm, and 19 mm zone sizes against *Staphylococcus aureus*; and 18 mm, 19 mm, and 18 mm zone sizes against *Pseudomonas aeroginosa*. The compound **DP-1** showed 31 mm, 29 mm, and 25 mm zone sizes against *Escherichia Coli*; 22 mm, 21 mm, and 21 mm zone sizes against *Staphylococcus aureus*;

Table 6. Antibacterial test for protected (**P**) and deprotected (**DP**) ureidopeptides.

Entry	Compound	Standard	Sample concentration (μl)		
	Escherichia coli	**50**	**50**	**100**	**200**
1	Boc-Leu-ψ[NHCONH]-Ala-OMe (**P-1**)	23 mm	25 mm	26 mm	28mm
2	Leu-ψ[NHCONH]-Ala-OMe (**DP-1**)	26 mm	31 mm	29 mm	25 mm
	Pseudomonas aeruginosa				
1	Boc-Leu-ψ[NHCONH]-Ala-OMe (**P-1**)	22 mm	18 mm	19 mm	18 mm
2	Leu-ψ[NHCONH]-Ala-OMe (**DP-1**)	27 mm	29 mm	30 mm	28 mm
	Staphylococcus aureus				
1	Boc-Leu-ψ[NHCONH]-Ala-OMe (**P-1**)	20 mm	20 mm	21 mm	19 mm
2	Leu-ψ[NHCONH]-Ala-OMe (**DP-1**)	21 mm	22 mm	21 mm	21 mm

and 29 mm, 30 mm, and 28 mm zone sizes against *Pseudomonas aeroginosa*. This indicates that the deprotected ureas have higher activity than protected ureas.

3. Conclusion

We herein report a simple and efficient protocol for the synthesis of biologically active N^a-protected ureidopeptides employing BDMS as an inexpensive activating agent via Curtius rearrangement under mild reaction conditions and the present work opens up a new aspect of the synthetic use of BDMS in the field of peptide chemistry. Docking results predict that the compounds **P-1** and **DP-1** have large value of negative binding energy with the active sites of selected targets such as *Escherichia Coli, Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Antibacterial study reveals that these molecules exhibited promising activities against all the three targets.

4. Experimental

4.1. General

All chemicals were purchased from Sigma-Aldrich and Merck and used without purification. IR spectra were recorded on Agilent cary-630 Fourier transform infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer using $(CH_3)_4Si$ as an internal standard and DMSO as a solvent. Mass spectra were recorded on a Micromass Q-ToF micro mass spectrometer. Melting points were calculated in open capillaries and were uncorrected. TLC (Thin Layer Chromatography) analysis was carried out using precoated silica gel F_{254}.

4.2. General procedure for the synthesis of N^a-protected urea derivatives (7a-7p)

To a solution of protected amino acid/dipeptide acids (1.0 mmol) in dry CH_3CN, NMM (*N*-methyl morpholine) (1.5 mmol) and BDMS (1.5 mmol) were added at 0°C and stirred for 15-20 min to get sulfonium intermediate. Then, NaN_3 (2.0 mmol) in DMSO (dimethylsulfoxide) (1 mL) was added and stirred for 15 min. The formed acyl azide was then sonicated for 45 min, followed by the addition of an amino acid ester (1.2 mmol) and stirring was continued until the completion of the reaction at 0°C. Finally, the reaction mixture was washed with water to get crude product of ureas. Then, purification was performed through recrystallization of DMSO-H2O to afford analytically pure products (Tables 1 and 2).

4.3. Spectral data of synthesized compounds

Methyl 2-(3-(1-(((9H-fluoren9yl)methoxy) carbonyl)ethyl)ureido)-methylbutanoate **(7a)***:*
Yield 90%; m.p. 180-182°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3349, 3288, 2978, 2979, 1720, 1669, 1344 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.79 (br, 6H), 1.16-1.94 (br, 3H), 3.05 (m. 1H), 3.55 (s, 3H), 4.0 (d, *J* 12.0 Hz, 1H), 4.15-4.24 (br, 1H), 4.51-4.82 (br, 2H), 5.13 (br, 1H), 6.31-6.37 (br, 3H), 7.22-7.94 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 18.34, 20.75, 31.28, 45.18, 51.35, 53.82, 59.74, 66.15, 126.53, 126.81, 127.12, 128.39, 141.12, 144.23, 156.02, 157.23, 174.12. MS: Calc. for $C_{24}H_{29}N_3O_5$: *m/z* 462.2005 (M + Na^+), found 462.2008.

*Methyl2-(3-(1-(((9H-fluoren-9-yl)methoxy) carbonyl)-2-phenylethyl)ureido)-3-hydroxypropanoate***(7b)***:*
Yield 81%; m.p. 170-172°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3418, 3318, 3202, 3063, 2968, 1678, 1610, 1331 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.0 (s, 1H), 2.48-2.52 (m, 2H), 3.40 (s, 3H), 4.19-4.25 (m, 2H), 4.25 (m, 1H), 4.51 (m, 1H), 4.76 (d, J 4.0 Hz, 2H), 6.20-6.90 (br, 3H), 6.61 (m, 1H), 7.29-7.88 (m, 13H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 40.12, 46.71, 51.81, 54.84, 59.92, 62.09, 65.44, 125.29, 126.33, 127.73, 128.22, 128.40, 128.70, 129.30, 137.80, 140.76, 143.87, 155.09, 156.33, 172.23. MS: Calc. for $C_{28}H_{29}N_3O_6$: *m/z* 526.1954 (M + Na^+), found: 526.1955.

Methyl 2-(3-(1-(benzyloxycarbonyl)-2-methylpropyl)ureido)acetate **(7c)***:*
Yield 85%; m.p. 163-165°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3352, 3282, 2973, 1723, 1686, 1336 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.82-0.84 (d, *J* 8.0 Hz, 6H), 3.30 (m, 1H), 3.61 (s, 3H), 4.01-4.19 (s, 2H), 4.86-4.88 (br, *J* 8.0 Hz, 2H), 5.26 (s, 1H), 6.35-6.37 (d, *J* 8.0 Hz, 3H), 7.20-7.41 (s, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.53, 32.43, 41.96, 51.55, 63.05, 65.36, 127.63, 128.27, 129.0, 155.10, 156.08, 156.83, 171.48. MS: Calc. for $C_{16}H_{23}N_3O_5$: *m/z* 360.1535 (M + Na^+), found: 360.1537.

Methyl 2-(3-(1-(benzyloxycarbonyl)-3-(methylthio)propyl)ureido)-3-phenylpropanoate **(7d)***:*
Yield 89%; m.p. 170-172°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3388, 3289, 3029, 2914, 2850, 1732, 1694, 1340 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ(ppm) 1.99 (s, 3H), 2.31-2.35 (t, *J* 8.0 Hz, 2H), 2.48-2.52 (m, 2H), 2.82-2.90 (m, 2H), 3.58 (s, 3H), 4.44 (t, *J* 8.0 Hz, 1H), 4.99 (s, 2H), 6.35-6.47 (d, *J* 8.0 Hz, 3H), 7.12-7.32 (m, 10H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.68, 29.23, 34.55, 37.75, 40.12, 51.69, 53.76, 57.51, 65.22, 126.55, 127.75, 128.21, 128.34, 129.60, 136.92, 137.01, 155.05, 156.00, 172.79. MS: Calc. for $C_{23}H_{29}N_3O_5S$: *m/z* 482.1726 (M + Na^+), found 482.1724.

Methyl 2-(3-(1-(tert-butoxycarbonyl) ethyl)ureido)-3-hydroxypropanoate **(7e)***:*
Yield 80%; gum. R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3325, 2980, 1146, 1069 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.15-1.16 (d, *J* 4.0 Hz, 3H), 1.36 (s, 9H), 2.49 (s, 1H), 3.28 (s, 3H), 3.97-4.01 (m, 2H), 4.95-5.00 (m, 1H), 5.87-5.99 (m, 1H), 6.85 (br, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 22.0, 28.5051.99, 56.70, 58.60, 60.15, 79.80, 156.20, 158.10, 171.60. MS: Calc. for $C_{12}H_{23}N_3O_6$: *m/z* 328.1487 (M + Na^+), found 328.1488.

Methyl 2-(3-(1-(tert-butoxycsarbonyl)-3-methylbutyl)ureido)propanoate **(7f)***:*
Yield 90%; gum. R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3336, 2958, 1685, 1365 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.88-0.90 (d, *J* 8.0 Hz, 6H), 1.40 (s, 9H), 1.52-1.54 (d, *J* 8.0 Hz, 3H), 1.75 (m, 2H), 1.80 (m, 1H), 3.60 (s, 3H), 4.62-4.68 (m, 1H), 5.60 (m, 1H), 6.10-6.12 (d, *J* 8.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.51, 19.25, 22.75, 28.15, 47.95, 51.60, 51.72, 59.10, 77.76, 154.78, 156.21, 174.11. MS: Calc. for $C_{15}H_{29}N_3O_5$: *m/z* 354.2005 (M + Na^+), found 354.2004.

Methyl 2-(3-(1-(((9H-fluoren-9yl)methoxy) carbonyl)-2-phenylethyl) ureido)propanoate **(7g)***:*
Yield 83%; m.p. 185°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3355, 3299, 2979, 2983, 1719, 1675, 1345 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.83 (s, 3H), 3.43 (m, 2H,), 3.49 (s, 3H), 4.32-4.52 (m, 2H), 4.61 (d, *J* 6.6 Hz, 1H), 4.72 (d, *J* 10.0 Hz, 2H, 5.05 (br, 3H), 5.56 (t, *J* 8.0 Hz,1H), 7.25-7.82 (m, 13H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.08, 38.13, 47.54, 48.79, 52.43, 62.51, 66.31, 120.55, 125.88, 126.92, 127.71, 128.29, 128.81,130.03, 138.42, 141.56, 144.51, 156.38, 157.10,174.89. MS: Calc. for $C_{28}4H_{29}N_3O_5$: *m/z* 510.2005 (M + Na^+), found 510.2010.

*Methyl 2-(3-(1-(((9H-fluoren-9-yl)methoxy) carbonyl)-3-methylbutyl)ureido)-3-methylpentanoate***(7h)***:*
Yield 84%; m.p. 178-180°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3306, 2959, 2876, 1735, 1691, 1233 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.96 (t, J 10.0 Hz, 3H), 1.06 (d, *J* 6.6 Hz, 3H), 1.10 (d, *J* 8.0 Hz, 6H), 1.18 (d, *J* 10.0 Hz, 2H), 1.7 (t, *J* 12.0 Hz, 2H), 1.86 (m, 1H), 2.99 (m, 1H), 3.70 (s, 3H), 4.44 (t, *J* 8.0 Hz, 1H), 4.50 (t, *J* 12.0 Hz, 1H), 4.80 (d, *J* 8.0 Hz, 2H), 5.70 (m, 1H), 6.2 (br, 3H), 7.28-7.90 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.40, 14.69, 20.0, 22.9, 24.81, 36.8, 46.40, 47.10, 52.0, 55.2, 56.1, 59.20, 67.6, 126.9, 128.3, 128.6, 128.10, 142.0, 144.0, 158.0, 172.0. MS: Calc. for $C_{28}H_{37}N_3O_5$: *m/z* 518.26 (M + Na^+), found 518.3424.

Methyl 2-(3-(1-(((9H-fluoren-9-yl)methoxy) carbonyl)-2-methylpropyl)ureido)propanoate **(7i)***:*
Yield 80%; m.p. 172-174°C. R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3282, 2953, 1736, 1690, 1250 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.81 (s, 6H), 1.19-1.21 (d, *J* 8.0 Hz, 3H), 3.32-3.45 (m, 1H), 3.59 (s, 3H), 4.14-4.28 (m, 2H), 4.82 (m, 2H), 5.55-5.57 (d, *J* 4.0 Hz, 1H), 6.21-6.26 (br, 2H), 6.47-6.49 (br, d, *J* 8.0 Hz, 1H), 7.30-7.87 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.80, 18.15, 32.41, 46.70, 51.67, 51.90, 62.97, 65.18, 125.19, 127, 01, 127.25, 128.89, 140.68, 143.89, 155.13, 156.20, 174.09. MS: Calc. for $C_{24}H_{29}N_3O_5$: *m/z* 462.2005 (M + Na^+), found: 462.2000.

Methyl 2-(3-(1-(((9H-fluoren-9-yl)methoxy) carbonyl)-2-(1H-indol-3-yl)ethyl)ureido) propanoate **(7j)***:*
Yield 87%; m.p. 203-205°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3350, 3279, 2980, 2969, 1726, 1666, 1355 cm^{-1}. ^1H NMR (400 MHz, DMSO-d−6): δ (ppm) 1.51(d, *J* 8.0 Hz, 3H), 3.10 (d, *J* 10.0 Hz, 2H), 3.61 (s, 3H), 4.44 (t, 1H), 4.60 (m, 1H), 4.80 (d, *J* 8.0 Hz, 2H), 6.09 (m, 1H), 6.3 (br, 4H), 6.95 (s,1H), 7.16-7.82 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 16.8, 35.70,48.0, 50.8, 52.1, 66.1, 67.9, 110.1, 111.2, 119.1, 120.2, 122.3, 122.9,126.9, 127.8, 128.2, 128.6, 128.9,137.5, 142.0, 143.8, 158.0, 158.6,171.8. MS: Calc. for $C_{30}H_{30}N_4O_5$: *m/z* 549.21 (M + Na^+), found 549.1925.

Methyl 2-(3-(1-(tert-butoxycarbonyl)-2-methylpropyl) ureido)propanoate **(7k)***:*
Yield 75%; gum. R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3349, 3277, 2970, 1724, 1655, 1354 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.84 (d, J 6.0 Hz, 6H), 1.25 (d, J 7.2 Hz, 3H), 1.36 (s, 9H), 1.87 (br, 1H), 3.64 (s, 3H), 4.25 (m, 1H), 4.76 (m, 1H), 6.22-6.58 (br, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.69, 17.79, 27.66, 31.91, 47.55, 51.17, 62.53, 75.38, 154.56, 156.26, 173.66. MS: Calc. for $C_{14}H_{27}N_3O_5$: m/z 340.1848 (M + Na^+), found 340.1825.

Methyl 2-(3-(1-(((9H-fluoren-9-yl)methoxy) carbonyl)-2-methylbutyl) ureido)-3-methylbutanoate **(7l)***:*
Yield 86%; m.p. 159-161°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3355, 3271, 2978, 2970, 1723, 1665, 1353 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.96 (t, J 10.0 Hz, 3H), 1.10 (d, J 6.0 Hz, 6H), 1.18 (d, J 10.0 Hz, 3H), 1.32 (m, 2H), 2.98 (m, 1H), 3.10 (m, 1H), 3.70 (s, 3H), 4.44 (t, J 8.0 Hz, 1H), 4.50 (t, J 12.0 Hz, 1H), 4.80 (d, J 8.0 Hz, 2H), 5.70 (m, 1H), 6.0 (br, 3H), 7.28-7.90 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.40, 12.50, 17.20, 22.60, 30.1, 38.9, 47.2, 51.90, 57.9, 66.4, 67.8, 126.8, 128.4, 128.6, 128.8, 141.2, 143.8, 156.2, 157.9, 171.8. MS: Calc. for $C_{27}H_{35}N_3O_5$: m/z 504.25 (M + Na^+), found 504.2214.

Methyl 2-(3-(1-(benzyloxycarbonyl)-2-hydroxypropyl) ureido)-3-methylbutanoate **(7m)***:*
Yield 90%; m.p. 165-167°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3303, 3236, 2959, 1715, 1684, 1218 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.10 (d, J 8.0 Hz, 6H), 1.31 (d, J 10.0 Hz, 3H), 2.01 (s, 1H), 3.10 (m, 1H), 3.60 (s, 3H), 4.49 (d, 1H, J 12.0 Hz), 4.70 (m, 1H), 5.40 (s, 2H), 5.80 (d, J 10.0 Hz, 1H), 6.3 (br, 3H), 7.30 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 16.8, 17.2, 31.0, 51.8, 58.1, 69.8, 66.0, 74.0, 127.4, 127.9, 129.0, 141.4, 156.5, 157.90, 171.8. MS: Calc. for $C_{18}H_{27}N_3O_6$: m/z 404.18 (M + Na^+), found 404.1435.

Methyl 2-(3-((2-(((9H-fluoren-9-yl)methoxy) carbonyl)-3-methylpentanamido)methyl) ureido)-4-methylpentanoate **(7n)***:*
Yield 75%; m.p. 161-162°C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3349, 3269, 2977, 2971, 1728, 1661, 1358 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.98 (t, J 10.0 Hz, 3H), 1.10 (d, J 8.0 Hz, 6H), 1.18 (d, J 10.0 Hz, 3H), 1.32 (m, 2H), 1.70 (m, 1H), 1.84 (t, J 8.0 Hz, 2H), 2.70 (m, 1H), 3.70 (s, 3H), 4.44 (m, 1H), 4.48 (t, J 8.0 Hz, 1H), 4.54 (t, J 10.0 Hz, 2H), 4.72 (d, J 12.0 Hz, 1H), 5.05 (s, 2H), 6.5 (br, 4H), 7.28-7.90 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.7, 14.8, 22.3, 22.9, 24.9, 36.6, 40.3, 47.0, 51.0, 51.9, 55.4 57.3, 67.6, 126.6, 128.2, 128.6, 128.8, 141.2, 143.6, 156.2, 157.5, 171.2, 171.8. MS: Calc. for $C_{30}H_{40}N_4O_6$: m/z 575.28 (M + Na^+), found 575.2545.

*Methyl 2-(3-(1-(2-(benzyloxycarbonyl)-3-phenylpropanamido)-3-methyl butyl) ureido)-3-methylpentanoate***(7o)***:*
Yield 72%; gum. R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3356, 3270, 2966, 2971, 1723, 1668, 1360 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.85 (t, 3H), 0.90-1.09 (m, 6H), 1.12-1.39 (m, 3H), 1.42 (m, 2H), 1.50-1.77 (m, 2H), 1.83 (m, 1H), 2.40-3.07 (m, 1H), 2.90 (d, J 12.0 Hz, 2H), 3.66 (s, 3H), 4.31 (m, 1H), 4.89-5.10 (m, 4H), 6.21-6.45 (br, 4H), 7.18-7.27 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.4, 15.6, 22.3, 22.4, 24.4, 24.8, 37.3, 37.6, 43.8, 51.6, 55.4, 56.2, 56.7, 65.3, 126.3, 127.5, 127.8, 128.1, 128.4, 129.3, 137.1, 138.2, 155.9, 156.5, 171.0, 173.2. MS: Calc. for $C_{30}H_{42}N_4O_6$: m/z 577.2997 (M + Na^+), found 577.3002.

Methyl 2-(3-(1-((S)-2-(benzyloxycarbonyl)-4-methylpentanamido)-2-phenylethyl) ureido)propanoate **(7p)***:*
Yield 73%; m.p. 186-188 °C; R_f ($CHCl_3$/MeOH 9:1) = 0.4, IR (ATR mode): 3364, 3272, 2966, 2951, 1724, 1656, 1362 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.87 (d, J = 5.6 Hz, 6H), 1.25-1.58 (m, 6H), 2.93-3.10 (m, 2H), 3.68 (s, 3H), 4.03-4.34 (m, 2H), 5.04 (s, 2H), 5.14-5.18 (m, 1H), 6.31-6.59 (br, 3H), 7.19-7.32 (br, 10H), 8.02 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.1, 21.5, 22.7, 24.4, 40.9, 47.9, 51.6, 53.3, 58.5, 65.7, 126.2, 127.6, 127.9, 128.4, 129.3, 136.8, 137.6, 155.7, 156.1, 171.9, 173.9. MS Calc. for $C_{27}H_{36}N_4O_6$: m/z 535.2544 (M + Na^+), found 535.2535.

Acknowledgement

The authors thank the Principal and Director of Siddaganga Institute of Technology, Tumakuru, Karnataka, for the research facilities. One of the authors (HSL) is thankful to the Vision Group of Science and Technology (VGST), Department of Information Technology, Biotechnology and Science & Technology, Government of Karnataka, for providing funds under CISEE programme (GRD No. 472) to carry out the present research work by means of a sponsored project.

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