Indian Journal of Biochemistry & Biophysics
Vol. 62, August 2025, pp. 909-918
DOI: 10.56042/ijbb.v62i8.15101

Self-assembly of novel ureido dipeptide esters and investigation of its gelation property

Prajakta Patil[1], Saurabh Shete[1,2]*, Manoj Gavali[2]*, Prasanna Ranade[3], Veena Khilnani[1], Nanabhau Karanjule[1] & Dilip Kumar Yadav[1]

[1]Department of Chemistry, K J Somaiya College of Science and Commerce, Vidyanagar, Vidyavihar, Mumbai-400 077, Maharashtra, India

[2]Department of Chemistry, University of Mumbai, Mumbai-400 098, Maharashtra, India

[3]Vivekanand Education Society's College of Arts, Science and Commerce (Autonomous), Sindhi Society, Chembur, Mumbai-400 071, Maharashtra, India

Received 15 November 2024; *revised 28 December 2024*

Ureido group is an interesting moiety as hydrogen donor and acceptor functionalities are present. Peptides are intriguing molecules as their properties are easily tuned and they are biocompatible. Therefore, four ureido dipeptide esters were synthesized using simple solution phase synthesis and characterized. Their biological activity was investigated against *Streptococcus pyogenes, Staphylococcus aureus* and *E. coli.* A rheological study was carried out to study the gelation properties of the synthesized compounds. Their ability to self-assemble into different morphologies was studied using SEM. The morphology of cubes, sheets, spheres, and rods was observed in the SEM study. These compounds will have potential applications in the medicinal field as drug delivery vehicles.

Keywords: Antibacterial, Hydrogels, Nanostructures, Self-assembly, Shear thinning, Thixotropic

Self-assembly is the spontaneous process of molecules into one or more supramolecular structures, led by multiple non-covalent interactions. A few of the interactions are electrostatic association, hydrogen bonding, hydrophobic effect, and van der Waals forces[1]. Peptides are composed of amino acids that can be joined together in various sequences to form a vast range of structures. Self-assembling peptides comprise of short amino acid chains that assemble to form nanostructures. The physicochemical and biochemical activity of peptide assemblies vary according to their accessibility of the reactive surface area, size, and shape[2]. Peptide-based nanomaterials that self-assemble into well-organized supramolecular gel structures have several benefits, including excellent mechanical, thermal, and optical stability as well as semiconductivity and piezoelectricity. Peptide self-assembly on various length scales offers outstanding possibilities for use in fields like nanotechnology, healthcare, and energy[3]. One of the most frequent outcomes of peptide self-assembly is the formation of hydrogels.

*Correspondence:
E-mail: saurabh@somaiya.edu
Suppl. data available on respective page of NOPR

Peptide-based hydrogels have garnered significant attention lately because of their remarkable combination of unique properties, which include similarity to biological molecules, biocompatibility, biodegradability, hydrophilicity/hydrophobicity that can be easily adjusted, modular integration of stimuli sensitivity, and other adjustable mechanical stiffness/rigidity and functionalities[4]. The Fmoc protected peptides can self-assemble to form hydrogels that have potential nano-technological applications. These hydrogels are non-toxic, thixotropic, and the hydrogel formation is thermo reversible[5]. The peptide self-assembly into a gel network provides a versatile platform for dye capture from waste water[6]. Peptide-based hydrogels, powered by abundant non-covalent interactions that drive nanofibrillation, stand out as the ideal contenders for crafting shear-thinning hydrogels. Shear-thinning hydrogels have been designed for injection, these peptide-based systems undergo re-gelation after administration, creating a solid matrix at the target site[7]. Due to their focused administration, peptides have gained a lot of attention. For example, numerous attempts have been made to develop an efficient method of oral insulin delivery. When delivering oral

insulin, peptide-based carriers have demonstrated a remarkable outcome in terms of limiting insulin breakdown and promoting biocompatibility. Plant defensins, which are abundant in cysteine residues, have been investigated in a number of studies as potential templates for creating anticancer peptides. The structure and behavior of plant defensins can be efficiently analyzed using computational techniques, which are resulting in the new anticancer peptides.

Becart *et al*. has reported foldamers, which are aliphatic N,N′-linked oligoureas consisting of chiral elements of synergistic catalytic systems that enable efficient simultaneous activation of the electrophile and nucleophile at very low catalyst/substrate molar ratios[8]. Angiogenesis, invasion, and metastasis are all dependent on Aminopeptidase N (APN), an enzyme responsible for the growth and spread of cancer. APN is a viable target for novel anti-tumor medications because of its crucial role. Leucine ureido-based APN inhibitors affect their activity and are even better at blocking APN than the current best drug, Bestatin[9]. Aryl (and heterocyclic) ureido, aryl (and heterocyclic) carbamido, phenoxy isobutyric acids, and related compounds were found to be effective inhibitors for glycation and the generation of advanced glycation end products by *in vitro* assay methods[10]. Eight-residue oligoureas are reported to be highly effective against a variety of bacteria & MRSA (methicillin-resistant *Staphylococcus aureus*). They were designed to have the global amphiphilic properties of natural host-defense peptides[11]. Pioneering research revealed the first examples of tetrameric helix bundles with mixed α-peptides and α/β-peptide foldamers, representing a novel form of heterogeneous quaternary structure[122]. N,N′-linked oligoureas are included in the ranks of designer molecules that mimic proteins without their complex peptide chains[13]. Our group recently synthesized N-cinnamoyl dipeptide esters which self-assemble to form nanorods[14].

Researchers have reported that peptide coupling agents EDC and HBTU promote the rapid conversion of carboxylic acids to azides, ureas, and carbamate acids offering a quicker and more effective method for their synthesis[15]. We were interested in studying the self-assembly of urea-containing peptides. A series of hydantoin based peptidomimetics having an aspatic acid residue in an hydantoin heterocycle is reported using solution phase synthesis[16]. Todorov *et al*. has synthesized dipeptide mimetics having 5,5-Dimethyl hydantoin residue[17]. Solution phase synthesis has also been used to create oligomer series with a urea moiety. The purpose of the study was to comprehend how conformational constraints affects peptide association[18]. The urea derivatives displayed promising antimicrobial and anthelmintic potential Notably, a number of compounds showed strong toxicity against the nematode *Caenorhabditis elegans*, while others showed action against MDR strains of *Escherichia coli* and *Klebsiella pneumoniae*. These results indicate that more research into this group of substances may result in a development of new therapeutic compounds[19]. Interestingly the simple ureido dipeptide esters are not reported elsewhere in the literature. We therefore attempted to synthesize the ureido dipeptide esters using solution phase synthesis. Their structures were confirmed using IR, ^{1}H and ^{13}C NMR spectroscopy. The anti-bacterial activity was studied against gram positive bacteria mainly *Streptococcus pyogenes, Staphylococcus aureus* & against *E. coli* which is gram negative bacteria. A rheological study was carried out to investigate the gelation properties of the synthesized compound. The visco-elastic ity of these compounds was investigated using storage and loss modulus. The self-assembly of these Ureido dipeptide ester was investigated by SEM.

Experimental

The chemicals purchased from Sigma Aldrich & Thomas Baker, and Alfa Aesar were utilized without additional purification. The ^{1}H and ^{13}C NMR spectra are obtained using DMSO-d6 as the solvent. IR analysis was carried out on Jasco FT/IR – 4700 IR spectrophotometer

General Procedure for the Synthesis of Ureido Dipeptide Esters (Fig. 1)

Step: I

Synthesis of Phenylglycine ethyl ester hydrochloride (1a-1d)[20]

Phenylglycine (7 mmol) was suspended in 27 mL of ethanol. The resulting suspension was cooled in ice and thionyl chloride (10 mmol) was subsequently added to it. The reaction mixture was then refluxed for 3.5 h. The excess ethanol was removed under a vacuum. The Phenylglycine ethyl ester hydrochloride crystals obtained were recrystallized from 90 % pet ether-ethyl alcohol mixture. The compound was dissolved in pet ether which on cooling gave white needle shaped crystals which was filtered and dried.

Step: II

Synthesis of Ureido amino acid (2a-2d)[21]

Amino acid (11 mmol) and urea (91 mmol) were refluxed in 25 mL of water for 6 h. The solution was then cooled in ice and 1: 1 HCl was added to it till pH 3 was reached. The resulting solid was filtered, washed with cold water, and recrystallized from 50 % aqueous alcohol.The compound was dissolved in 50 % aqueous alcohol under hot conditions and on cooling an amorphous white solid was obtained, which was filtered and dried.

Step: III

Synthesis of Ureido Dipeptide ethyl ester (3)

Ureido amino acid (2 mmol), HBTU (2.2 mmol) were suspended in 8 mL DMF. The reaction mixture was cooled in ice. Triethylamine (7 mmol) and Phenylglycine ethyl ester hydrochloride (3 mmol) were subsequently added to it. The resulting precipitate was filtered & washed with saturated Sodium bicarbonate & 0.05N Hydrochloric acid. The compound was dissolved in 50 % aqueous alcohol under hot conditions and on cooling, an amorphous white gel was obtained. The gel was dried in an oven at 70°C to obtain a white solid (Refer Table 1).

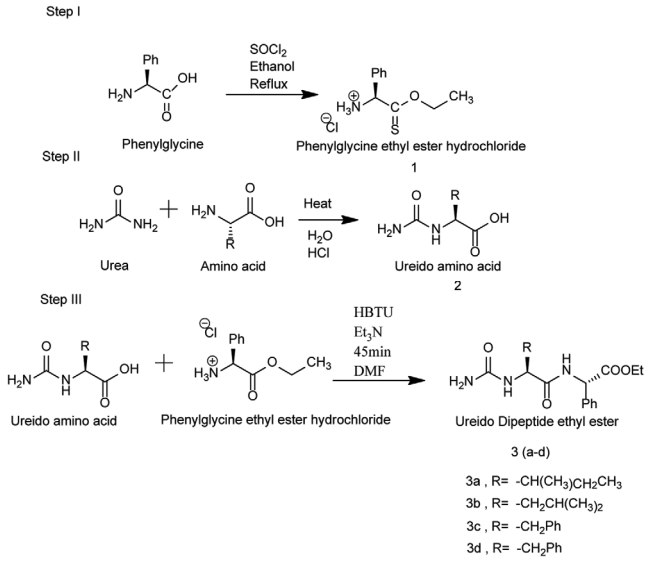

Fig. 1 — General Scheme for the synthesis of Ureido Dipeptide Esters 3 (a-d)

Spectral Details

3a: Figure S1 (supplementary Information): Ureido-L-Ile-L-Phg-OEt :m.p :158-160°C IR (KBr) ν cm^{-1}: 3477,3271 (N-H Stretching), 3073 (Ar-H Stretching), 1730 (C=O ester), 1638 (C=O Urea), 1598, 1547 (C=C), 1024 (C-O Stretching).

Figure 2A & Figure S2 (supplementary Information): ^{1}H NMR (300 MHz , DMSO - d6) δ (ppm): 0.8-0.9 (m, 6H, δ, γ'-2 x CH_3, IIe), 1.0 (m, 1H, β-CH, IIe), 1.1 (t, 3H, J=6Hz ,CH_3, ester), 1.4 (m, 1H, γ-CH_2, IIe), 1.6 (m, 1H, γ-CH_2, IIe), 4.0 (q, 2H, J=6Hz, CH_2, ester), 4.1 (m, 1H, α-CH, IIe), 5.3 (d, 1H, CH, Phg), 5.5 (s, 2H, NH_2, Ureido), 6.1 (d, 1H, NH, Ureido), 7.3 (s, 5H, Aromatic), 8.7 (d, 1H, NH, Phg).

Figure 2B & Figure S3 (supplementary Information): ^{13}C NMR (75 MHz , DMSO - d6) δ (ppm): 11.2 (CH_3, ester), 13.9 (γ'-CH_3,Ile), 15.2 (δ-CH_3,Ile), 24.1 (γ-CH_2, Ile), 37.7 (β-CH, IIe), 56.3 (α-CH, IIe), 56.4 (CH, Phg),60.8 (CH_2, ester), 127.9, 128.2, 128, 135.9 (CH, Aromatic), 158.2 (C=O, Ureido), 170.3 (C=O, Amide), 172.2 (C=O, ester).

3b: Figure S4 (supplementary Information): Ureido-L-Leu-L-Phg-OEt: m.p: 178-180°C IR (KBr) ν cm^{-1}: 3394, 3209, 3361 (N-H Stretching), 1732 (C=O ester), 1641 (C=O Urea), 1524 (C=C), 1022 (C-O Stretching).

Figure S5 (supplementary Information): ^{1}H NMR (300 MHz , DMSO - d6) δ (ppm): 0.8-0.9 (m, 6H, δ, δ'-2 x CH_3 ,Leu), 1.13 (t, 3H, J=6Hz, CH_3, ester), 1.2-1.5 (m, 2H, β -CH_2, Leu), 1.6-1.7 (m, H, γ-CH, Leu), 4.1 (q, 2H, J=6Hz, CH_2 , ester), 4.2 (m, 1H, α-CH, Leu), 5.4 (d, 1H, CH, Phg), 5.5 (s, 2H, NH_2, Ureido), 6.1 (d, 1H, NH, Ureido) 7.4 (s, 5H, Aromatic), 8.7 (d, 1H, NH, Phg).

Figure S6 (supplementary Information): ^{13}C NMR (75 MHz, DMSO - d6) δ (ppm): 14.4 (CH_3, ester), 22.5 (δ-CH3, Leu), 23.6 (δ'-CH_3, Leu), 24.7 (γ -CH, Leu), 42.6 (β-CH_2, Leu), 51.3 (α-CH, Leu), 56.9 (CH, Phg), 61.4 (CH_2 ester), 128.4, 128.7, 129.1, 136.6 (CH, Aromatic), 158.6 (C=O, Ureido), 170.9 (C=O, Amide), 173.81 (C=O, ester).

Table 1 — Yield & physical constant of the Ureido Dipeptide Ethyl Ester

Compd.	R	% Yield	Melting Point (°C)
3a	-$CH(CH_3)CH_2CH_3$	67	158-160°C
3b	- $CH_2CH(CH_3)_2$	73	178-180°C
3c	-CH_2Ph	64	183-185°C
3d	-Ph	65	180-182°C

3c: Figure S7 (supplementary Information): Ureido-L-Phe-L-Phg-OEt :m.p : 183-185°C IR (KBr) ν cm^{-1}: 3401, 3315, 3206 (N-H Stretching), 1720 (C=O ester), 1644 (C=O Urea), 1597, 1554(C=C), 1023 (C-O Stretching).

Figure S8 (supplementary Information): ^{1}H NMR (300 MHz, DMSO - d6) δ (ppm): 1.1 (t, 3H, J=6Hz, CH_3, ester), 2.7-3.0 (m, 2H, CH_2 ,Phe, Ureido), 4.1 (q, 2H, J=6Hz, CH_2, ester), 4.5 (m,1H, CH, Phe), 5.4 (d,1H, CH, Phg), 5.5(s, 2H, NH_2, Ureido), 6.1 (d, 1H, NH, Ureido), 7.2-7.4 (m, 10H, Aromatic), 8.8 (d, 1H, NH, Phg).

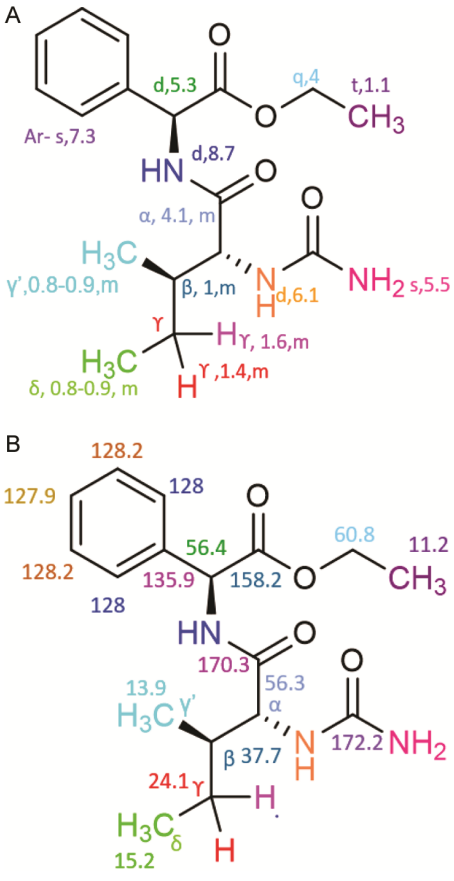

Fig. 2 — (A) ^{1}H NMR; and (B) ^{13}C NMR representative interpretation of 3a

Figure S9 (supplementary Information): ^{13}C NMR (75 MHz, DMSO - d6) δ (ppm): 14.4 (CH_3, ester), 38.9 (CH_2, Phe), 54.0 (CH, Phe), 56.7 (CH_2, Phg), 61.4 (CH_2 ester), 126.6, 128.2, 128.4, 128.7, 129.1, 129.8, 136.6, 138.3(CH, Aromatic), 158.5 (C=O, Ureido), 170.8 (C=O, Amide), 172.78 (C=O, ester).

3d: Figure S10 (supplementary Information): Ureido-L-Phg-L-Phg-OEt: m.p : 180-182°C IR (KBr) ν cm^{-1}: 3479, 3292, 3063 (N-H Stretching), 1726 (C=O ester), 1641 (C=O Ureido), 1591, 1536 (C=C), 1106, 1021 (C-O Stretching).

Figure S11 (supplementary Information): ^{1}H NMR (300 MHz, DMSO - d6) δ (ppm): 1.0 (t, 3H, J=6Hz, CH_3, ester), 4.0 (q, 2H, CH_2, J=6Hz, Ester), 5.4 (d,1H, CH, Phg), 5.5 (d, 1H, CH, Ureido), 5.7 (s, 2H, NH_2, Ureido), 6.7 (d, 1H, NH Ureido), 7.2-7.4 (m, 10H, Aromatic), 9.1 (d, 1H, NH, Phg).

Figure S12 (supplementary Information): ^{13}C NMR (75 MHz, DMSO - d6) δ (ppm): 13.8 (CH_3, Ester), 55.6 (CH, Phg), 56.4 (CH_2, Ester), 60.8 (CH, Ureido Phg), 126.7, 127.1, 127.8, 128.1, 128.3, 128.7, 136.0, 140,0 (CH, aromatic), 157.7 (C=O, Ureido), 170.0 (C=O, Amide),170.65 (C=O, ester).

Biological activities ureido dipeptide ethyl ester (3a-d)

The synthesized compounds have been evaluated for their antibacterial activity against Gram-positive *Streptococcus pyogenes, Staphylococcus aureus* and Gram-negative *E. coli* at concentrations of 1000 ppm in DMF using the cup plate method. The zones of inhibition were measured after 24 h of incubation at 37°C. Antibiotic Gentamicin was used as a reference to study the antibacterial activityfor Gram-positive bacteria. The biological activity of Ampicillin against *E. coli* is tabulated (see Table 2) as reported in the literature[22].

All compounds exhibited good inhibitory activity against tested (Gram Negative bacteria) *E. Coli* (Figs 3 & 4 and Table 2). These compounds were not exhibiting activity against Gram positive bacteria *Streptococcus pyogenes* & *Staphylococcus aureus* as

Table 2 — Zone of Inhibition against *E.coli* Gram Negative (3a-d)

Sr. No.	Sample Name	Zone of Inhibition in mm				
		1st Experiment	2nd Experiment	3rd Experiment	Average	standard deviation
1	3a	18	17	18	17.67	0.58
2	3b	18	16	17	17.00	1.00
3	3c	17	15	16	15.67	1.00
4	3d	16	12	16	15.00	2.31
5	Ampicillin			16.5[22]		

shown in (Fig. 4B & C). The Gentamicin activity against the *Streptococcus pyogenes* & *Staphylococcus aureus* is as shown in (Fig. 5A & B). Based on one-way ANOVA, the compounds (3a-3d) differ significantly in their biological activity against *E. coli.* Hence, we reject the null hypothesis. Compound 3a and 3b have a slightly higher zone of inhibition than compound 3c & 3d. The statistical treatment details are mentioned in the supporting information.

Rheology measurements

The gel preparation is discussed in supporting information. Rheology measurements were conducted on Anton Paar Mechanical Analyzer (MCR 702e MultiDrive) with a plate geometry of PP8 mm. As previously mentioned, Ureido dipeptides esters solutions of the appropriate concentrations were prepared. The gel was instantly loaded onto the rheometer, subsequently, the upper parallel plate was immediately lowered to the appropriate gap (1 mm), and the measurement was initiated.

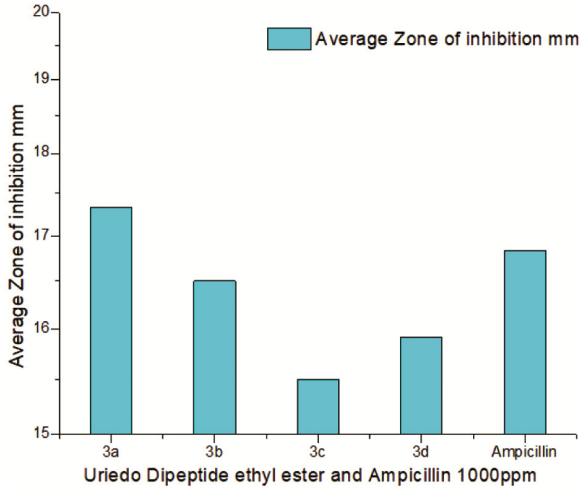

Fig. 3 — Anti-bacterial activity of Ureido Dipeptide Ethyl Ester 3(a- d) against *E. coli*

An amplitude sweep was performed, and the outcomes demonstrated no change in elastic modulus (G') and viscous modulus (G") up to 0.001% strain. The temporal evolution of the elastic and viscous moduli was obtained at 25°C, Shear Strain (0.1%), and frequency (0.628-628.31 rad s^{-1}) in the linear visco-elastic region.

The rheological characteristics of ureido dipeptides esters were investigated as shown in (Figs 6-9). The viscosity of ureido dipeptides esters gel is measured at 25°C & the at shear rate 0.1 to 100 s^{-1} which is shown in (Fig. 10). The result exhibited that viscosity decreased with an increment in shear rate which shows the shear thinning behaviour of ureido dipeptides esters gels. Further to study the shear thinning behaviour, the gel where subjected to reverse shear rate from 100 to 0.1 s^{-1} and thixotropic coefficient is calculated as mentioned in supplementary information. As shows in (Table 3 & Fig. 7), Thixotropic coefficient value of **3a** is 3454.547 Pa.s which is higher as compared to thixotropic coefficient of other ureido dipeptide esters. Compound **3d** shows the lowest thixotropic coefficient *i.e.*,27.1702 Pa.s.

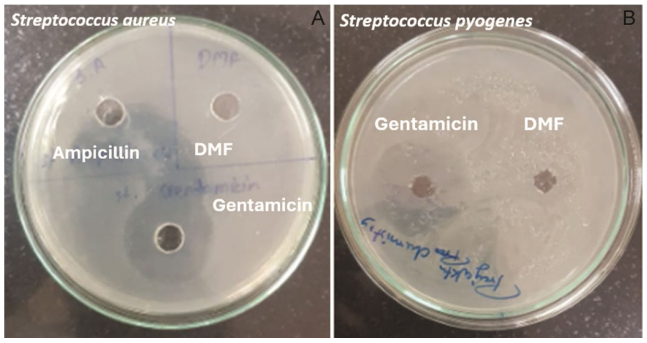

Fig. 5 — Zone of Inhibition of Gentamicin against (A) *Streptococcus aureus*; and (B) *Streptococcus pyogenes*

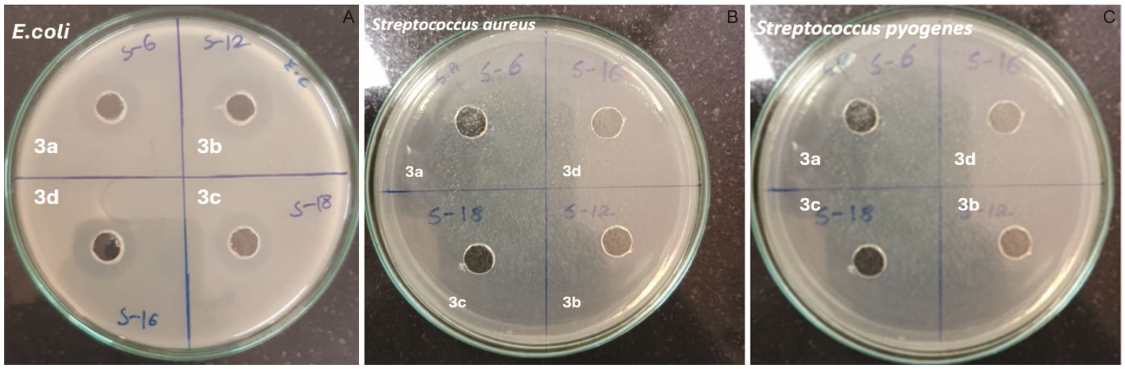

Fig. 4 — Zone of Inhibition of Ureido Dipeptide Ethyl Ester 3(a-d) against (A) *E. coli*; (B) *Streptococcus aureus*; and (C) *Streptococcus pyogenes*

Amplitude Sweep test graph

Figure 8 illustrates the storage (elastic) modulus (G') and loss (viscous) modulus (G") of ureido dipeptides esters gel based on amplitude sweep at a constant angular frequency. There was linear behavior in the elastic modulus up to 0.01% strain and a decreasing pattern after that strain %. Above 0.01 the storage (elastic) modulus (G') and loss (viscous) modulus (G") are undercrossing and give us yield point.

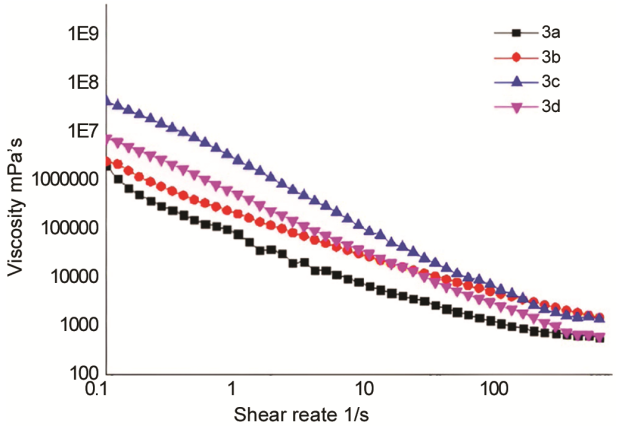

Fig. 6 — Shear rate *vs* Viscosity graph for 3(a-d)

Angular frequency *vs* storage & loss modulus

To study the visco-elastic characteristics of the synthesized compound the frequency sweep was conducted. The visco-elastic characteristics of ureido dipeptides esters gel based on angular frequency are shown in (Fig. 9). The elastic modulus and viscous modulus were measured according to the angular frequency range (0.01–100 rad s^{-1}) at fixed 0.1 % strain. Elastic modulus and viscous modulus are shows constant angular frequency from 3a:35.3-0.0199 rad s^{-1}, 3b: 62.8-0.0199 rad s^{-1}, 3c: 112- 0.0112 rad s^{-1} & 3d: 199- 0.0628 rad s^{-1} as demonstrated in (Fig. 9) at fixed 0.1 % shear strain. The elastic modulus was slightly higher than the viscous modulus in overall angular frequency range. At 25°C, a slight variation in the elastic modulus indicates the formation of gel. The formation of viscous gel is supported by all these visco-elastic characteristics.

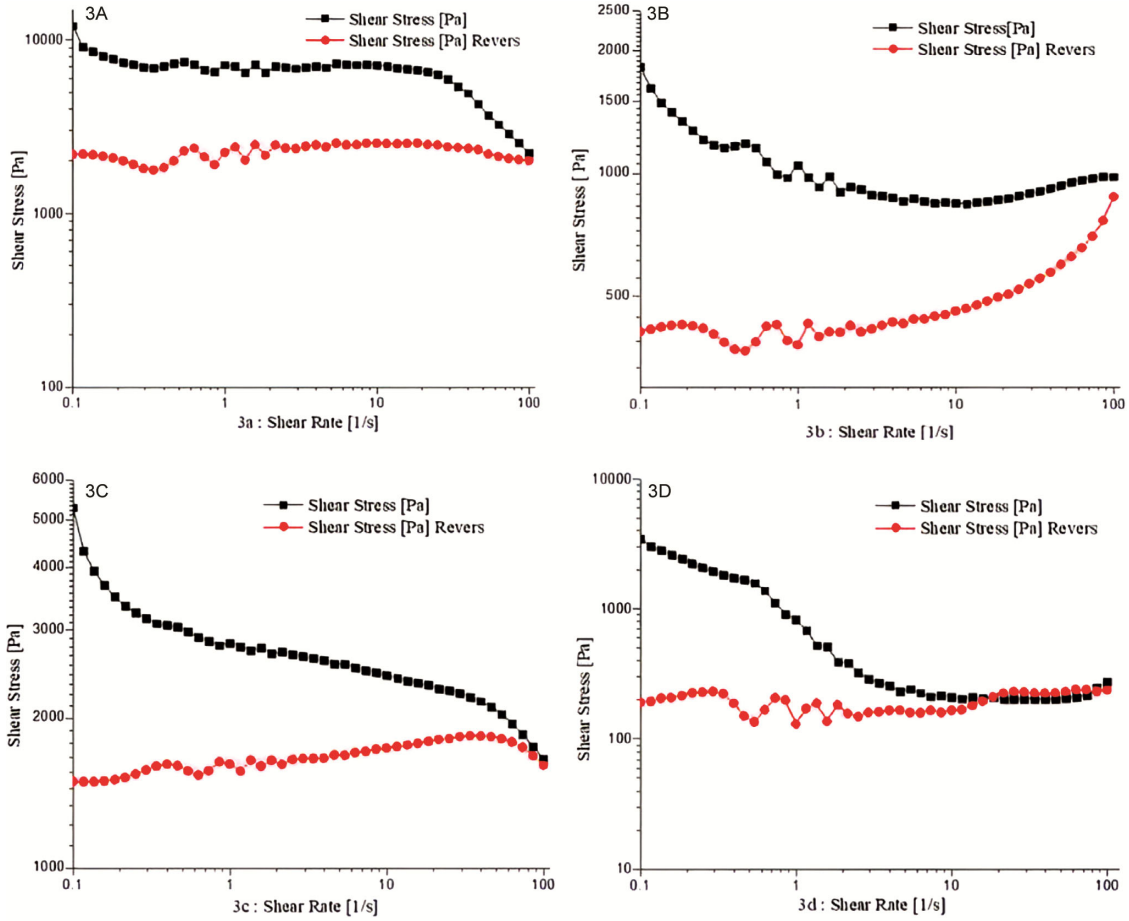

Fig. 7 — Shear stress *vs* Shear rate for 3(a-d) for Calculation of Thixotropic Coefficient

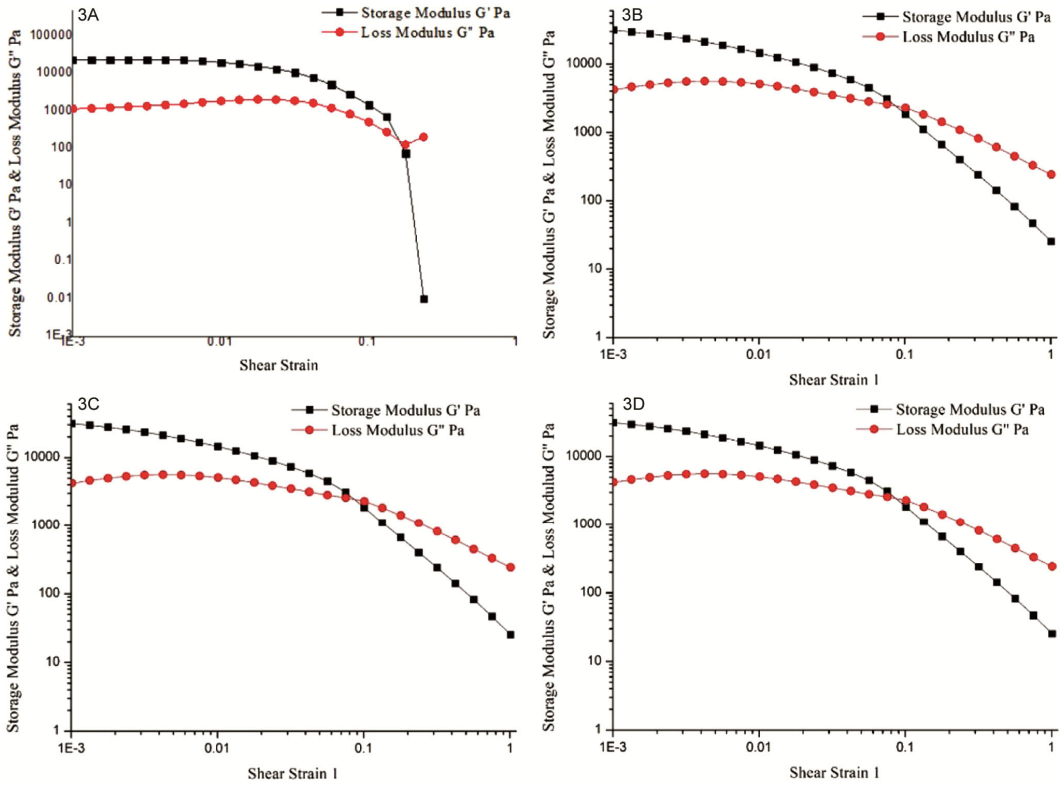

Fig. 8 — Storage & Loss Modulus *vs* Shear Strain for 3(a-d)

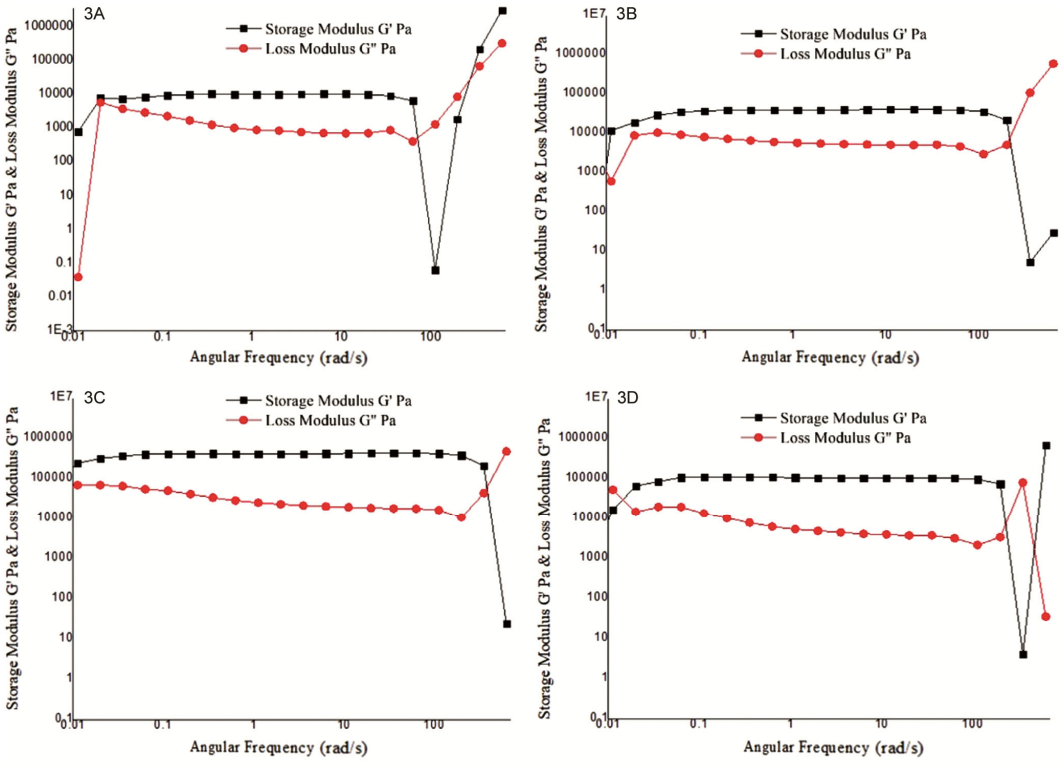

Fig. 9 — Storage & Loss Modulus *vs* Angular Frequency for 3(a-d)

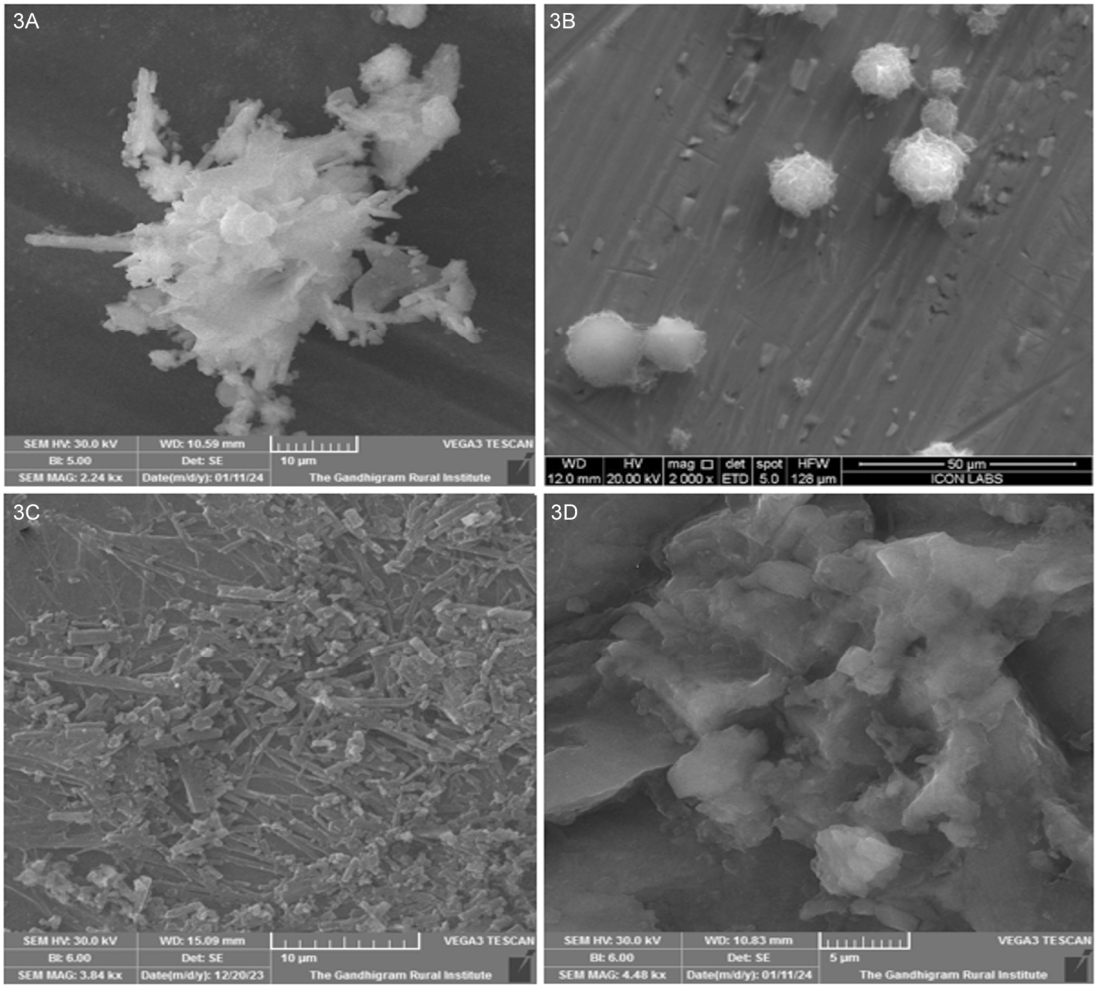

Fig. 10 — Scanning electron microscope (SEM) image of 3a (Ureido-L-Ile-L-Phg-OEt) and 3b (Ureido-L- Leu-L-Phg-OEt) 3c (Ureido-L-Phe-Phg-OEt) & 3d (Ureido-L-Phg-Phg-OEt)

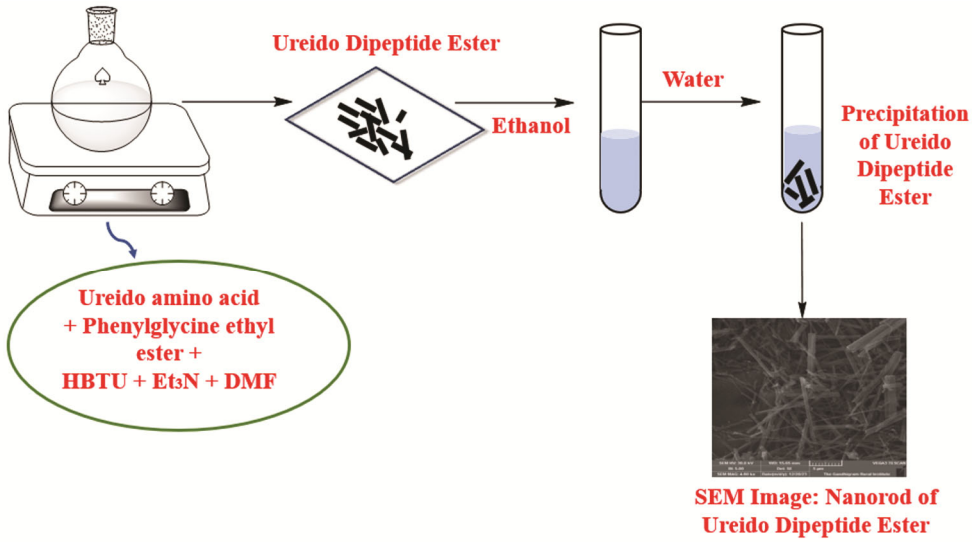

Fig. 11 — Graphical abstract for self-assembly formation

Table 3 — Thixotropic Coefficient from 3(a-d)

Sr. No.	Thixotropic Coefficient Pa.s
3a	3454.547
3b	326.2885
3c	418.7829
3d	27.1702

SEM Image

The surface morphology investigations were carried out using SEM analysis, analyses and the results are presented in (Fig. 10). According to the size distribution plot, most Ureide dipeptide ethyl ester particles are less than 100 nm.

Results and Discussion

Four novel ureido dipeptide esters were successfully synthesized in good yield. In an antimicrobial study, it has shown greater activity against Gram-negative bacteria *E. coli* than Ampicillin (Figs 3 & 4 and Table 2). The presence of a side chain alkyl group in ureido amino acid residue in the dipeptide ester (3a and 3b) enhances the bioactivity against *E. coli* and presence of an aromatic ring in ureido amino acid residue in the dipeptide ester (3c and 3d) diminishes their activity bioactivity. However, it does not exhibit any activity against Gram-positive bacteria *Streptococcus pyogenes* and *Staphylococcus aureus*.

The viscosity of these compounds decreases with increasing shear rate. The shear thinning properties is as shown in (Table 3 & Fig. 7). Compound **3a** exhibits better thixotropic behaviour compare to other synthesized compounds.The gel structures of ureido dipeptide esters have been characterized using the rheometer Anton Paar Mechanical Analyzer (MCR 702e Multidrive) with a plate geometry utilizing properties such as viscosity, storage & loss modulus (Figs 6-9). One of the important interactions that occur between ureido dipeptide esters is Hydrogen Bonding. It plays an important role in the formation of functional nanomaterials. Ureido dipeptide esters has both hydrogen bond donors (nitrogen atoms in the amide groups) and acceptors (carbonyl groups and lone pairs on nitrogen atoms). This allows for extensive hydrogen bonding with water molecules, creating a network that traps water and restricts its flow, leading to gel formation.

Their remarkable morphologies were elucidated through SEM analysis in (Fig. 10). The graphical abstract for the self-assembly formation of Ureido dipeptide esters is represented in (Fig. 11). These compounds showcased a captivating array of nanostructures, including spheres, sheets, rods & cubes within a size range of 100 nm to 20 μm. The nanosheets and homogeneous surface were visible in the SEM image of the Ureido-L-Ile-L-Phg-OEt surface morphology (Fig. 10, 3a). On the other hand, Ureido-L-Leu-L-Phg-OEt exhibits microsphere (Fig. 10, 3b); Ureido-L-Phe-L-Phg-OEt displays Nanorod (Fig. 10, 3c); and Ureido-L-Phg-L-Phg-OEt displays nanocubic (Fig. 10, 3d).

Conclusion

The ureido dipeptide esters were synthesized in good yield using inexpensive solution phase synthesis. The compounds were purified & structural characterization was carried out. The synthesized ureido dipeptide esters (3a-d) compounds were found to be effective against *E. coli*. Ureido-L-Ile-L-Phg-OEt**(3a)** & Ureido-L-Leu-L-Phg-OEt**(3b)** exhibited superior biological activity against *E. coli* compared to the standard drug Ampicillin.

Uriedodi petides esters are viable & low molecular weight supramolecules that demonstrate the gelation properties. They are more viscous and shear-thinning in nature. They have potential applications as drug delivery vehicles in biomedical applications due to their biocompatibility. They exhibit a fascinating variety of nanostructures such as cubes, sheets, spheres and rods which was evident from the SEM analysis.

Acknowledgement

We would like to thank K J Somaiya College of Science & Commerce for Seed money grant& Department of Microbiology, K J Somaiya College of Science & Commerce for study of biological activity of the synthesized compounds. We are also grateful to Gandhigram Institute for SEM Images & SAIF, IIT Bombay for the gelation study.

Conflict of interest

All authors declare that no conflicts of interest.

References

1 Stephanopoulos N, Ortony JH & Stupp SI, Self-assembly for the synthesis of functional biomaterials. *Acta Mater*, 61 (2013) 912.

2 Lee S, Trinh HTT, Yoo M, Shin J, Lee H, Kim J, Hwang E, Lim Y & Ryou C, Self-Assembling Peptides and Their Application in the Treatment of Diseases. *Int J Mol Sci*, 20 (2019) 5850.

3 Wang J, Liu K, Xing R & Yan X, Peptide self-assembly: thermodynamics and kinetics. *Chem Soc Rev*, 45 (2016) 5589.

4 Das S & Das D, Rational Design of Peptide-based Smart Hydrogels for Therapeutic Applications. *Front Chem*, 9 (2021) 770102.

5 Jacob RS, Ghosh D, Singh PK, Basu SK, Jha NN , Das S, Sukul PK, Patil S, Sathyaye S, Kumar A, Chowdhury A, Malik S, Sen S & Malik SK, Self healing hydrogels composed of amyloid nano fibrils for cell culture and stem cell differentiation. *Biomater Sci*, 54 (2015) 97.

6 Nandi N, Baral A, Basu K, Roy S & Banerjee A, A dipeptide-based superhydrogel: Removal of toxic dyes and heavy metal ions from waste water. *Biopolymers*, 108 (2017) e22915.

7 Dowari P, Saha S, Pramanik B, Ahmed S, Singha N Ukil A & Das D, Multiple Cross-Linking of a Small Peptide to Form a Size Tunable Biopolymer with Efficient Cell Adhesion and Proliferation Property. *Biomacromolecules*, 19 (2018) 3994.

8 Becart D, Diemer V, Salaun A, Oiarbide M, Nelli YR, Kaufmann B, Fisher L, Claudio P & Guichard G, Helical Oligourea Foldamers as Powerful Hydrogen Bonding Catalysts for Enantioselective C-C Bond-Forming Reactions. *J Am Chem Soc*, 139 (2017) 12524.

9 Cao J, Zang J, Kong X, Zhao C, Chen T , Ran Y. Dong H, Xu W & Zhang Y, Leucine ureido derivatives as aminopeptidase N inhibitors using click chemistry. Part II. *Bioorg Med Chem*, 27 (2018) 978.

10 Rahbar S & Figarola JL, Novel inhibitors of advanced glycation end products. *Arch Biochem Biophys*, 419 (2003) 63.

11 Violette A, Fournel S, Lamour K, Chaloin O, Frisch B, Briand JP, Monteil H & Guichard G, Mimicking helical antibacterial peptides with nonpeptidic folding oligomers. *J Chem Biol*, 13 (2006) 531.

12 Price JL, Horne WS & Gellman SH, Discrete heterogeneous quaternary structure formed by α/β-peptide foldamers and α-peptides. *J Chem Biol*, 129 (2007) 6376.

13 Semetey V, Rognan D, Hemmerlin C, Graff R, Briand JP, Marraud M & Guichard G, Stable helical secondary structure in short-chain N,N'-linked oligoureas bearing proteinogenic side chains. *Angew Chem Int Ed Engl*, 41 (2002) 1893.

14 Shete S, Gavali M, Ramana MMV, Maduskar M, Karanjule N & Yadav DK, Synthesis of N-Cinnamoyl dipeptide esters and investigation of their self-assembly leading to Nanorods formation. *Indian J Chem*, 62 (2023) 11.

15 Sureshbabu VV, Lalithamba HS, Narendra N & Hemantha HP, New and simple synthesis of acid azides, ureas and carbamates from carboxylic acids: application of peptide coupling agents EDC and HBTU. *Org Biomol Chem*, 8 (2010) 835.

16 Caramiello AM, Bellucci MC, Marti-Rujas J, Sacchetti A & Volonterio A, Turn-Mimic Hydantoin-Based Loops Constructed by a Sequential Multicomponent Reaction. *J Org Chem*, 88 (2023), 15790.

17 Todorov PT & Naydenova ED, Synthesis and characterization of novel dipeptide mimetics with hydantoin. *C R Chimie*, 13 (2010) 1424.

18 Hartwig S, Schwarz J & Hecht S, From Peptides to Their Alternating Ester-Urea Analogues: Synthesis and Influence of Hydrogen Bonding Motif & Stereochemistry on Aggregation. *J Org Chem*, 75, (2010) 772.

19 Resende PE, Nisler J, Voller J, Kadlecova A & Gibbons S, Antimicrobial and anthelmintic activities of aryl urea agents. *J Glob Antimicrob Resist*, 33 (2023) 114.

20 Vogel AI, Furniss B S, Hannaford AJ, Tatchell AR & Smith PWG (5th ed) *Vogel's Textbook of Practical Organic Chemistry (Longman)*, 1989.

21 Verardo G, Geatti P &Strazzolini P, Rapid & Efficient MicrowaveAssisted Synthesis of N-Carbamoyl-L-amino Acids. *Synth Commun*, 37(2007) 1833.

22 Homsi A & Kasideh A, Synthesis of some N-phthalimide amino acids derivatives & evaluation of their biological activity. *Pharm Chem J*, 2 (2015) 33.