Self-assembled Structures Formed by Fmoc modified aliphatic amino acids

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Abstract

Herein, we report the self-assembled structures formed by Fmoc modified aliphatic uncharged single amino acids. The self-assembling properties of (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanine **(Fmoc-Ala-OH)**, (((9H-fluoren-9-yl)methoxy)carbonyl)-L-leucine **(Fmoc-Leu-OH)**, (((9H-fluoren-9-yl)methoxy)carbonyl)-L-isoleucine **(Fmoc-Ile-OH)**, and (((9H-fluoren-9-yl)methoxy)carbonyl)-L-valine **(Fmoc-Val-OH)** were studied under varying conditions such as concentration and temperature. **Fmoc-Ala-OH** shows flower-like self-assembled structure at both low and high concentration under room temperature as well as on heating at 70ºC. We also studied self-assembly of the modified branched chain amino acids (BCAA) i.e. **Fmoc-Leu-OH**, **Fmoc-Ile-OH**, and **Fmoc-Val-OH**. **Fmoc-Leu-OH** forms flower-like morphology at both low and high concentration under room temperature which changes to small tube-like structure on heating. **Fmoc-Ile-OH** on the other hand shows fibres-like self-assembly at lower and higher concentration at room temperature. While, on heating at lower concentration they formed a tube like self-assembled structure and at higher concentration they formed a fibres-like morphology. In the case of **Fmoc-Val-OH** they form a flower-like morphology at lower concentration at room temperature and at higher concentration they formed fibres-like assembly at room temperature. On the other hand, on heating **Fmoc-Val-OH** shows a fibres-like assembly at

lower and higher concentration. Once the self-assembled structure of all Fmoc single amino acid characterized through the optical microscopy then our future aims to characterized those self-assembled structure through sophisticated microscopy and spectroscopy techniques and understand the mechanisms of self-assembled structure. Hence, the modified amino acids may pave the way for the design of novel self-assembled architectures which can controllable manipulated to impart desired function..

Keywords

Self-assembly; Fmoc modified single amino acid; aliphatic amino acids; flower; fibers

Introduction

Design of novel nano/macro architecture with the help of self-assembly is a fast growing fied of research due to wide range of applications. Self-assembled architectures based on the amino acids are of particular interest owing to their applications in different fields which include biomedical application,[1-3] sensing,[4] tracking,[5] fabrication[6] etc purpose increase due to its biocompatibility,[7, 8] and stability.[9] Amino acid based self-assembled structure formed various types of morphology at supramolecular level due to its amphiphilic character.[10] The shape of the self-assembled structure may be the fibers,[11-13] rod,[14, 15] spherical,[16, 17] micelles,[18] tube,[19] broomstick and elongated fibers,[20] and vesicles[21] etc. Amino acids based self-assembled structures have also received tremendous attention due to their association with amyloid disease which can open new avenues for understanding the role of single amino aggregation in amyloid disease.[12, 22] Gazit et al. for the very first time reported the self-assembly of short dipeptide Phe-Phe,[11] followed by phenylalanine,[13] tyrosine,[23] and tryptophan[24]. In other study done by Wangoo et al. reported the self-assembly of aliphatic single amino amino acids (Ala, Leu, Ile, and Val).[26] However, when the amino acid conjugated with fluorenylmethoxycarbonyl (Fmoc-) group it may get gel like properties due to ability of fluorenylmethoxycarbonyl (Fmoc-) function group form the thick entangled

fibres having ability to trap the water molecules inside the entangled fibres which facilitated material to form the gel like properties.[27, 28] Previous literature reports suggest that various Fmoc protected amino acids show gel-like properties such as Fmoc-F, Fmoc-M, Fmoc-Y, Fmoc-G, Fmoc-W, and Fmoc-I etc while Fmoc-alanine, Fmoc-Valine, Fmoc-leucine did not form the gel-like[27] properties due to ambiguous behaviours. Recently In past extensive work has been reported by the various groups which may include self-assembly Fmoc-L-Lysine in different organic solvents done by Kundu et al.[31] In other study reported by Panda et al. demonstrated that Fmoc-cysteine forms sphere like self-assembly and its application in drug delivery.[32] Gazit et al demonstrated that fluorenyl-methoxy-carbonyl-β,β-diphenyl-Ala-OH (Fmoc-Dip-Ala) to opel gemstone-like structure[17]. Another study done by Sato et al reported the self-assembly Fmoc-lysine in DMSO: water mixture[33] and Bai et al reported Fmoc-dipeptide and used in catalytic role as thermolysin.[34] In another study did by Gazit et al. co-assembly of Fmoc diphenylalanine and diphenylalanine form the 3D fibers viscous network.[35]

Our group is interested in studying the self-assembly of single amino acid,[12, 25, 36, 37] modified single amino acids,[20, 29, 30] peptides,[38-43] and heterocyclic compounds.[44-48] In this direction, our group has reported self-assembly of aliphatic single amino acid cysteine and methionineto amyloid like structures.[12] Subsequently, we also reported unusual self-assembled structures formed by proline, hydroxy proline and lysine.[25] Hence, motivated from our studies on single amino acid based structures we were also interested to assess self-assembly of modified single amino acids. In this context, our group has studied the self-assembled structure formed Fmoc variant of threonine N-(9-Fluorenylmethoxycarbonyl)-O-tert-butyl-L-threonine (Fmoc-Thr(tbu)-OH) and Fmoc variant of serine N-(((9H-fluoren-9-yl)methoxy)carbonyl)-O-(tert-butyl)-L-serine (Fmoc-Ser(tbu)-OH) at various concentration and temperature and reported formation of different morphologies such as sphere, double

sided broom-stick, dumbbell like self-assembled structure.[20] In another study, we reported self-assembled structure formation by different CBZ protected aromatic amino acids which include Z-Phe, Z-Trp, and Z-Tyr under varying concentration and temperature.[29] Recently, our group also reported the self-assembled structure formed by the modified charge amino acids, Fmoc-Glu(OtBu)-OH, Fmoc-Asp(OtBu)-OH, and Fmoc-Lys(Boc)-OH.[30] Herein. this manuscript, we have reported the self-assembly of Fmoc variant of alanine (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanine (**Fmoc-Ala-OH**), (((9H-fluoren-9-yl)methoxy)carbonyl)-L-leucine (**Fmoc-Leu-OH**), (((9H-fluoren-9-yl)methoxy)carbonyl)-L-isoleucine (**Fmoc-Ile-OH**), (((9H-fluoren-9-yl)methoxy)carbonyl)-L-valine (**Fmoc-Val-OH**) under varying concentration and temperature and controlled morphological changes associated with it.

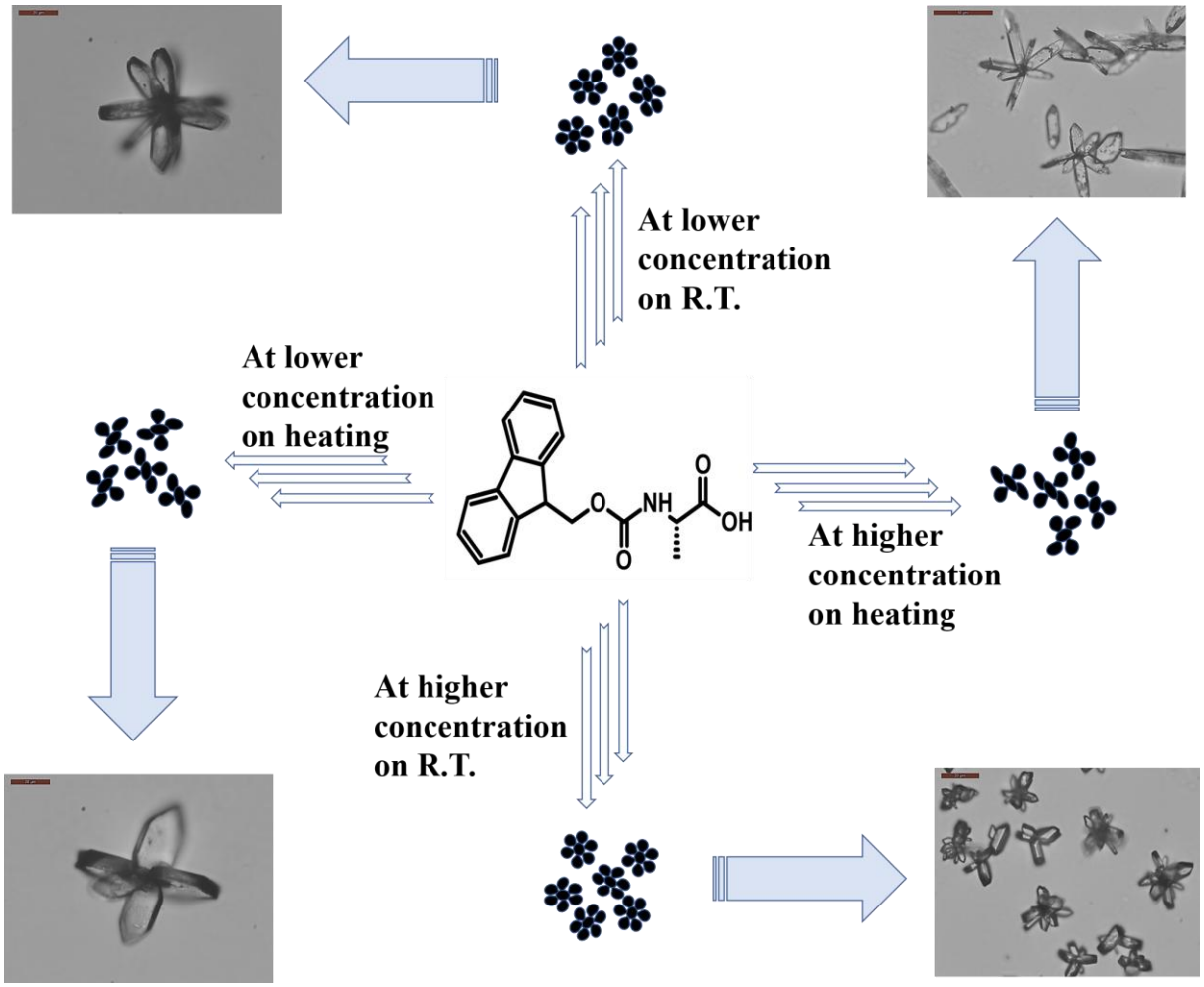


Figure 1. Morphological changes observed in the self-assembled structures formed by **Fmoc-Ala-OH** under varying concentration and temperature.

Figure 1 shows the graphical representation of the self-assembled structure formed by **Fmoc-Ala-OH** under varying conditions**.** We found that **Fmoc-Ala-OH** shows a flower-like assembly at both lower and higher concentration under room temperature condition. While on heating the assemblies were not affected and they formed a flower-like structure in both lower and higher concentration.

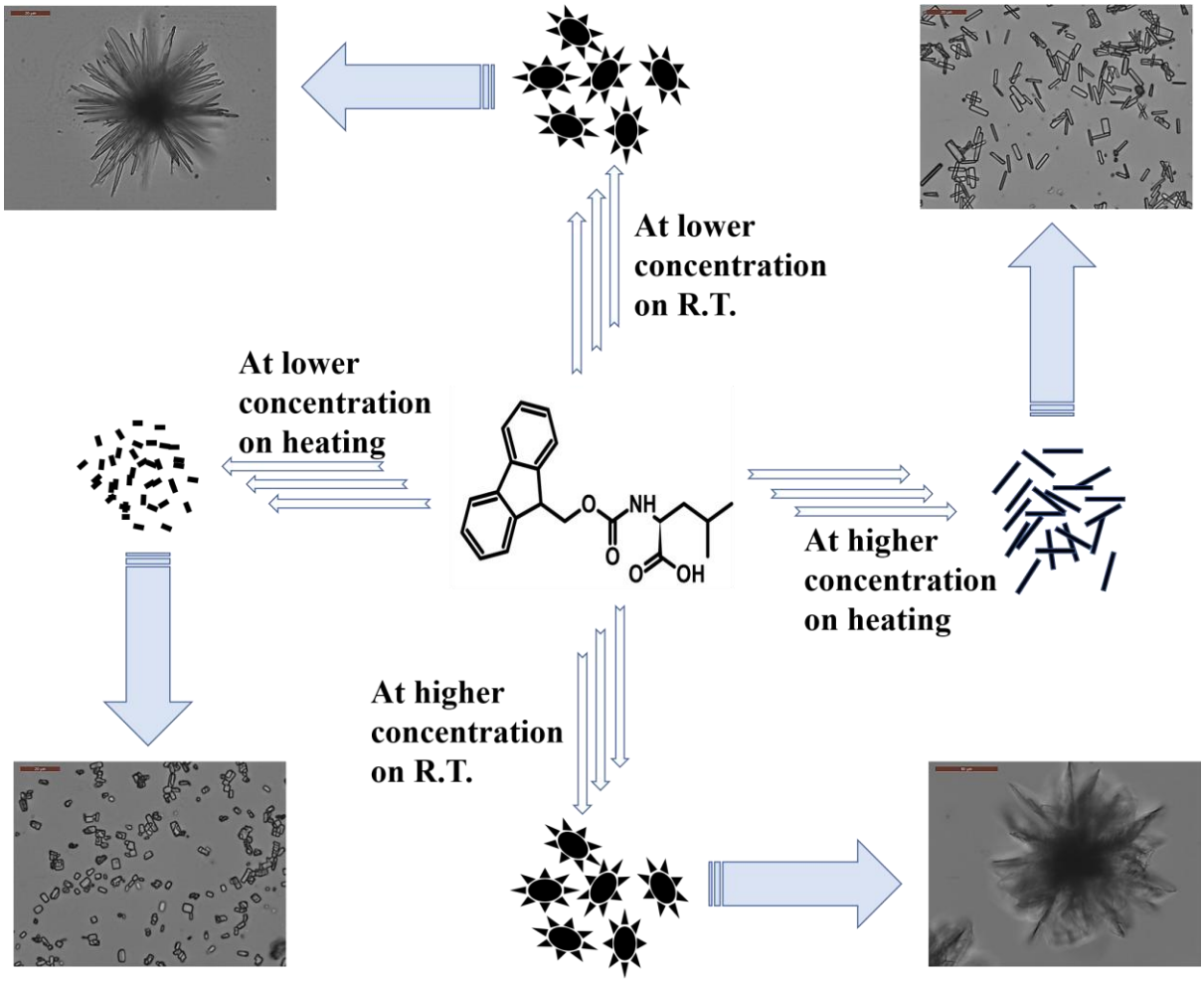


Figure 2. Morphological changes observed in the self-assembled structures formed by **Fmoc-Leu-OH** under varying concentration and temperature.

Figure 2 shows the graphical representation of self-assembled structure formed by Fmoc variant of Leu i.e. **Fmoc-Leu-OH**. **Fmoc-Leu-OH** shows a flower-like morphology at room temperature in both lower and higher concentration. While on heating the flower-like morphology changed to the small tube-like structure in both lower and higher concentration.

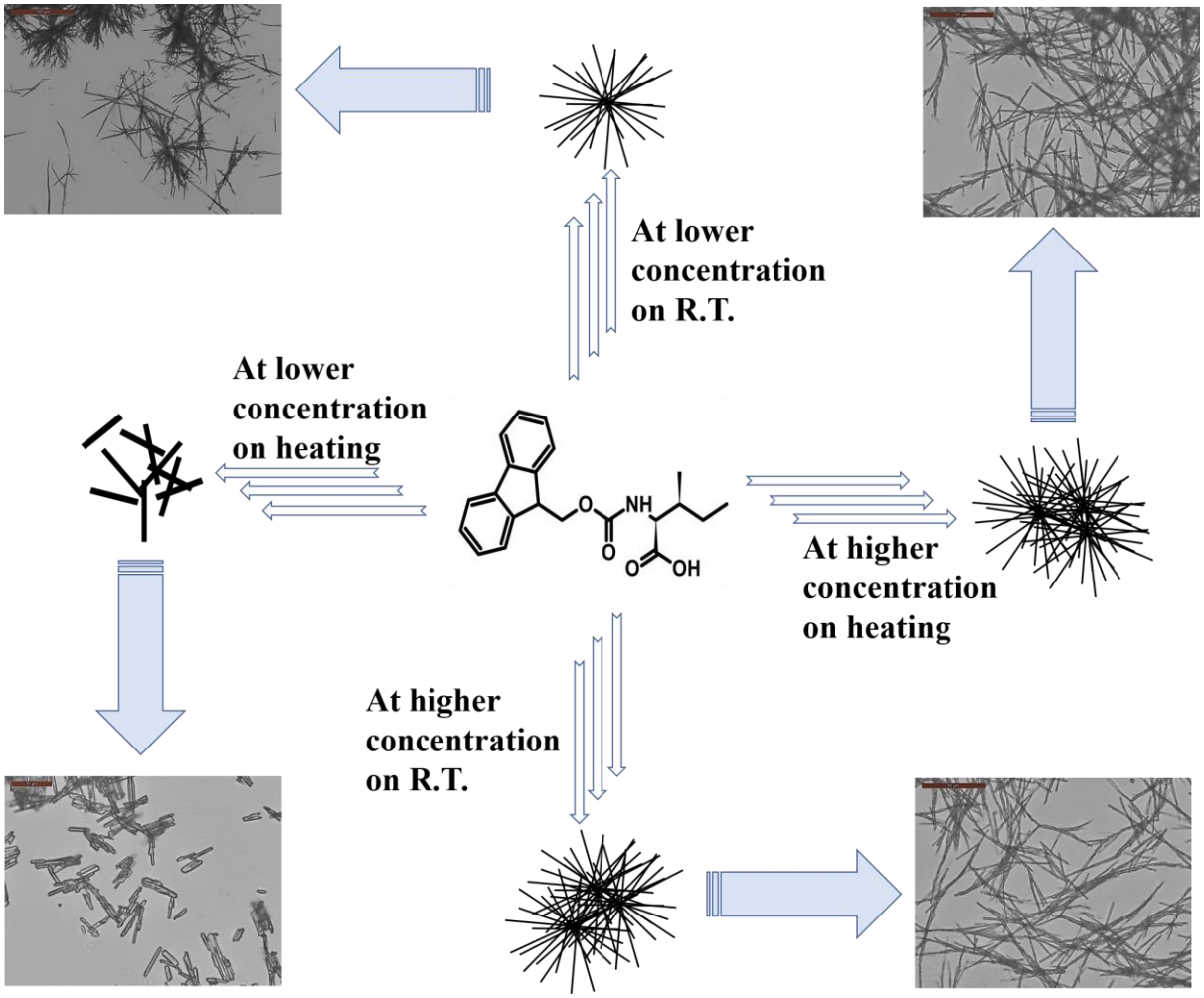


Figure 3. Morphological changes observed in the self-assembled structures formed by **Fmoc-Ile-OH** under varying concentration and temperature.

Figure 3 shows the graphical representation of the self-assembled structure formation by **Fmoc-Ile-OH. Fmoc-Ile-OH** formed a fiber like self-assembled structure at both lower and higher concentration under room temperature condition while on heating at lower

concentration the fibers like structure changes to small tube-like morphology. The fibers formed by **Fmoc-Ile-OH** at higher concentration are not affected by heating.

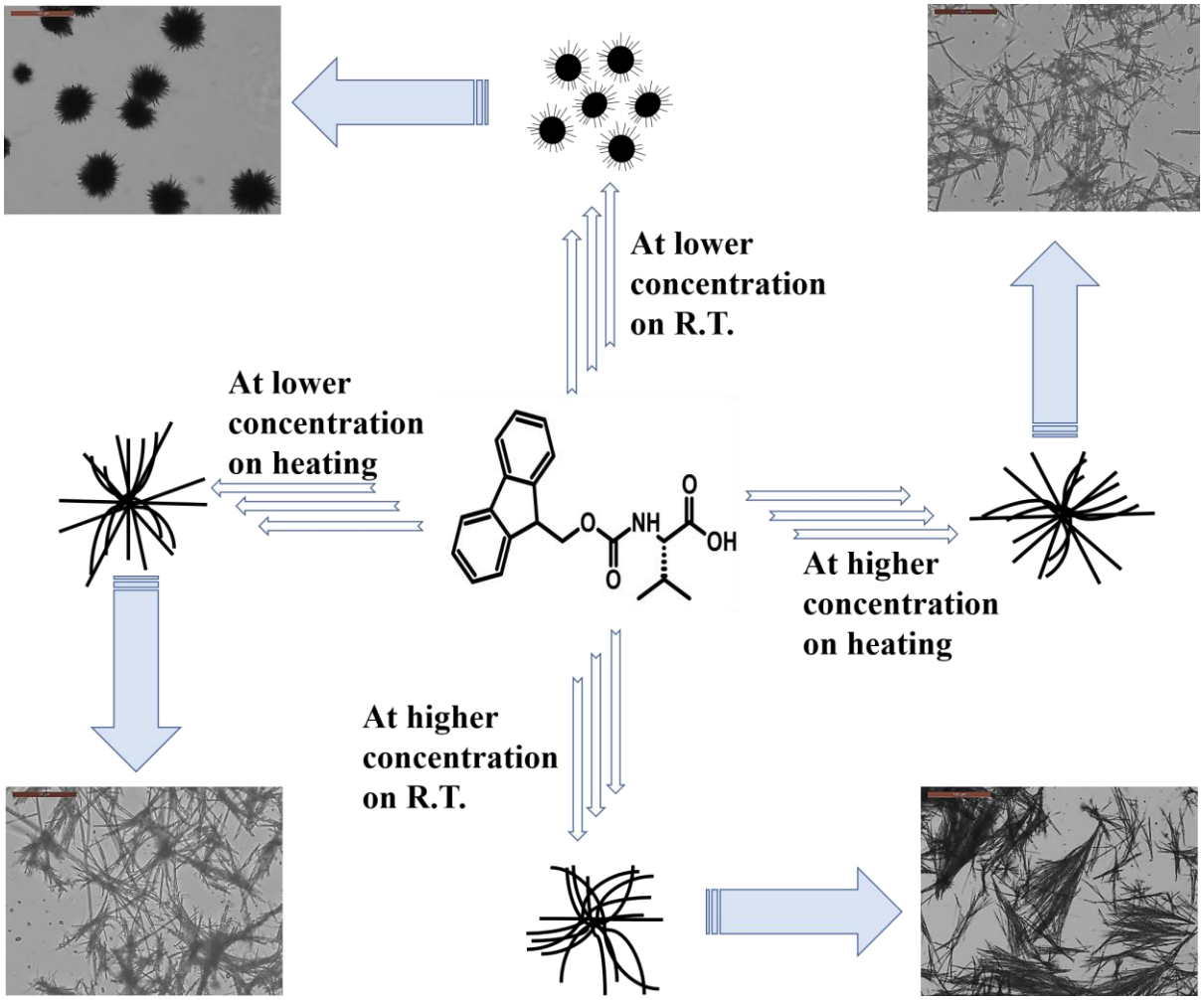
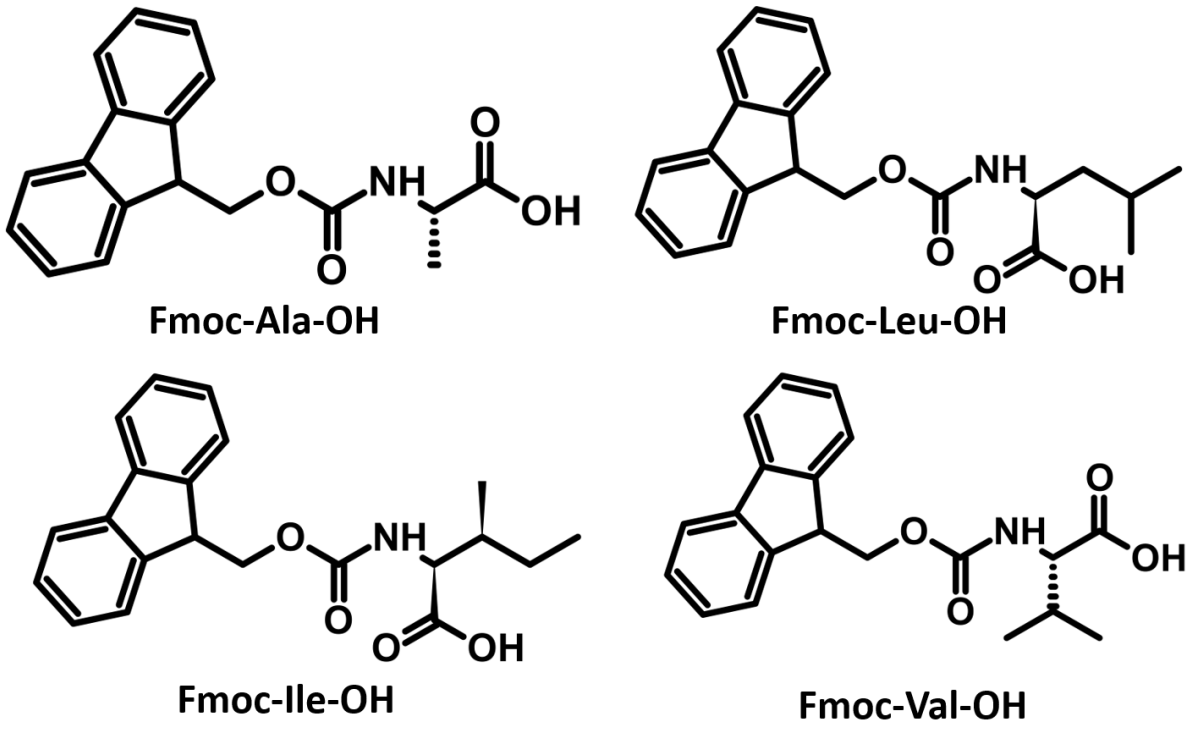


Figure 4. Morphological changes observed in the self-assembled structures formed by **Fmoc-Val-OH** under varying concentration and temperature.

Figure 4 shows the graphical representation of self-assembly formation by **Fmoc-Val-OH**. Our study suggests that **Fmoc-Val-OH** shows a flower-like self-assembled structure at lower concentration at room temperature while on heating it forms a fiber-like structure at room temperature. On heating they form the same fiber like morphology at both lower and higher concentration.

Result and Discussion



Scheme 1: Chemical structure of **Fmoc-Ala-OH, Fmoc-Leu-OH, Fmoc-Ile-OH,** and **Fmoc-Val-OH**

The chemical structure of **Fmoc-Ala-OH, Fmoc-Leu-OH, Fmoc-Ile-OH,** and **Fmoc-Val-OH** is shown in Scheme 1. The self-assembled structures formed by all the non-aromatic modified amino acids were extensively studied by optical microscopy at various concentration and temperature.

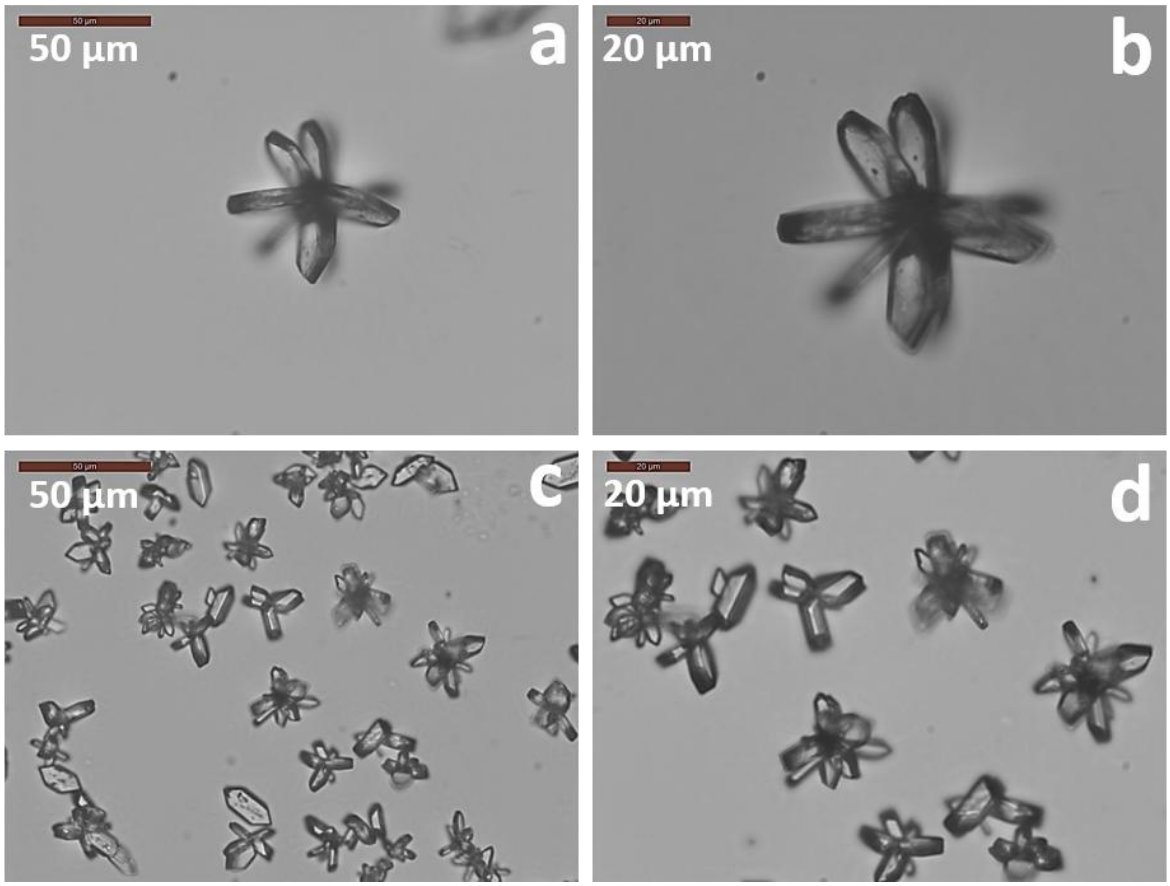


Figure 5. Self-assembled structures formed by **Fmoc-Ala-OH** at room temperature (a) Optical microscopy image at 3 mM under 40X; (b) Optical microscopy image at 3 mM under 63X; and (c) Optical microscopy image at 8 mM under 40X; (d) Optical microscopy image at 8 mM under 63X.

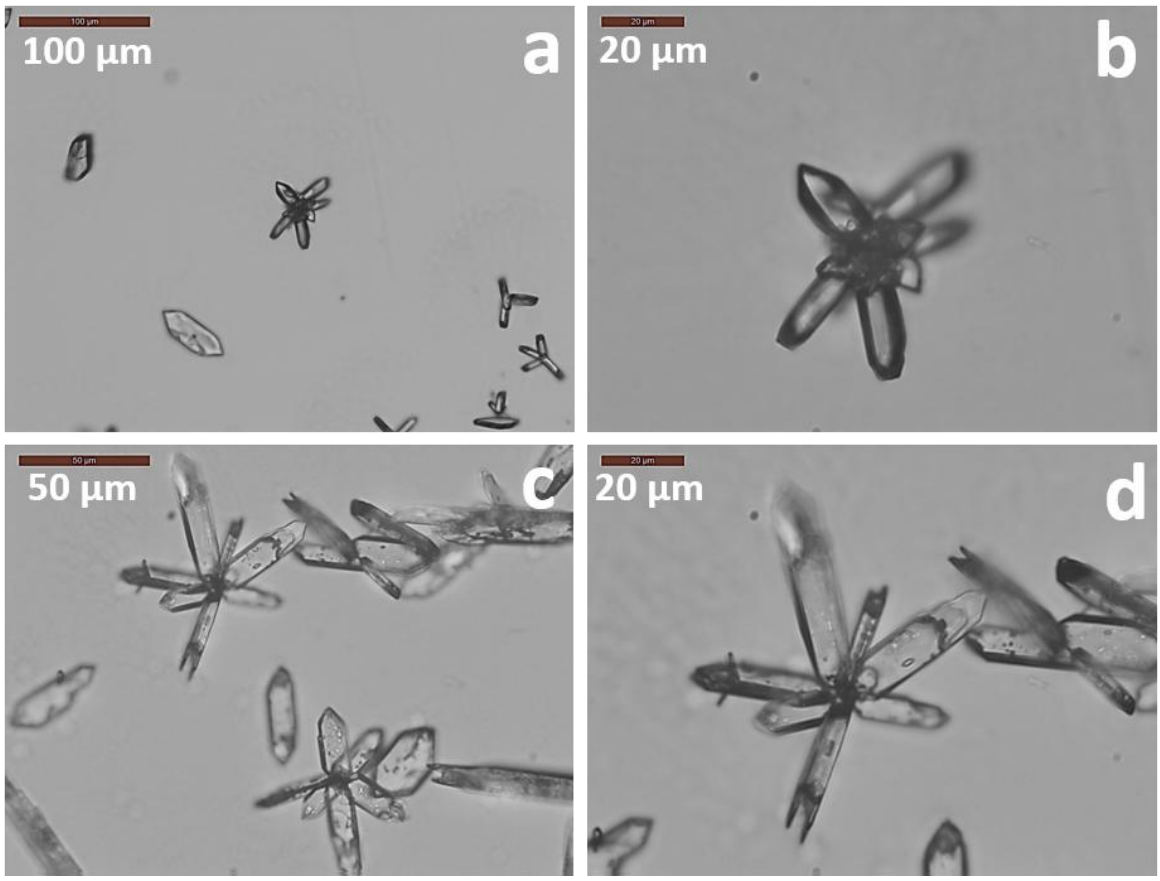


Figure 6. Self-assembled structures formed by **Fmoc-Ala-OH** on heating at 70 ^{0}C (a) Optical microscopy image at 3 mM under 40X; (b) Optical microscopy image at 3 mM under 63X; and (c) Optical microscopy image at 8 mM under 40X; (d) Optical microscopy image at 8 mM under 63X.

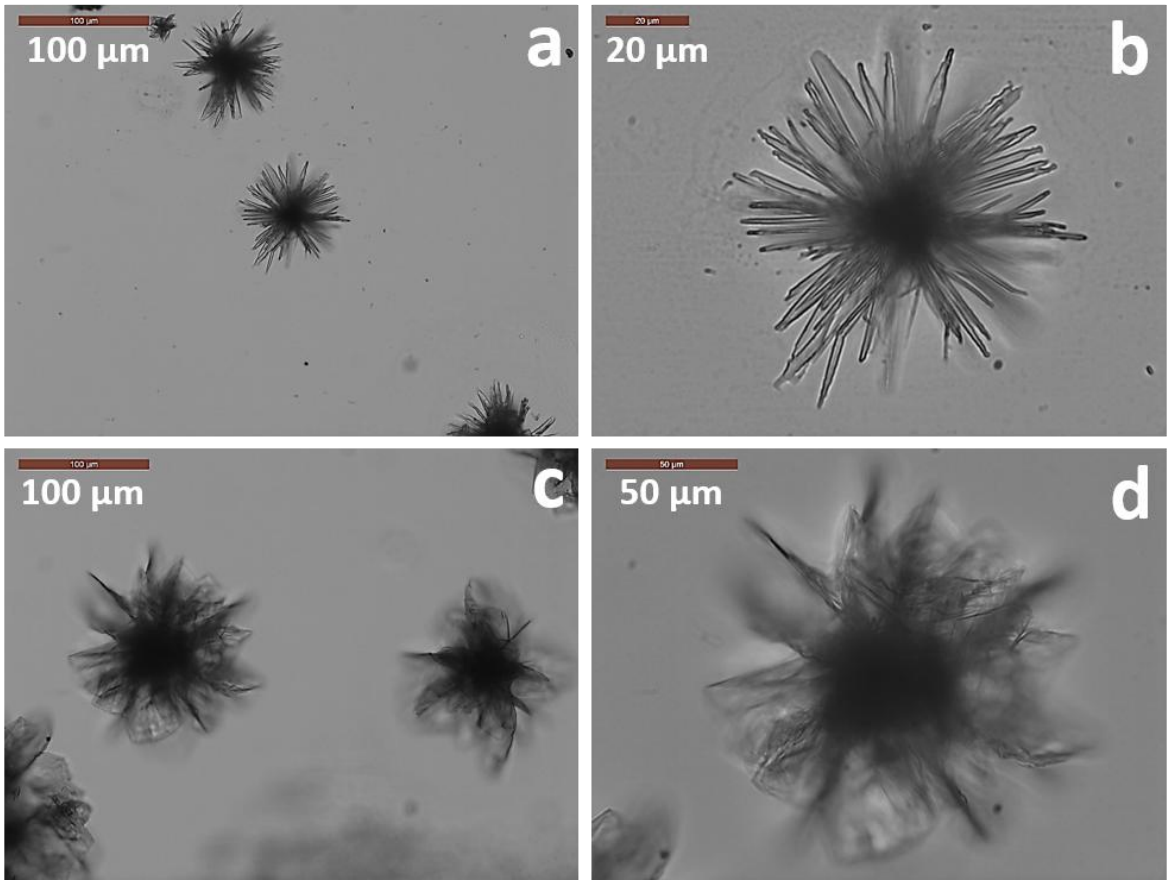


Figure 7. Self-assembled structures formed by **Fmoc-Leu-OH** at room temperature (a) Optical microscopy image at 2 mM under 20X; (b) Optical microscopy image at 2 mM under 63X; (c) Optical microscopy image at 7 mM under 20X; (d) Optical microscopy image at 7 mM under 40X.

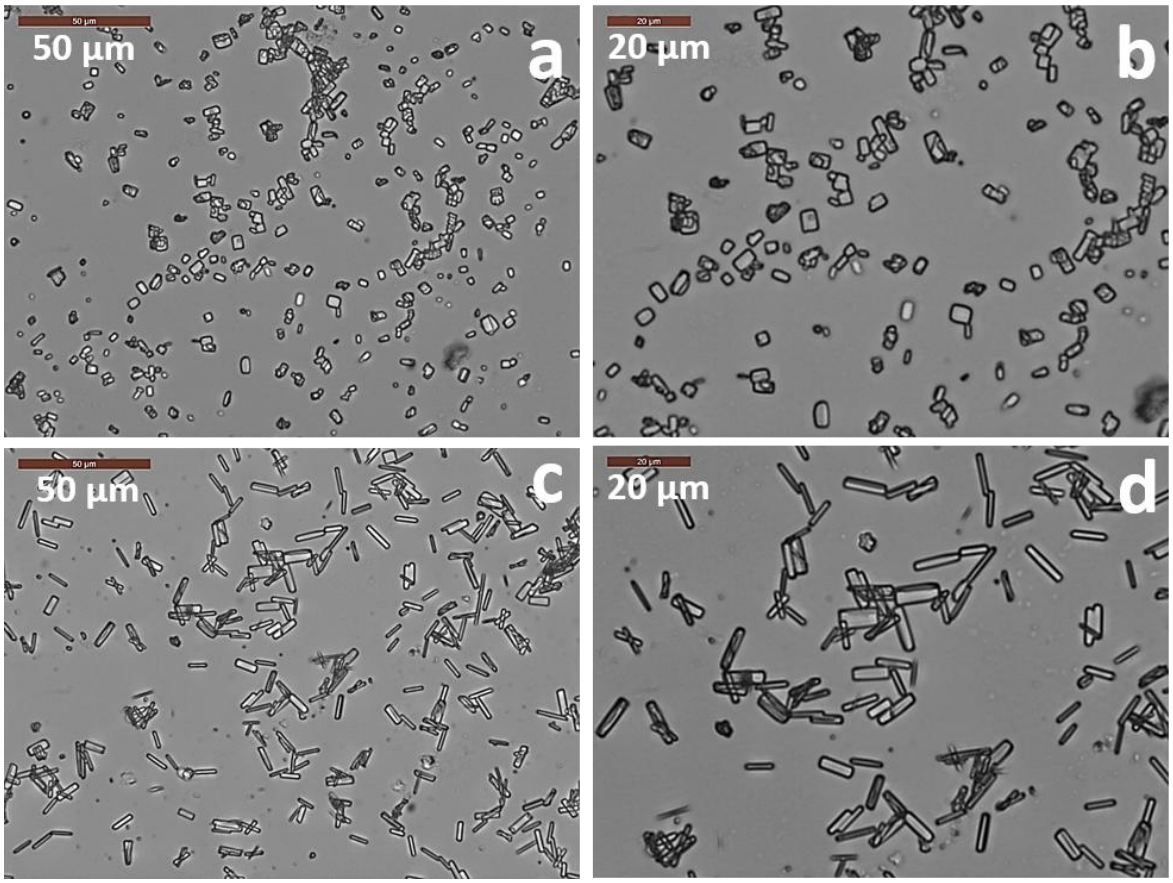


Figure 8. Self-assembled structures formed by **Fmoc-Leu-OH** on heating at 70 ^{0}C (a) Optical microscopy image at 2 mM under 40X; (b) Optical microscopy image at 2 mM under 63X; and (c) Optical microscopy image at 7 mM under 40X; (d) Optical microscopy image at 7 mM under 63X.

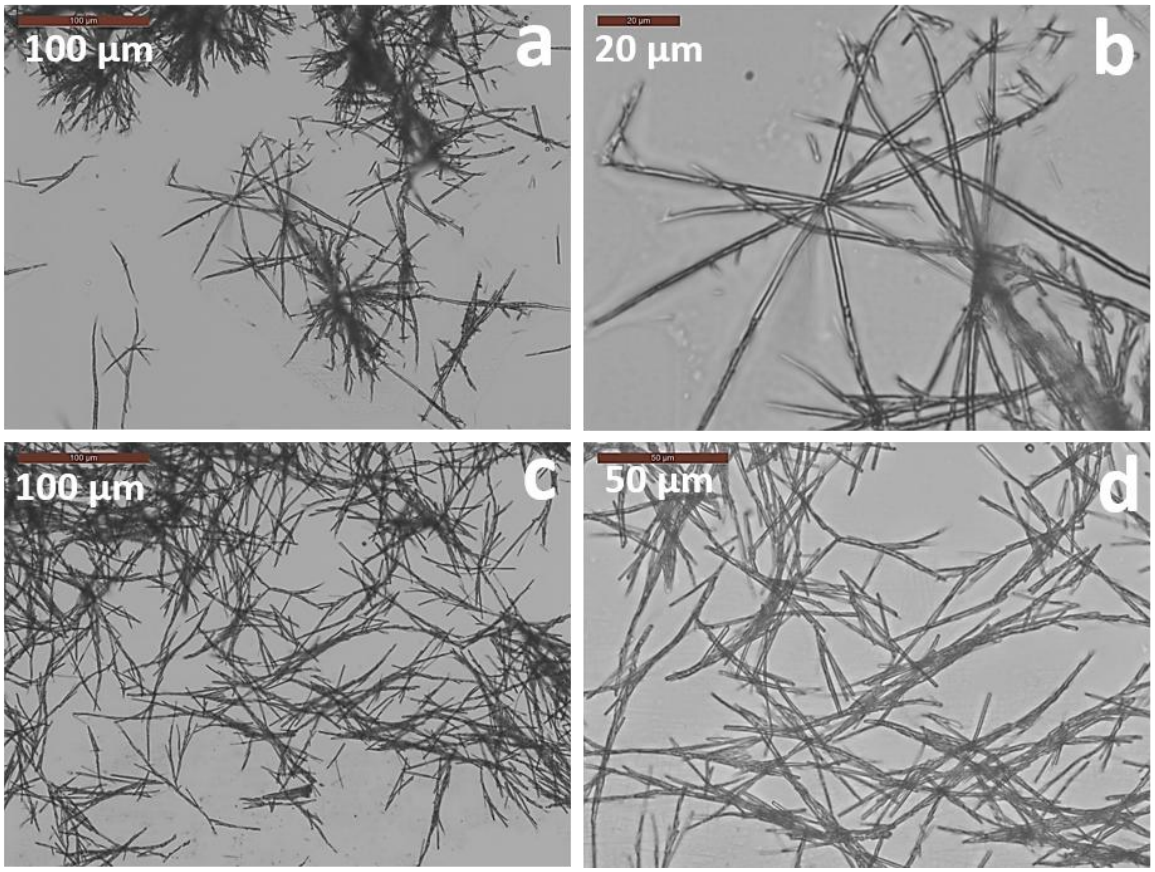


Figure 9. Self-assembled structures formed by **Fmoc-Ile-OH** at room temperature (a) Optical microscopy image at 3 mM under 20X; (b) Optical microscopy image at 3 mM under 63X; (c) Optical microscopy image at 8 mM under 20X; (d) Optical microscopy image at 8 mM under 40X.

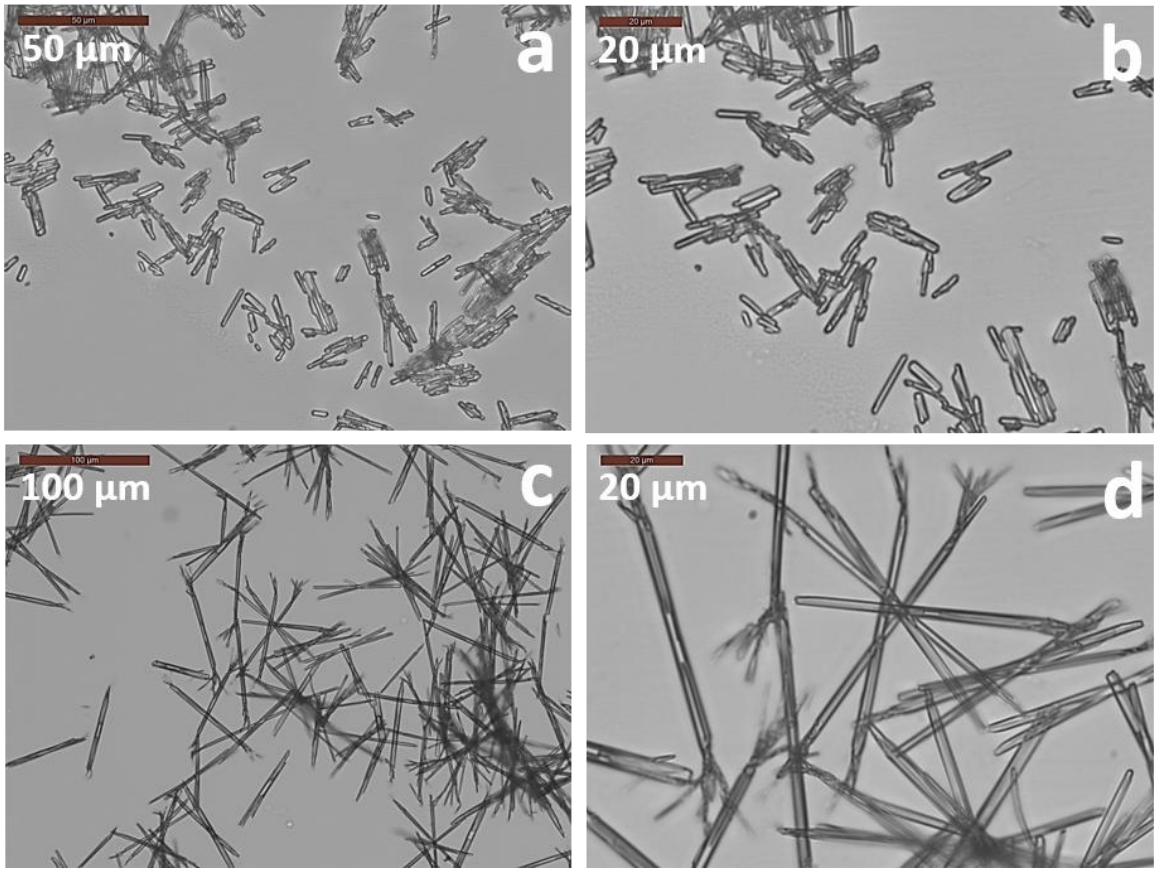


Figure 10. Self-assembled structures formed by **Fmoc-Ile-OH** on heating at 70 ^{0}C (a) Optical microscopy image at 3 mM under 40X; (b) Optical microscopy image at 3 mM under 63X; (c) Optical microscopy image at 8 mM under 20X; (d) Optical microscopy image at 8 mM under 63X

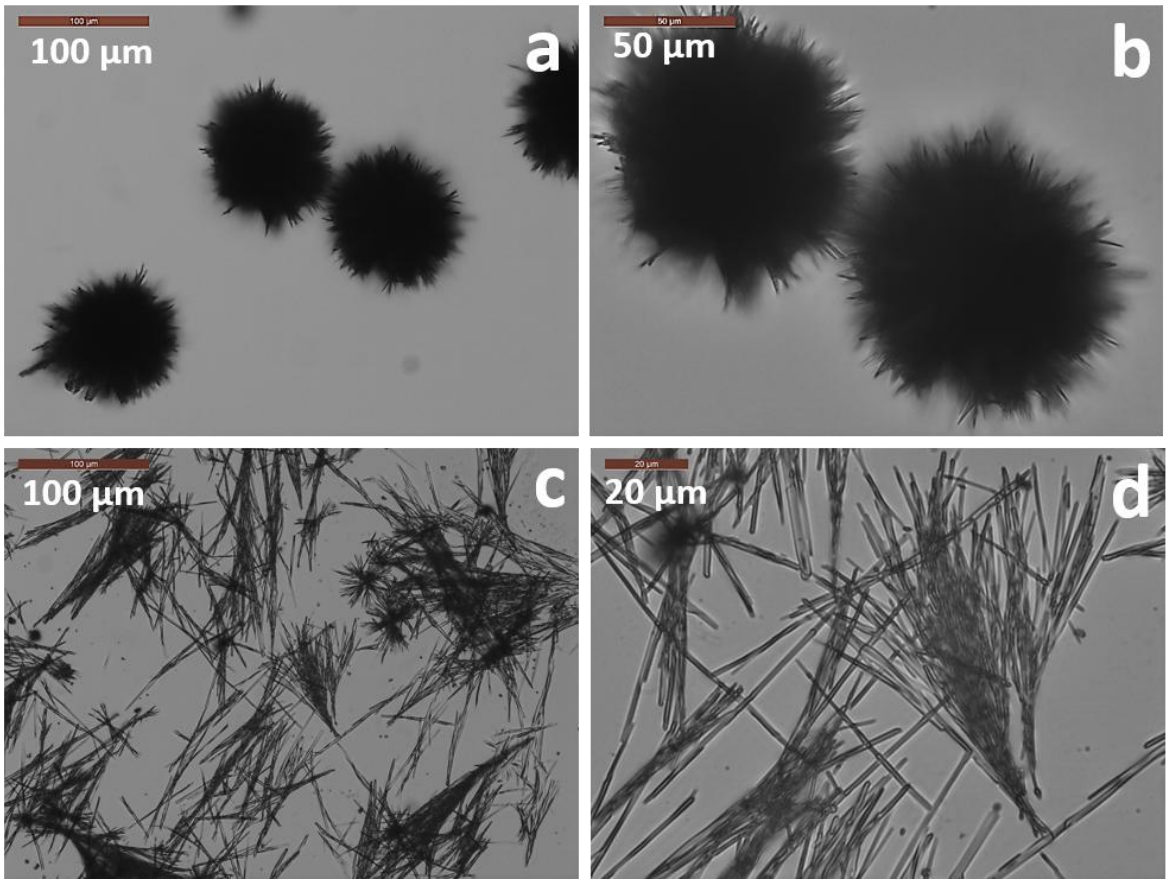


Figure 11. Self-assembled structures formed by **Fmoc-Val-OH** at room temperature (a) Optical microscopy image at 3 mM under 20X; (b) Optical microscopy image at 3 mM under 40X; (c) Optical microscopy image at 9 mM under 20X; (d) Optical microscopy image at 9 mM under 20X.

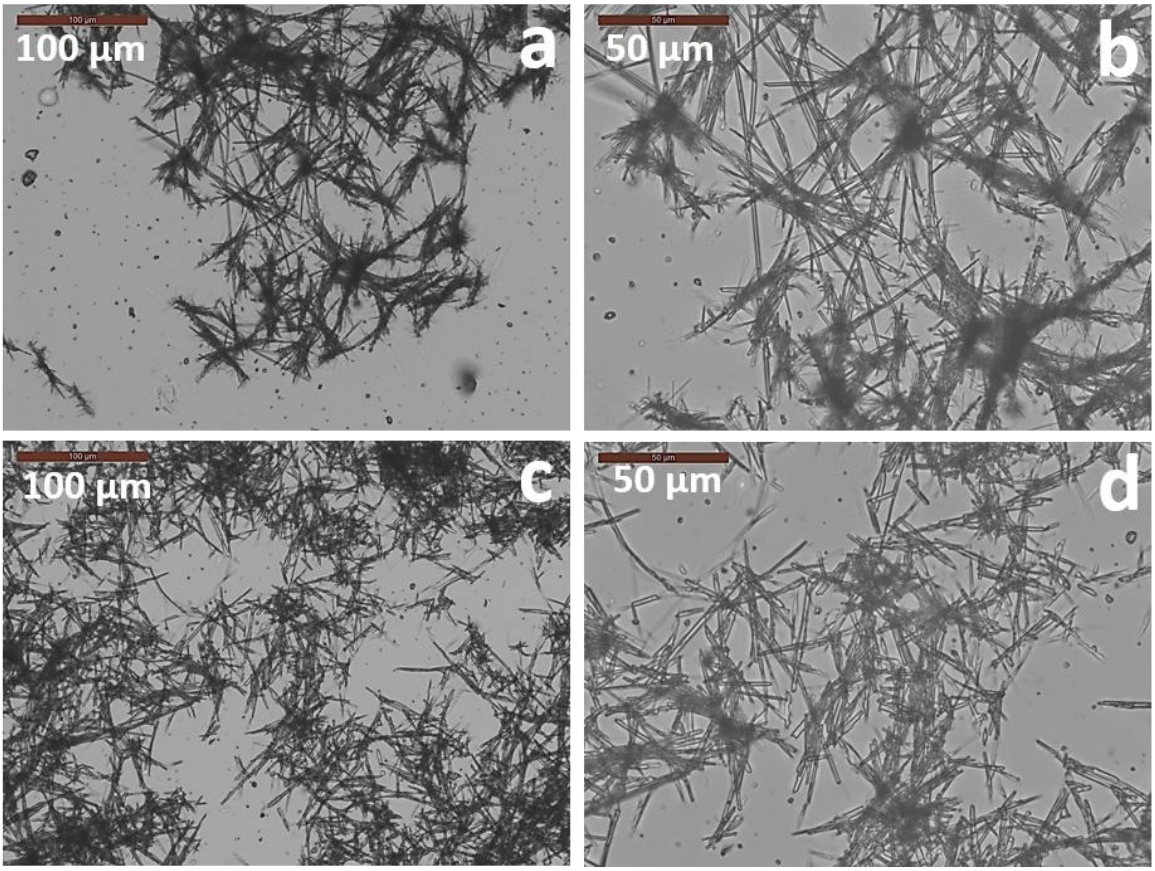


Figure 12. Self-assembled structures formed by **Fmoc-Val-OH** on heating at 70 ^{0}C (a) Optical microscopy image at 3 mM under 20X; (b) Optical microscopy image at 3 mM under 40X; (c) Optical microscopy image at 9 mM under 20X; (d) Optical microscopy image at 9 mM under 40X.

Table 1: Summary of morphological transition observed by the modified single amino acid at varying conditions.

Modified Amino Acid	**Concentration**	**Morphology**	**Condition**
Fmoc-Ala-OH	Lower (3 mM)	Flower	RT
Fmoc-Ala-OH	Higher (8 mM)	Flower	RT
Fmoc-Ala-OH	Lower (3 mM)	Flower	On heating at 70 ^{0}C
Fmoc-Ala-OH	Higher (8 mM)	Flower	On heating at 70 ^{0}C
Fmoc-Leu-OH	Lower (2 mM)	Flower	RT

Fmoc-Leu-OH	Higher (7 mM)	Flower	RT
(Fmoc-Leu-OH)	Lower (2 mM)	Tube-like structure	On heating at 70 ^{0}C
(Fmoc-Leu-OH)	Higher (7 mM)	Tube-like structure	On heating at 70 ^{0}C
Fmoc-Ile-OH	Lower (3 mM)	Fiber	RT
Fmoc-Ile-OH	Higher (3 mM)	Fiber	RT
Fmoc-Ile-OH	Lower (8 mM)	Tube-like structure	On heating at 70 ^{0}C
Fmoc-Ile-OH	Higher (8 mM)	Fiber	On heating at 70 ^{0}C
Fmoc-Val-OH	Lower (3 mM)	Flower	RT
Fmoc-Val-OH	Higher (9 mM)	Fiber	RT
Fmoc-Val-OH	Lower (3 mM)	Fiber	On heating at 70 ^{0}C
Fmoc-Val-OH	Higher (9 mM)	Fiber	On heating at 70 ^{0}C

Conclusion

In conclusion, we assessed the self-assembled structure formation by Fmoc variant of alanine and branched chain amino acids. Our study reveal that **Fmoc-Ala-OH**, **Fmoc-Leu-OH**, **Fmoc-Ile-OH**, and **Fmoc-Val-OH** all assemble to well defined self-assembled structures and also reveal morphological transition as we alter the concentration and temperature.. The results presented here has immense application to design of novel structures via bottom–up approach. There is ever increasing demand to find new bioorganic scaffolds for the design of novel nanoarchitectures through self-assembly. The study of modified single amino acid self-assembly research is important step in this direction due to its good biocompatibility and ease of chemical modification due to which it may have wide range of biomedical applications

Materials and method

General

All chemicals used in these studies were of purity greater than 99%. All the solvents and **Fmoc-Ala-OH**, **Fmoc-Leu-OH**, **Fmoc-Ile-OH**, and **Fmoc-Val-OH** were purchased from commercial suppliers. All the compounds were used without further purification. All the studies were done using distilled solvents. Ultrapure water was used for all the studies.

Optical Microscopy

A 20 mM stock solution of **Fmoc-Ala-OH, Fmoc-Leu-OH, Fmoc-Ile-OH,** and **Fmoc-Val-OH,** were prepared in 50 % aqueous solution of methanol and heat it with sonication to get a clear solution. The solution was further diluted at 1 to 10 mM concentration by using Milli Q water. A turbid solution has been observed on dilution with water. The self-assembly formed by this amino acid was first assessed by optical microscopy. For optical microscopy a drop casting a 20 μL solution on a glass slide and dry it at room temperature. The same solutions were heated at 70 ^{O}C and then immediately drop casting 20 μL solution of this solution on a clean glass slide. For all the microscopic study always a fresh stock solution and fresh samples has been prepared. The samples were visualized using a Leica DM2500 upright fluorescent microscope at different magnifications.

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Conflicts of interest

There is no conflict of interest to declare.

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