Ph. D. Open Seminar

Department of Chemistry, IISER Bhopal

Title of Thesis: **Synthesis and evaluation of functionalized arylamide scaffolds for improved drug delivery and protein aggregation inhibition**

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Poylamides based on aromatic scaffolds have recently been a subject of immense attention due to their interesting structural properties and biological activities[1]. Depending on the specific functionalization, these molecules demonstrate new physicochemical properties, and show various biological activities such as biomolecular recognition, assembly formation, protein inhibition etc[2].

We have employed N-substitution with long hydrophobic chains on the arylamide scaffold, which led to the formation of gemini type amphiphilic molecules. These molecules formed sub-micrometre sized non covalent assembly in aqueous solution likely owing to their long hydrophobic chains. The nature of the assembly was characterized by NMR, DLS and TEM techniques. We utilized these assemblies to enhance the solubility and stability of the pharmacologically important hydrophobic molecule curcumin, which is practically insoluble in aqueous medium. The molecule with decyl chain also showed enhanced encapsulation of an anticancer agent doxorubicin. The *in vitro* pH dependent release and slow toxicity of the encapsulated doxorubicin (compared to free doxorubicin) inside cells over time can be utilized for selective targeting of cancer cells[3].

We have further shown that derivatized arylamide scaffolds can be used for preventing the aggregation of insulin[4]. Insulin is a vital hormone essential in management of diabetes, and is known to form amyloid aggregates during production, and under aberrant physiological conditions that lead to the reduction of its biological activity[5]. We have synthesized several oligoamide molecules decorated with hydrophobic functionalities to inhibit insulin aggregation. These molecules were screened by thioflavin-T assay and resulted in identification of a few hit molecules that showed reduction in the insulin fibril formation. These results were further supported by TEM, NMR and CD analyses[6].

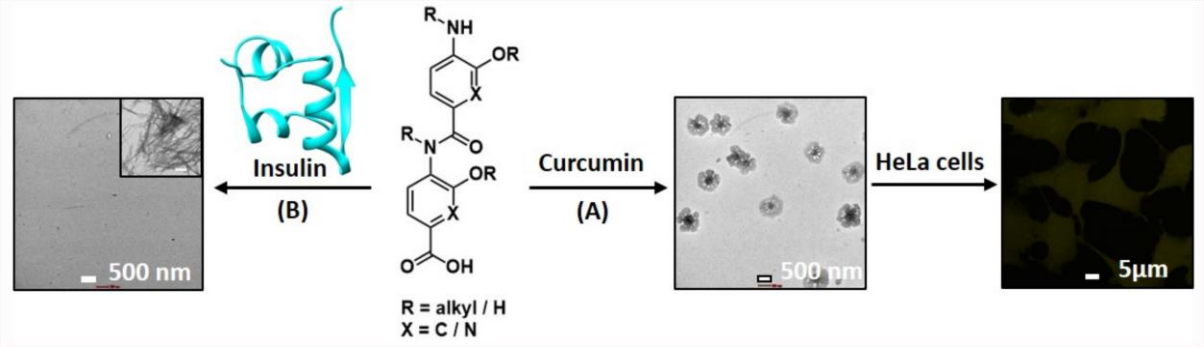


**Figure: (A)** Curcumin encapsulation and cellular delivery by derivatized arylamide. **(B)** Insulin aggregation inhibition after treatment with arylamide derivatives. Inset shows insulin fibril formation without treatment with molecule.

**References:**


(1) Zhang, D. W.; Zhao, X.; Hou, J. L.; Li, Z. T. *Chem. Rev.* **2012**, *112* (10), 5271–5316..

(2) (a) Kumar, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **2017**, *139* (16), 5744–5755. (b) Barnard, A.; Long, K.; Martin, H. L.; Miles, J. A.; Edwards, T. A.; Tomlinson, D. C.; Macdonald, A.; Wilson, A. J. *Angew. Chemie - Int. Ed.* **2015**, *54* (10), 2960–2965.

(3) Gangarde, Y. M.; Sajeev, TK.; Panigrahi, N.R.; Mishra, R.K.; Saraogi, I. (*Manuscript under preparation*).

(4) Das, A.; Gangarde, Y. M.; Tomar, V.; Shinde, O. R.; Upadhyay, T.; Alam, S.; Ghosh, S.; Chaudhary, V.; Saraogi I. (*Manuscript submitted*).

(5) Nielsen, L.; Khurana, R.; Coats, A.; Frokjaer, S.; Brange, J.; Vyas, S.; Uversky, V. N.; Fink, A. L. *Biochemistry* **2001**, *40* (20), 6036–6046.

(6) Gangarde, Y. M.; Das, A.; Saraogi, I. (*Manuscript under preparation*).