**PI: Dr Abhijit Hazra,**
**Young Scientist (SERB-DST), NIPER-Kolkata**
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**Project Title:** Synthesis of Enantiopure, Regio & Diastereomeric Bis-pyrrolizidine fused-di-spiro Oxindolo Curcuminoids; A Novel Class of Natural Product Hybrids via Application Of An 'Age-Old Reaction' On 'An Age Old' Substrate.

**Summary:** As part of our recent endeavor to synthesize new spiro/dispiro, fused pyrrolidino/pyrrolizidino oxindole analogs via dipolar cycloaddition I have used an important source of dipolarophiles i.e natural products with active double bond like andrographolide, withanolide, curcumin etc. Various groups worldwide had used curcumin as a lead to develop numerous analogues with structure–activity relationship (SAR) study. Although, the unavailability of report on development of resistance against curcumin has been its most characteristic feature but poor aqueous solubility, unsatisfactory pharmacokinetics had been highlighted as its major drawback. This circumvented into a new imaginary concept of 'super curcumin', to be cultivated under two broad catagories, namely (1) synthetic analogues (2) formulations, which will be free from these problems and with efficacy equal to/better than that of the curcumin. The promising biological activity of previously prepared semi-synthetic compounds prompted us to explore the electron deficient double bonds of curcumin to construct the imaginary 'super curcumin' skeleton.

**Work done:** The proposed reaction protocols have the possibility of cycloaddition at one double bond (in 1:1 mole), and at both double bonds (in 1:2 mole in a racemic manner) under one-pot sequence. So far 40 compounds have prepared, isolated and their structure and stereochemistry has been established using detailed spectroscopic study and X-ray crystallographic study. Separation of enantiomers in case of one diastereomers has been performed using HPLC on a chiral OD-H column and the CD spectra of the separated enantiomers have been done. It was already published in ***Organic letters.***

**Future proposition:** (i) To complete whole library of compounds (~50 compounds) using established methodology; (ii) Separation of enantiomers using chiral HPLC followed by optical rotation and CD measurement; (iii) DFT energy calculations for formation pathway will be performed; (iv) Absolute configuration determination for enantiomers via comparison of theoretical and experimental vibrational CD spectral data and confirming them with x-ray image will be another major goal; (v) We also contemplate a stepwise manner to utilize one double bond for cycloaddition with one type of isatin and amino acid which after isolation and characterization will be employed for further reaction with another set of isatin/ acenapthoquinone and amino acid. The success will enable us to prove mechanism as well as creation of new chemical entities (NCEs) with mixed bis spirooxindole/spiro-acenapthylene-2-one curcumin analogs. This will lead us to a library of almost ~500 compounds.

A library of a good no. of new chemical entities (NCEs) will be generated. Further biological evaluation like antibacterial, antiviral, antifungal, anticancer, antiulcer, antileishmanial (as the proposed institutes have a very good set up for conducting these bioactivity experiments) may be done for generating some highly potent molecules. The most potent molecules may be evaluated for further study for detailed biological studies and pharmacokinetic studies and also patent application could be submitted.

**Reference:** Bharitkar, Y.P.; Das, M.; Kumari, N.; Kumari, M.P.; **Hazra, A**.; Bhayye, S.; Natarajan, R.; Shah, S.; Chatterjee, S.; Mondal, N.B.; **2015**; Synthesis of Bis-pyrrolizidine-Fused Dispiro-oxindole Analogues of Curcumin via One-Pot Azomethine Ylide Cycloaddition: Experimental and Computational Approach toward Regio- and Diastereoselection.; ***Organic Letters***, *17*, 4440−4443