

In order of importance, list of best papers of the candidate, highlighting the important discoveries/contributions described in them briefly (not to exceed 3000 words):

i) “*Cyclodepsipeptide Alveolaride C: Total Synthesis and Stereochemical Assignment*” **Sanu Saha**, Debobrata Paul and Rajib Kumar Goswami*; **Chem. Sci.**, 2020, 11, 11259-11265. (Highlighted in *ChemistryViews.org* and published as literature coverage in *Synform*, 2021/03, A43–A45).

[In 2018, an US agency Dow Agro Sciences discovered and isolated for the first time alveolaride A-C, a family of cyclodepsipeptides while searching for naturally occurring benign. *In vitro* inhibition studies of these cyclodepsipeptides showed promising efficacy against hazardous plant pathogens, named *Pyricularia oryzae*, *Zymoseptoria tritici*, *Ustilago maydis*, *Puccinia triticina*, and *Phakopsora pachyrhizi* which prompted us to build a synthetic pathway for this family of natural products. Architecturally, alveolarides are 17-membered macrocycles with the rarely found 2,3-dihydroxy-4-methyltetradecanoic acid (DHMTDA) as the non-peptide unit, where the configurations of all three stereocenters remain undetermined since isolation. The DHMTDA segment of alveolaride B was found to be slightly different from the segments of alveolaride A and C in terms of having a C39-C40 olefin. *D*- β -phenylalanine, *L*-glutamine, and *D*-serine are residues common to all members of this family of cyclodepsipeptides. Derivatives of *L*-glutamic acid with two additional undefined stereocenters in alveolarides A and B and *L*-tryptophan in alveolaride C were observed as the other amino acid counterparts, respectively. The establishment of the stereochemistry of the unassigned centers in the common nonpeptide segment of this family of molecules is very crucial and essential to synthesize the other members in order to get clearer picture of their pharmacological importance and mode of action. There are three undetermined stereocenters in the molecule providing the possibility of eight configurational isomers among which one could be expected to be the actual structure of alveolaride C. To narrow down these possibilities, we depended on the reported NMR spectral data of the DHMTDA counterpart of alveolaride C. Two diastereomers of the purported structure of alveolaride C having the stereochemistry 29-(*R*)/30-(*S*)/31-(*R*) and 29-(*S*)/30-(*R*)/31-(*S*) were synthesized initially as the specific rotation value of DHMTDA was not reported. Comparison of the NMR data of these synthesized molecules with those of isolated alveolaride C showed that the latter isomer was more consistent with some differences from the β -phenylalanine counterpart. We outlined a convergent and versatile strategy for the first stereoselective total synthesis of the actual structure of alveolaride C, which enabled us to recognize precisely the unassigned stereocenters (C-29, C-30, and C-31) and to correct the wrongly assigned configuration of β -phenylalanine (C-3). This finding paved the way for future research into natural pesticides and set the stage for understanding the chemistry of other alveolarides family members. Pharmaceutically, this research is essential to the advancement of subsequent biological development.]

ii) “*Late-Stage Functionalization: Total Synthesis of Beauveamide A and Its Congeners and Their Anticancer Activities*” **Sanu Saha**, Sourya Shankar Auddy, Akash Chatterjee, Prosenjit Sen, and Rajib Kumar Goswami*; **Org. Lett.**, 2022, 24, 7113–7117. (One of the most read/downloaded papers for the month September-October, 2022).

[Cyclodepsipeptides are a family of natural products with potential pharmaceutical and agrochemical value. In 2021, Puno and co-workers discovered seven new cyclotetradepsipeptides, beauveamides A-G along with known one, beauverolide Ka. The structures of these 13-membered macrocycles, which share a fatty acid moiety, 3-hydroxy-4-methyldecanoic acid (HMDA), and three amino acids of a peptide segment that vary between members, were investigated by spectroscopic analysis, Marfey, and NMR computational methods. Beauveamides A and B showed protective effects on the mouse auditory cell line (HEI-OC1), while belveamides A, D, and E stimulated glucose uptake in cultured rat L6 myoblasts. The first total synthesis of Beauveamide A was performed using a late-stage functionalization approach where a common intermediate was designed to provide various analogs with modified HMDA units for understanding its biological efficacies. To determine the most efficient cyclization route, a macrolactamization strategy including two potential locations was investigated. The adopted late-stage functionalization approach diversified the synthesis, which initially provided quite effectively two analogues of the original natural product. The anticancer activity of Beauveamide A and its two analogues was evaluated for the first time. Interestingly, the effect of modifications in the HMDA fragment of the target natural product is reflected in its bioactivity. However, it was found that the analogue with an enyne moiety was less active than the parent molecule, while the analogue embedded with a conjugated ester showed the best apoptotic results. It is possible that the reason for the difference is the existence of a Michael acceptor in HMDA segment. This study left an opportunity to investigate different variants of beauveamide A by combining several suitable partners with a key vinyl intermediate to understand their structure-activity relationships.]

iii) **“Total Synthesis of Pestalotioprolide E and Structural Revision of Pestalotioprolide F.”** Debobrata Paul, Sanu Saha and Rajib Kumar Goswami*; **Org. Lett.**, **2018**, *20*, 4606–4609.

[Many human diseases, including cancer, can be successfully treated with natural products. Pestalotioprolides E and F are the 14-member macrolides which were discovered under the supervision of Liu and Proksch *et al.* from the endophytic fungus *Pestalotiopsis microspore* identified in fresh fruits of the mangrove plant *Drepanocarpus lunatus* in 2016. These were shown to have promising cytotoxicity against murine lymphoma cell lines (L5178Y) with IC₅₀ values of 3.4 and 3.9 μ M, respectively, whereas pestalotioprolide E exhibited potential activity against human ovarian cancer cell line (A2780) with an IC₅₀ value of 1.2 μ M. We have proposed a impactful and convergent route for the first asymmetric total synthesis of these natural products under the influence of intramolecular HWE reaction which is rarely used in the synthesis of 14-member macrocycle. With the help of our synthetic study, we were able to demonstrate that the proposed structure of pestalotioprolide F was inaccurate and need a correction. Importantly, through this study we have revised the structure of pestalotioprolides F where the configurations of C-4 and C-9 hydroxy centers are found opposite to the proposed structure of the molecule. Further, our recent study (*unpublished*) revealed the unexplored anticancer activity of our synthesized macrolide, Pestalotioprolide E and its underlying signaling cascade. This study provides experimental evidence that Pestalotioprolide E exhibits a potent anticancer effect on a triple-negative breast cancer cell line MDA-MB-231 by inactivating TRXR1, a prime target in cancer therapy. Thioredoxin reductase functions as a key player in the cancer-associated redox-sensitive signaling cascades that regulate cell growth, proliferation, apoptosis, and metastasis. Pestalotioprolide E can directly interact with TRXR1 and inhibits its enzymatic activity. This inhibition leads to the induction of apoptosis via TRX1/ASK1/p38 MAPK death signaling cascade

and causes retardation of metastasis through modulating several metastasis-associated proteins (VEGF, MMP-2, MMP-9, E-cadherin, N-cadherin) in MDA-MB-231 cells. This study is thus bears a great pharmaceutical significance as it discloses the mechanism underlying the biological activity of Pestalotioprolide E, and aids in understanding its action in cancer therapy.]

iv) “**Total Synthesis and Stereochemical Assignment of Bipolamide A Acetate.**” Sourya Shankar Auddy, **Sanu Saha** and Rajib Kumar Goswami*; **Org. Biomol. Chem.**, **2022**, **20**, 3348-3358.

[Plant endophytic fungi are one of the rich sources of a variety of secondary metabolites. Many of them have interesting chemical structures and diverse biological activities. During the search for new secondary metabolites from medicinally important plants in Thailand, in 2014, Siriwach *et al.* isolated bipolamides A and B from the endophytic fungi *Bipolaris* sp. MU34 collected from the plant *Gynura hispidia*. A detailed spectroscopic analysis revealed the existence of common 10-carbon fatty acid amide moiety containing three conjugated *E*-olefins with a chiral methyl center at the C-8 position of the fatty acid chain whose stereochemistry remained undetermined in both the molecules. The structurally intriguing rarely found bipolamide A having a branched five-carbon acyloin moiety consisting of two stereocenters among which one is tertiary, was found to be unstable and thus with the help of relatively stabler acetate analogue of bipolamide A structural analysis of the parent molecule was performed. Our initial effort found an efficient and convergent route for the total synthesis of bipolamide A acetate which eventually established its actual structure for the first time. Although, initial antimicrobial activity assay did not clearly disclose the role of these secondary metabolites to the fungus or the host plant due to the scarcity and instability of the molecule itself. However, they could be a potential precursor(s) for synthesizing the signaling molecules to regulate the metabolism in the fungus and/or host plant as similar precedent exists in the literature where some fatty acid amides are known to serve an important role in chemical signaling in plants and animals for physiological processes. Thus, our ongoing study on the development of synthetic routes for the quick access of various analogues and their subsequent biological evaluation may have a crucial impact to medicinal chemistry world.]