



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Effect of Anthranilic Acid Insertion in β -Sheet Breaker Hybrid Peptidomimetics (BSBHps) on hIAPP aggregation.

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SHORT ABSTRACT

The thesis describes a systematic investigation of design, synthesis, characterization along with study of amyloid inhibition and disruption of preformed amyloid via anthranilic acid containing β -sheet breaker hybrid peptidomimetics (BSBHps). In the introductory chapter, we described broad insight into amyloid aggregation and its relation to various human diseases, with emphasis on Type II Diabetes (T2D) caused by deposition of hIAPP amyloid in pancreatic β -cell, an introduction to literature on β -sheet breakers, various developed strategies and their drawbacks, modification in peptide based strategy and biological importance of Ant (anthranilic acid) group.

In the second chapter, aryl β , γ and δ amino acids were introduced into the short hIAPP₂₂₋₂₇ aggregation sequence and observed as impressive inhibitors of hIAPP amyloid fibril formation and its disruption. We demonstrated that BSBHps containing ortho (2-Abz) and meta (3-Abz) isomer were highly effective inhibitors against hIAPP amyloid formation. On the other hand, the para (4-Abz) isomer could hardly inhibit hIAPP aggregation; rather, it enhances the aggregation process, which might be due to its structural lack of kink formation efficiency. Moreover, we also expressed that these BSBHps containing the ortho and para isomers effectively disrupt the preformed amyloid of hIAPP into non-toxic fragments as confirmed by membrane leakage assay. Peptides containing β and γ -amino acids are proteolytically more stable than standard α -analogs.

The third chapter described the exopolits through similar studies involving peptidomimetics containing β , γ and δ amino benzoic acids at two positions (G24 and I26) of the short hIAPP₂₂₋₂₇ aggregation sequence. From the investigations, we observed that double mutant ortho (2-Abz) and meta (3-Abz) isomer containing BSBHps were more effective inhibitors against the amyloid formation of hIAPP than the single mutant peptidomimetics. However, the para (4-Abz) isomer does not act as an inhibitor; instead, it enhances the aggregation process similarly to its single mutant analog. We have also discussed that these double breaker containing BSBHps disrupts the preformed amyloid of hIAPP efficiently into non-toxic fragments as confirmed from membrane leakage assay. Further, the double breaker comprising BSBHps were observed to be highly stable in the presence of proteolytic enzymes.

In the fourth chapter, we investigated the effect of insertion of anthranilic acid (Ant) in the long hIAPP₈₋₃₇ aggregating sequence individually at two different positions. Insertion of Ant moiety resulted in removal of amyloidogenicity and acted as excellent inhibitors of amyloid formation at significantly lower concentrations. Variation in position did not show any significant changes in their inhibition effects. Longer peptidomimetics were found to be far better inhibitor than the shorter peptides. The improved efficacies of the long peptidomimetics may be attributed to their better sequence recognition and packed binding to the fibrillar assembly generated by hIAPP over the smaller one.

In the fifth chapter, two side-chain to tail stapled peptides (SPs) in presence and absence of Ant moiety were synthesized along with their linear analogs. From the systematic studies, it was cleared that both the stapled peptides (SPs) are potent inhibitors of the highly aggregated amyloid fibrils generated from hIAPP at relatively lower concentrations. Further, these two SPs can potentially disrupt the preformed amyloid fibrils of hIAPP into non-toxic species, as confirmed by the dye leakage assay. The structural rigidity of the SPs contributes to their efficiencies as better inhibitors only in two-fold molar excess in contrast to other breaker strategies. Moreover, these two SPs showed far better efficiencies towards inhibition and disruption than their linear analogs. Further, the potential of the SPs towards suppressing the hIAPP-induced aggregation was independent of the turn-inducing moiety (Ant), which indicated the factor of 'peptide stapling' in terms of conformational restriction plays a vital role in arresting the amyloids formed.