Synthesis and optimization of Tirzepatide by employing hybrid approach with better control on the impurities.

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The process for the synthesis of Tirzepatide (TZP) is described, it is a 39 amino acid synthetic peptide with a fatty acid side chain at 20th amino acid (AA), and with two unnatural amino acids placed at 2nd and 13th position in the sequence. The C-terminus of the molecule is functionalized as amide and N-terminus as free amine. US-FDA is approved TZP for the treatment of type 2 diabetes in the year 2022. It is a glucose dependent insulinotropic polypeptide (GIP) and Glucagon like peptide agonist and it is commercially available under the brand name Mounjaro.

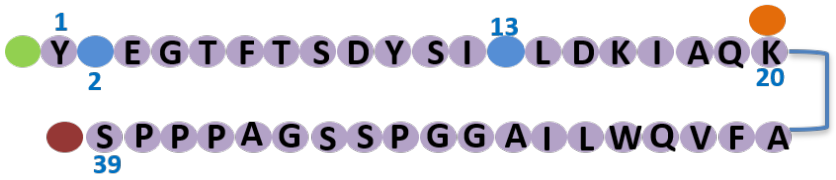

Figure 1. Structure of Tirzepatide

NH_2
AIB
AEEAc-AEEAc-ϒ-Glu -Carboxynonadeconyl
$CONH_2$

We have explored various possible approaches for the synthesis of TZP like, 1. Linear solid phase peptide synthesis: this involves sequential assembling of 39 amino acids on a solid support followed by global cleavage, purification and Lyophilization. 2. Block approach: consist synthesis of block 1(1-19AA) and block II (20-39 AA) on suitable resins followed by partial deprotection of individual blocks and converging in to protected 39 amino acid peptide in solution phase. This up on global deprotection, purification followed by Lyophilization resulted pure peptide. 3. Fragment approach involves dissecting the peptide in to 4 suitable fragments, these fragments are synthesized on solid phase peptide synthesis on suitable solid support. After the synthesis, these protected fragments are sequentially assembled in solution phase to generate 39 amino acid protected peptide. This upon global deprotection, purification, and followed by lyophilization resulted the pure Tirzepatide.

Tirzepatide generated from the above three approaches is compared and fragment approach is taken for optimization followed by manufacturing and the same is described in detail.

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