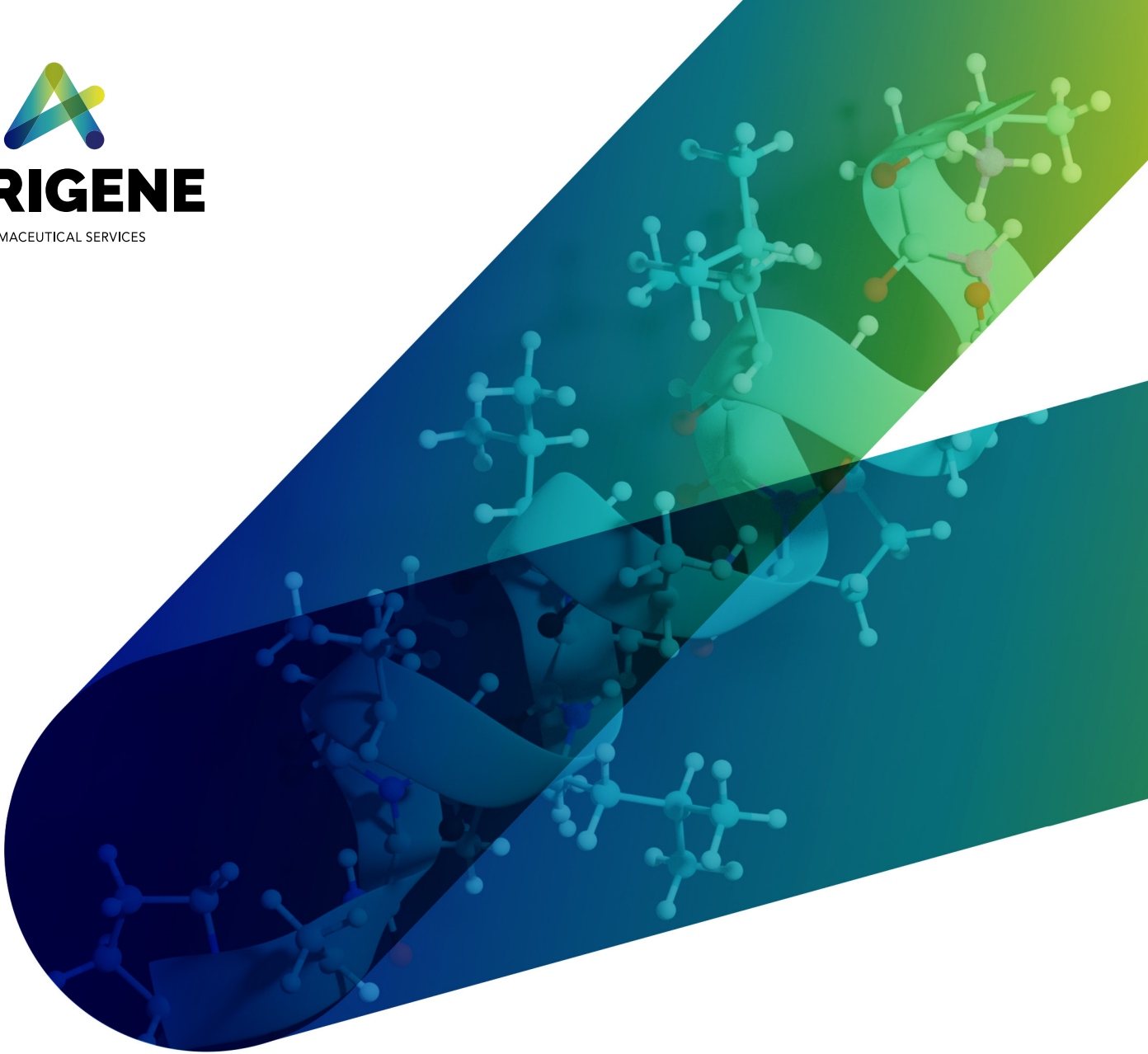




AURIGENE

PHARMACEUTICAL SERVICES



Case Study

Mitigating the manufacturing challenge of a New Chemical Entity comprising peptidomimetic molecule in order to achieve the desired scale-up.



Objective:

A pharmaceutical company approached Aurigene to develop and manufacture a new chemical entity containing peptidomimetic molecule. There is an increasing demand for modified peptide molecules with better stability and biological function, however there are challenges like poor absorption, low stability to proteolytic digestion, and rapid clearance. The molecular instability of peptides remains crucial in the novel synthetic approach.

Challenges:

Peptidomimetic molecule: The major challenge in the synthesis of this molecule is to mimic a peptide containing three amino acids, which involves 8 linear stages and one side chain.

Chiral Purity Requirements: The presence of unwanted isomers in the structures needs to be suppressed to meet the optimal chemical and chiral purity requirements.

Stability concerns: For the final de-protection step, the stability of the reaction was identified to be only 6 hours.

Elaborate Process: Another challenge is multiple steps for isolation and purification of final API involving distillation of Trifluoroacetic acid (TFA), reverse phase column purification, and lyophilization



Solution:

- We developed a peptidomimetic molecule by analysing a peptide with a known structure which was selected based on a rational structure-activity relationship (SAR) study that presented 100% activity. As a result, a peptidomimetic molecule comprising three amino acids with 8 linear stages and one side chain was developed successfully.
- All chiral purity requirements were met by purifying the final API with acetonitrile and water, resulting in optimum product recovery with chemical purity >99% and chiral purity >99%.
- Reaction stability was achieved by using three isolation stages and by eliminating the steps of column purification and lyophilization.
- Reverse phase column purification and lyophilization are time consuming techniques; A process was developed, which resulted in high purity and ease of scaling-up.

Outcome:

- Simplified the procedure by developing a three-stage isolation process that isolates stage-3, stage-6, and the final API stage-8. In the final stage, TFA distillation was avoided by developing a suitable procedure, which included washing with Methy-tert Butyl Ether (MTBE) to remove TFA.
- Established an isolation process: By developing suitable crystallization process and avoiding the preparatory HPLC and lyophilization. This robust crystallization process helped in controlling the other 7 isomeric impurities.

Terminologies:

Peptidomimetic molecule:

A peptidomimetic molecule is a protein-like chain designed to mimic a natural peptide containing required molecular properties or elements (pharmacophore) and has the ability to interact with the target and produce a desired biological effect.

Industrial importance of Peptidomimetic molecules:

Synthesized peptidomimetic molecules help in protein-protein interactions in molecular recognition. Hence, they are valuable in drug discovery.



Thank You



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