Recombinant Production of Bivalirudin-18mer

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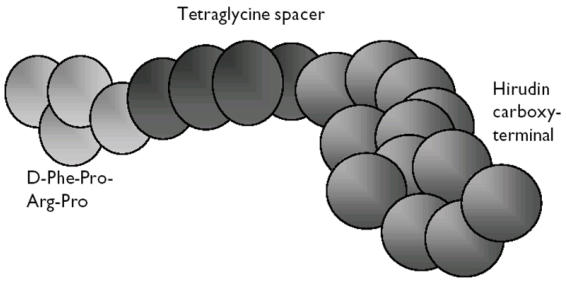
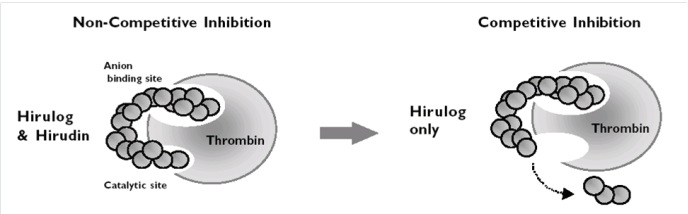
Angiomax™ (bivalirudin)

Bivalent Thrombin Inhibitor



Pharmacology



Advantage of Hirudin Family

- Bivalent direct thrombin inhibitor
- High specificity and potency
- Lack of dependence on antithrombin-III
- Effect on clot-bound & free thrombin
- Lack of effect on platelets
- No inhibition by PF4 and others

***Plus* Reversibility**

- Slow cleavage by thrombin of Arg_3-Pro_4 bond
- Preservation of anion-binding exosite binding
- Recovery of thrombin catalytic site functions
- Faster clearance from plasma

Semisynthesis of Bivalirudin

AMINO TERMINAL FRAGMENT CHEMICAL SYNTHESIS (UCB-Bioproducts)	CARBOXY TERMINAL FRAGMENT RECOMBINANT SYNTHESIS IN *E. coli* (Lonza)

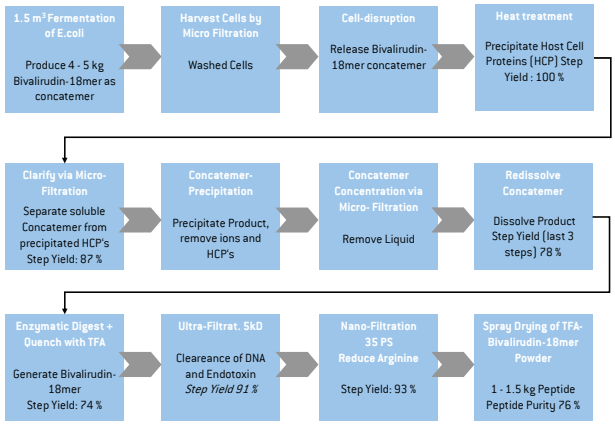
BOC-D-Phe-Pro-COSuc +

↓ FRAGMENT CONDENZATION, DEPROTECTION AND FINAL PURIFICATION

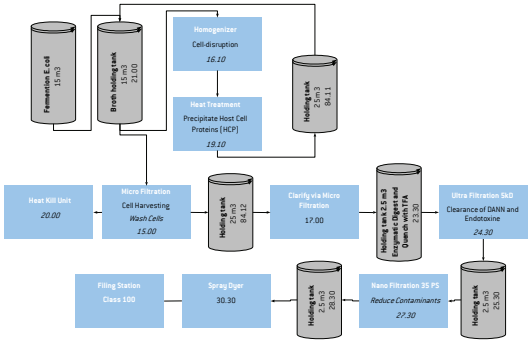
D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu

Bivalirudin

Bivalirudin-18mer Process Overview at 1.5 m^3 Piloting Scale

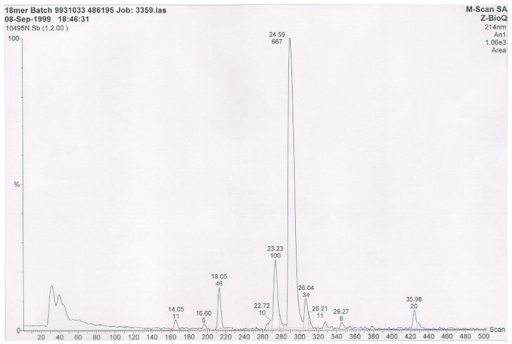


Technical Capabilities for Recombinant Bivalirudin-18mer Peptide Production at 15 m3 Scale



The peptide impurity profile of recombinantly produced Bivalirudin-18mer by LC-MS

The peptide impurity profile of the recombinantly produced 18mer fragment is equivalent to that of the chemically synthesised material



Summary

Bivalirudin is a potent bivalent thrombin inhibitor with applications as a replacement for Heparin in Acute Coronary Syndromes.

A semisynthetic process for the manufacture of Bivalirudin was acquired by TMC.

The process for the recombinant Bivalirudin-18mer fragment was modified, developed and scaled up to 1.5 m3 by Lonza.

This new process has considerable potential to facilitate the large scale low cost production of Bivalirudin.