

## Efficient synthesis of fertirelin acetate as a reproductive control drug: a GnRH hormone analogue

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**Background and Aims:** Fertirelin acetate is a peptidic GnRH agonist intended for the treatment of ovarian follicular cysts in mammals and for the improvement of conception rates. It induces ovulation in mammals, and it is used as a drug for cows. Herein we wish to report the synthesis of Fertirelin acetate. It was shown that the 100- and 200µg doses of Fertirelin acetate increase pregnancy rates in virgin heifers and tended to improve pregnancy rates in suckled cows when injected during the midluteal phase after insemination.

**Methods:** Synthesis was carried out using 2-chlorotrityl chloride resin (1.0 mmol/g) following standard Fmoc strategy and at last, a novel method was used for ethyl amidation of the C-terminal of nonapeptide using ethyl ammonium hydrochloride in solution phase, in good yield. The product was purified using preparative HPLC and the structure was confirmed by the MALDI-Mass spectrometry data.

**Results:** Fertirelin acetate is an amidated C-terminal peptide. There are different methods for the synthesis of C-terminal amidated peptides such as; a) enzymatic amidation, b) using of amide resins in SPPS, c) using carboxypeptidase in the presence of ammonia, d) conversion of the C-terminus of peptides to the methylester and addition of Ethyl amine at low temperature. All of the reported methods have some drawbacks such as: a) laborious reaction conditions, b) high price of enzymes and limitation of solubility parameters, c) using of ammonia or alkylamines as gas and performing the reaction at low temperature, Separation and purification of enzymes need more time and energy. According to these drawbacks, we used ethylammonium hydrochloride in solution phase for the synthesis of ethylamidated form of C-terminal peptides.

**Conclusions:** Fertirelin acetate as a reproductive drug was synthesized in combination of solid and solution phase peptide synthesis and this method could be done in large scales.

**Keywords:** SPPS; GnRH Analogue; Fertirelin Acetate