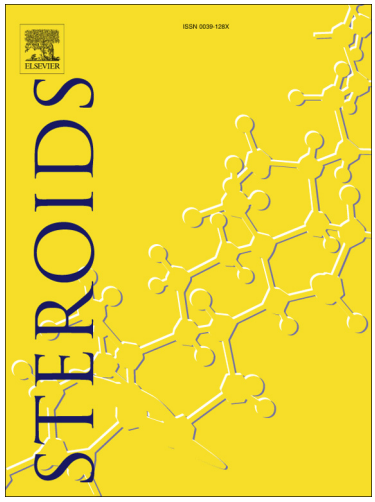

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Frederick A Meece, Gulzar Ahmed, Hareesh Nair, Bindu Santhamma, Rajeshwar R Tekmal, Chumang Zhao, Nicole E Pollok, Julia Lara, Ze'ev Shaked, Klaus Nickisch

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Esters of levonorgestrel and etonogestrel intended as single, subcutaneous-injection, long-lasting contraceptives

Frederick A Meece[a], Gulzar Ahmed[a], Hareesh Nair[a], Bindu Santhamma[a], Rajeshwar R Tekmal[b], Chumang Zhao[a], Nicole E Pollok[a], Julia Lara[a], Ze'ev Shaked[a], Klaus Nickisch[a]

[a]*Evestra, Inc, 6410 Tri County Pkwy, Schertz TX, 78154*
[b]*University of Texas Health Science Center San Antonio, 7703 Floyd Curl Dr., San Antonio, TX, 78229*

Abstract

An effort with the goal of discovering single-dose, long-lasting (>6 months) injectable contraceptives began using levonorgestrel (LNG)-17-β esters linked to a sulfonamide function purposed as human carbonic anhydrase II (hCA 2) ligands. One single analog from this first series showed noticeably superior anti-ovulatory activity in murine models, and a subsequent structure-activity relationship (SAR, the relationship between a compound's molecular structure and its biological activity) study based on this compound identified a LNG-phenoxyacetic acid ester analog exhibiting longer anti-ovulatory properties using the murine model at 2 and 4 mg dose than medroxyprogesterone acetate (MPA). The same ester function linked to etonogestrel (ENG) furnished a compound which inhibited ovulation at 2 mg for 60 days, the longest duration of all compounds tested at these doses. By comparison, MPA at the same dose inhibited ovulation for 32 days.

Keywords: Injectable contraception, MPA, levonorgestrel, etonogestrel, prodrug

1. Introduction

As of 2011, forty million women worldwide used injectable contraception [1] which is a preferred delivery system of contraceptive agents especially in southeastern Asian countries such as Thailand, the Philippines, and sub-Saharan Africa. While the method remains popular with users, one obstacle to regular use is availability, due to regional product unavailability and/or no clinical access, among other reasons [2]. The idea of injectable contraception lasting over six months which reduces side effects and improves safety profiles could in theory prove valuable in negating the availability issues, while benefiting women and health care systems globally.

MPA a widely used injectable contraceptive, and is commercially available as two different products- one is a intramuscular injection containing 150 mg of MPA and the other a sub-cutaneous injection containing 104 mg of MPA. Depo-Sub Q Provera 104 is a sub-cutaneous single-injectable formulation of the progestin medroxyprogesterone acetate (MPA) which among other uses, provides a contraceptive effect for 13 weeks post injection by preventing ovulation at a typical failure rate of 3% [3,4]. The approved dose for Depo Provera is 150 mg in 1 ml for intramuscular injection and 104 mg in 0.65 ml for sub-cutaneous injection-formulation [5]. There