Steroids 78 (2013) 255–267

Contents lists available at SciVerse ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Synthesis and biological evaluation of partially fluorinated antiprogestins and mesoprogestins

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ARTICLE INFO

Article history:
Received 23 July 2012
Received in revised form 11 September 2012
Accepted 25 September 2012
Available online 21 November 2012

Keywords:
Mesoprogestins
Fluorine
Antiproliferation

ABSTRACT

A series of antiprogestins have been synthesized by partially fluorinating the steroid molecule in positions relevant for receptor binding. By introducing fluorine at the exo-methylene of the 17 spirofuran ring, we obtained partial agonists (mesoprogestins) with significant applications for antiproliferative and antiovulatory treatment strategies in gynecological therapy such as uterine fibroids, endometriosis and heavy menstrual bleeding. Compared to the standard drug RU486, our synthesized compounds exhibited considerable dissociation between antiprogestational and antiglucocorticoid PR receptors. Furthermore, our studies have shown that pure antiprogestins can be generated by partially fluorinating the 17 propenyl and propynl group or by substituting the 4′ acetyl phenyl group in the 11 position using trifluromethyl group.

1. Introduction

1.1. SARs considerations for choice of compounds (PRMs) to be synthesized

Progesterone antagonists of the RU486 (Mifepristone) family comprise pharmacodynamically different compounds. These pharmacodynamic differences result from compound-specific interactions with nuclear receptors apart from the PR (progesterone receptor) for example the GR (glucocorticoid receptor). Furthermore, the respective compounds also differ in terms of their biological effects at the PR, due to the relative amount of PR-antagonistic and PR-agonistic properties as well as the mechanism of type I and type II antagonists [1]. Up until now, progesterone receptor antagonists (PRMs) have been clinically developed by different strategies ever since Mifepristone (RU486) was first discovered by Teutsch et al. [2]. The first approach deals with "PR-antagonists" for the purpose of investigating different types of fertility control and cancer indications, such as post-coital contraception, therapeutic pregnancy termination (Mifepristone, CDB-2914), and breast cancer (Onapristone, ZK-230211). The second approach requires a partial agonistic profile as was first observed with Asoprisnil for the treatment of gynecological indications, such as endometriosis and fibroids [3,4]. The beneficial implications of both PR antagonists and partial agonists (mesoprogestins) have resulted in efforts to better understand the structure–activity relationships [5,6] and have led to the synthesis of new antiprogestins depicted in Fig. 1.

SARs lead to the understanding that the substitution pattern at 17 position of the steroid establishes binding to the PR and/or GR receptor. The 17-alpha propinyl group of Mifepristone leads to equal strong binding to both receptors therefore limiting its long term application. Substitution of the 17-propinyl group with a 3-hydroxypropyl, (Z)-3-hydroxyprop-1-enyl group [7], a 17,17-spiro-oxazole group [8], a 17-acetoxyprogesterone side chain [9], or the 17,17 spiro ether group [10] and most recently, ZK-230211 [11] a perfluoralkyl steroid leads to potent antiprogestins with significantly reduced antiglucocorticoid activity.

In contrast substitution at the 11 position influences the ratio of agonistic to antagonistic activity of the steroid molecule. Mesoprogestins were first observed with Asoprisnil [3] and later with other derivatives [13,14]. Partial agonistic profile can be explained by crystal structure investigations of the progesterone receptor binding domain complexed with Asoprisinil and the nuclear receptor corepressor and SMRT [12].

The concept of partial fluorination was applied on different moieties in the 11 and 17 positions of the steroid molecule in order to accomplish two objectives, the first aim was to acquire antiprogestins with reduced binding to the GR receptor and our second

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0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2012.09.010

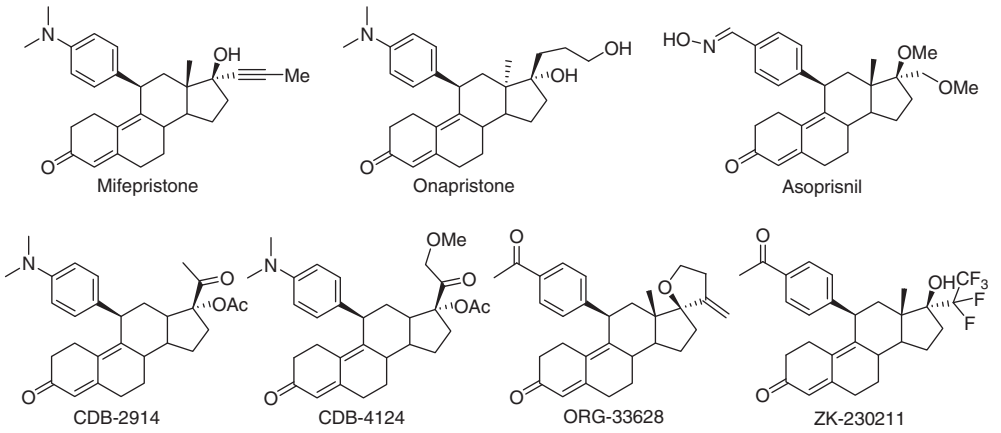

Fig. 1. Significant RU486 derivatives.

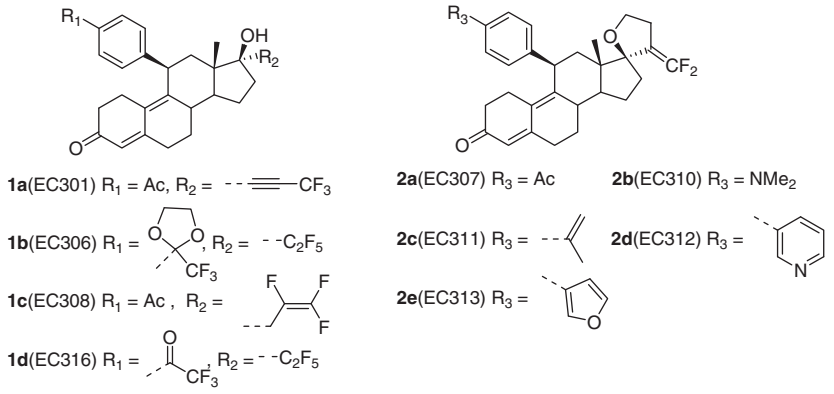

Fig. 2. Compound design.

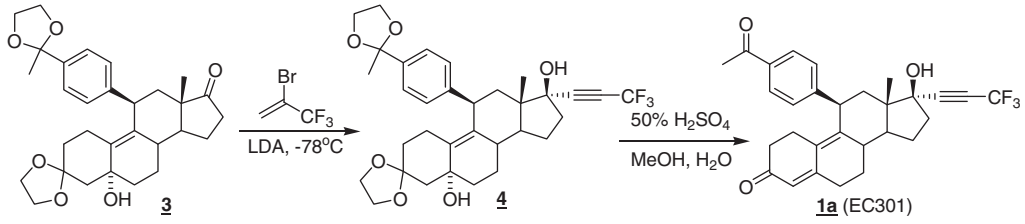

Fig. 3. Synthesis of compound **1a** (EC301).

aim was to synthesize pure antiprogestins and mesoprogestins (refer to Fig. 2). The paper covers basic molecular studies pertaining to partially fluorinated steroids and a preliminary first qualitative in vivo assay which permits a corresponding distinction (Fig. 3).

1.2. Pharmacodynamic concept

SERMs (*specific estrogen receptor modulators*) are known to generate a tissue-dependent mosaic of ER-agonistic and/or antagonistic effects [15,16]. The blend of estrogenic and antiestrogenic effects is advantageous for the use of SERMs (Tamoxifen and Raloxifen) for prevention and treatment of estrogen-dependent mammary gland tumors in human. Moreover, SERMs have the capability to partially abolish the negative effects of endogenous and exogenous estrogens because the blend of effects induced by SERMs varies in tissues and is sharply different compared to low doses of estrogen. By analogy to SERMs at the progesterone receptor, PRMs or SPRMs (*selective progesterone receptor modulators*) can induce a unique blend of PR-agonistic (e.g., kind of secretory transformation) and PR-antagonistic changes (e.g., thick-walled spiral arteries) in the human endometrium [17]. This has lead to ongoing studies to modulate PR-agonistic PRMs by improving the ratio of PR-agonist over PR-antagonistic effects. For example, one significant compound that does exhibit higher PR agonist over PR antagonistic response is RU486. RU486 is not a pure antagonist at the PR [1,3,18] and has shown remarkable PR-agonistic activity in the guinea pig model. The PR-agonistic activity due to RU486 may explain lower labor conditioning effects when combined with a prostaglandin; and lower labor inducing properties when administered without a prostaglandin as compared to pure PR antagonist Onapristone [19].