Journal of Fluorine Chemistry 185 (2016) 48–85

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Review

Fluorinated steroids and their derivatives

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ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form 15 March 2016
Accepted 16 March 2016
Available online 18 March 2016

Keywords:
Fluorination
Corticosteroids
Estrogen receptor ligands
Radiolabelling
Positron emission tomography (PET)

ABSTRACT

Fluorinated steroids have found entry into the list of important pharmaceuticals. Fluorinated corticosteroids are being used as topical drugs against rheumatism and inflammatory skin diseases or as inhalation drugs again asthma. A number of fluorinated steroids bind strongly to the estrogen or the progesterone receptor. With the availability of [^{18}F]fluorine as a radiolabel, radiofluorinated steroids are being developed as potential positron emission tomography (PET) imaging agents. This article presents an overview of preparative methods to fluorinated steroids as well as of the uses of these compounds.

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1. Introduction

Fluorinated drugs form an integral part of marketable pharmaceuticals worldwide. It has been reported that, already by 1990 around 220 fluorinated drugs were on the market, comprising 8% of all launched synthetic drugs at the time, up from

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http://dx.doi.org/10.1016/j.jfluchem.2016.03.009
0022-1139/

about 2% in 1970, with 1500 compounds under development [1]. Currently, the contribution of fluoro-containing pharmaceuticals has risen to 25% of the total. A number of these important fluorinated pharmaceuticals are steroids with anti-cancer and anti-inflammatory properties. Thus, fulvestrant (**1**) has been developed as an estrogen receptor antagonist and has been approved as a second-line therapy for advanced breast cancer in postmenopausal women. Dexamethasone (**2**) is used as an anti-emetic in cancer treatment [2]. It is also employed as a direct anti-cancer agent in the treatment of multiple myeloma [3]. Difluprednate (**3**), a topical corticosteroid, is used for controlling postoperative inflammation. Fluticasone propionate (**4**), used in combination with salmeterol xinafoate (**5**) against asthma was the sixth largest selling drug worldwide in Q1 2014 (Fig. 1). These are but a few examples of a host of fluorinated steroids currently in service.

The introduction of a fluoro atom in place of a hydrogen or a hydroxyl group in the molecule often does not lead to a large change in steric factors. Nevertheless, the interaction of the fluoro substituent with other functional groups within a compound can give rise to a different conformation in the molecule. The metabolism of the fluorinated compound is often slowed down in comparison to the non-fluorinated parent compound. Frequently, fluorinated compounds exhibit higher stability, better solubility and better bioavailability, partly due to a generally better lipophilicity [4], than their non-fluorinated counterparts. In certain cases the fluoro substituent can replace a hydroxyl substituent as a hydrogen acceptor site, although the possibility of a real fluoro-hydrogen bond o small molecules such as steroid with receptor proteins has been a point of debate [4,5].

Recent reviews on fluorinated pharmaceuticals have appeared with sections on fluorinated steroids [6]. Also, reviews devoted to fluorinated steroids have been published previously, but none of those published in English are recent [7]. Nevertheless, fluorinated steroids merit an overview of their own. The following gives an overview of the synthesis and application of these molecules with a concluding look at synthetic fluorinated steroidal receptor ligands and at radiofluorinated steroids as PET agents.

2. Typical synthetic pathways to fluorinated steroids

2.1. Addition of a fluoro-containing substituent or annelation of a fluoro-containing cyclic structure

The inclusion of fluoro substituents in steroids can be achieved by addition of a group that already contains one or more fluoro atoms, typically in form of a fluorinated alkyl chain. An example of this approach can be found in the synthesis of 3-β-hydroxy-3α-perfluoroalkylandrost-5-en-17-ones (**8**) as biologically active analogs of dehydroepiandrosterone that cannot be metabolized to estrogens [8a]. Here, the 17-*O*-silyl protected androst-4-en-3-one-17β-ol (**6**) was reacted with perfluoroalkyl lithium, prepared by mixing first perfluoroalkyl iodide to an ethereal solution of the steroid, followed by methyllithium at −78 °C in a procedure developed by Gassman and O'Reilly [8b]. The 17-*O*-silylated 3α-perfluoroalkyl-androst-4-en-3β,17β-diols **7** could be reacted by established methods to the target 3α-perfluoroalkylandrost-4-en-3β-ol-17-ones **8** (Scheme 1) [8a].

Analogously, perfluoroalkyl substituents have been added to the 17-keto function of steroids [9a] (Scheme 2). Also, fluoro-substituted ethynyl or ethenyl moieties have been introduced at C17, either by a 1,2-addition of trifluoromethylacetylide, produced *in situ* from 2-bromo-3,3,3-trifluoropropene (**13**), to a C17-keto function of steroids **12** (Scheme 3), or by nucleophilic attack of lithium trifluoroethenylide (**16**), prepared *in situ* from 1,1,1,2-tetrafluoroethane and *n*-BuLi, to epoxides of type **15** (Scheme 4).

Compounds derived from the trifluoroethenyl derivative **17** have been found to be mesoprogestins and may have applications

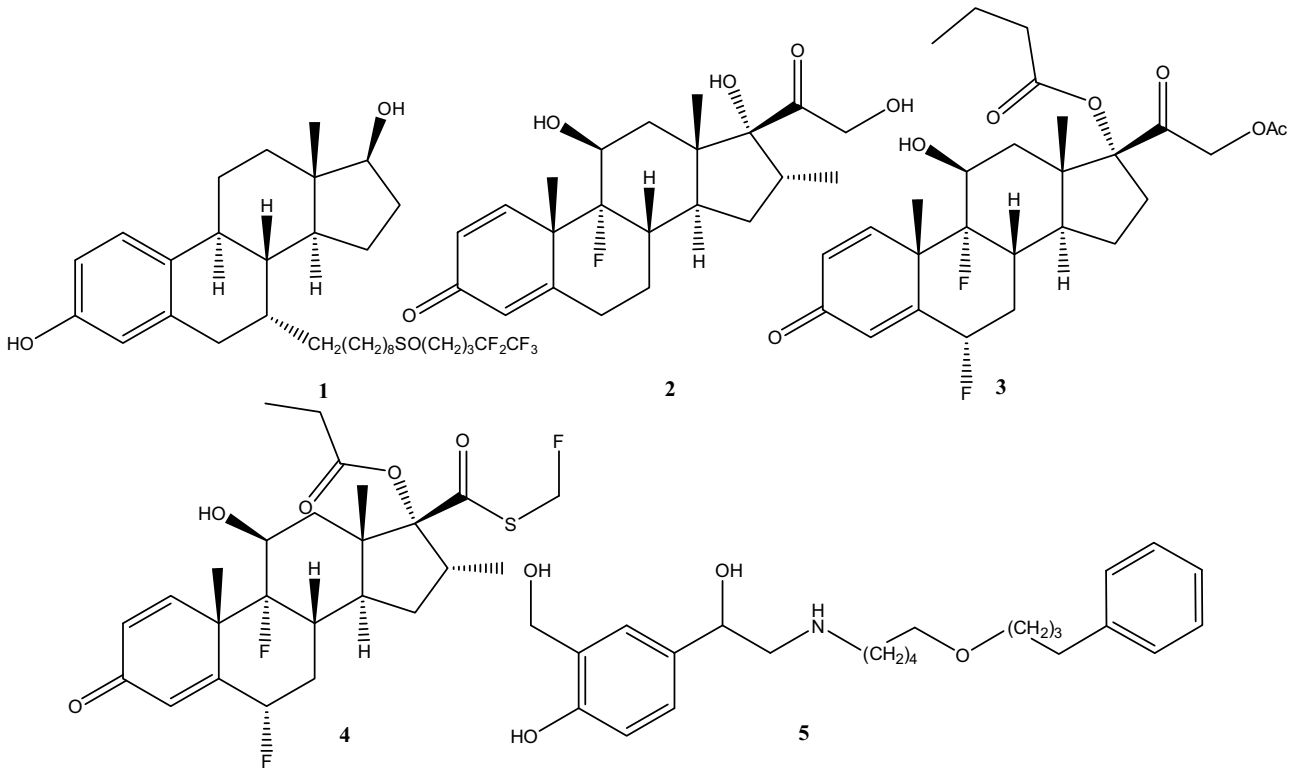

Fig. 1. Representative fluorinated steroids as important pharmaceuticals.