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Mini-review

Quest for steroidomimetics: Amino acids derived steroidal and nonsteroidal architectures

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ABSTRACT

The chiral pool amino acids have been utilized for the construction of steroidal and non-steroidal architectures in the quest for steroidomimetics. Chirality derived from amino acid-based architectures provides new and easy to incorporate chiral chemical space, which is otherwise very difficult to introduce and comprised of several synthetic steps for asymmetric steroids. The different and exciting ligand-receptor interactions may arise from the use of each amino acid enantiomer that was introduced into the chiral steroidal backbone. The A and D rings of steroidal architectures can be mimicked by the phenyl group of the amino acid tyrosine. The Mitsunobu reaction, nucleophilic substitution and elimination, etc. were utilized for constructing diverse tri- and tetracyclic steroidal skeletons as well as benzofused seco-steroids from amino acids. These benzofused, amino acid-derived steroidal and nonsteroidal molecules had promising biological activity in hormonal related disorders.

1. Introduction

Steroids belong to a class of natural and synthetic organic compounds characterized by a rigid framework of 17 carbon atoms formed from four fused rings with varying levels of functionalization. The rings characteristically are three six-membered rings and one five membered ring arranged in 6-6-6-5 manner and the rings are identified by capital letters and the numbering of carbon atoms are shown in Fig. 1 [1]. Steroids are widely distributed in nature, having diversity in the structures and possess a broad biological activity profile due to their ability to penetrate cell membranes and bind to nuclear and membrane receptors. The most significant steroidal compounds are a) sex hormones [2–4], including androstane, pregnane and estrane series, which exhibit various hormonal activities; b) bile acids [5] responsible for lipid digestion and absorption; c) corticosteroids [6] involved in several physiological processes such as regulation of inflammation, carbohydrate metabolism, protein catabolism and blood electrolyte level; d) cardiac glycosides [7] used for heart failure treatment; e) sterols [8] as important constituents of cell membranes having a significant role in their stability, cell growth, proliferation as well as precursor of bile acids and hormonal steroids (Fig. 1). The diverse action and wide spectrum of biological activities of steroids have not only inspired biochemists and endocrinologists, but also encouraged organic chemist to develop synthetic strategies for partial and total synthesis of steroids. In recent years the structurally modified steroids have attracted much attention owing to the increasing challenges in the development of new therapeutic agents with minimum side effects and for the specific, selective physiological activity.

Hydrophobic steroids have wide occurrence, rigid framework with diverse functionalization, extensive biological activity profile and ability to penetrate cell membranes and bind to specific hormonal receptors and thus steroids are considered as promising scaffold for further modifications either through alteration of ring or changes at the periphery [9]. The steroidal skeletons are usually altered by partial cleavage followed by reconstruction through simultaneous incorporation of heteroatoms or other structural moieties. Based on the type of alteration performed on the steroidal skeleton, the modified steroids can be divided into different categories: a) heterosteroids [10–12] as the replacement of one or more

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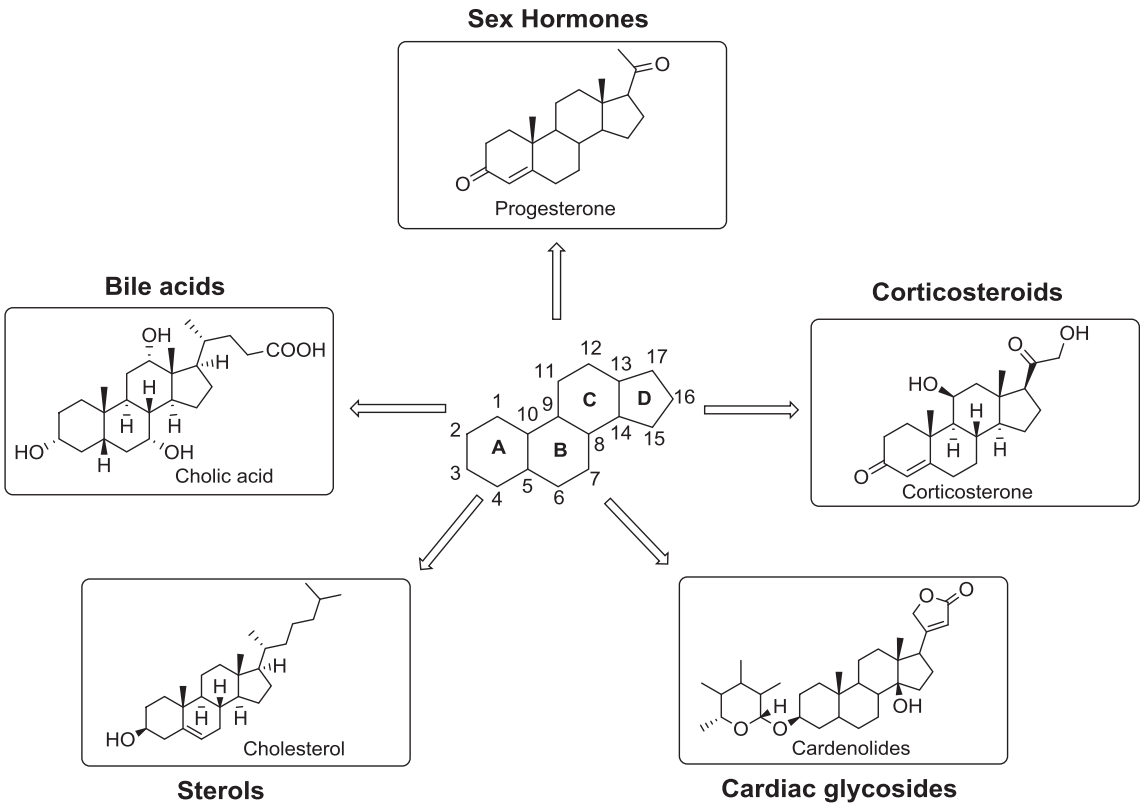

Fig. 1. Steroid skeleton and the structures of most significant steroids.

carbon atoms of a steroid molecule with heteroatoms, affecting the chemical properties of a steroid and having examples like azasteroids, oxasteroids and thiasteroids; b) homosteroids [13,14] with expansion of one or more carbon atoms to the ring skeleton in any of the four rings; c) steroidal hybrids/conjugates [15] by integration and/or linkage of steroids with other biomolecules such as amino acids, polyamines and carbohydrates, drugs and other functional molecules; d) steroidal architectures containing new ring fused to ring A, ring D or bridging rings A and B [16]. Most of these steroidal skeletons have proven to be promising candidates in pharmaceuticals; several of them are currently in the market as anti-inflammatory, immuno depressant and anti-cancer agents. However, in the therapeutic application steroids are associated with several deficiencies due to their poor bioavailability and side effects due to hormonal imbalance. Additionally, the chemical structures of steroids are very complex which makes it difficult to synthesize and thus being expensive. Therefore the medicinal chemist's thought was to develop more potential therapeutic agents for the hormonal related disorders with minimum side effect as well as cost effective. This led to the discovery of highly effective and selective non-steroidal molecules, deprived of steroidal framework and with minimum side effects.

A number of tailored steroid molecules have been synthesized as potent inhibitors of specific enzymes such as aromatase, sulfatase and P450 etc. for the treatment of hormone dependent cancer [17–20]. During the past few years for the treatment of hormone-resistant cancers, the development of steroidal derivatives, which inhibit the angiogenesis, tubulin polymerization and the up regulation of apoptotic pathways through complex signal transduction mechanisms, has attained much attention [21]. The new steroidal scaffolds with reduced undesirable hormonal activity were developed through various synthetic ways, such as: elimination or modification of functional groups responsible for binding to the hormone receptor, reducing the substrate-receptor interactions by introducing the chemical substituents near the original group to increase the steric hindrance, varying the number of ring members or primary stereo structure or designing the heterocyclic derivatives not recognized by the receptor protein due to the difference with the natural hormone in specific structure or geometry [22–26].

While going through the vast literature of steroidomimetics leading to steroidal and nonsteroidal molecules, it appears to us amino acids as chiron were not utilized to mimic the skeleton of steroids to evaluate their possible properties. The importance of chirally pure α-amino acids in asymmetric synthesis of structurally complex or simple drug or drug-like molecules is well documented [27]. The easy availability of amino acids in enantiomerically enriched form and possibility of functional group transformation made it an important scaffold for the pharma industries, and this leads to the synthesis of several molecules for various therapeutic areas such as antimicrobials, infectious diseases, cardiovascular and nervous system disorders, genital tract diseases, estrogen-related disorders and bone remodeling. The molecules derived from amino acids are very much like natural ligands with high level of biocompatibility, water solubility and enhanced resistance to proteolysis. The promising biological activity profile and scope of structural modification of the steroid and amino acids scaffold encouraged us to utilize the amino acids as a chiral pool to develop novel steroidomimetics with potent therapeutic activity. We designed initially asymmetric heterosteroids with synthetic possibility from chiral amino acids and later we shifted our attention towards the synthesis of amino acid derived non-steroidal structures having structural similarities of steroidal framework. In this case study, we have compiled the amino acid derived steroidal and