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Editorial Article

Formation of Steroid-Type Skeletons: An Ubiquitous Natural Product

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ABSTRACT

Steroids are one of the essential classes of bioactive compounds and are involved in many biochemical processes which include their role as signaling compounds, the alteration of membrane fluidity and the regulation of a variety of metabolic processes. In order to identify novel compounds with valuable pharmacological action, the synthesis of improved steroids is gaining much attention in recent times. Among those analogs, heterosteroids particularly azasteroids are one of the most important classes which display a variety of biological activities, often free from undesirable side effects. The challenges in the synthesis of steroids, particularly azasteroids, and the potential of azasteroids as novel drugs has prompted numerous investigations in this field. The synthetic methods leading to steroidal derivatives (azasteroids) with one or more nitrogen atoms are very limited. There are reports on the major skeletal types of steroids and their associated range of biological activities. In addition, there are increasing studies in which known non-steroidal pharmacophore are attached to the steroid skeleton with the aim that the latter might provide lipid solubility, receptor selectivity or membrane-binding properties. All these are testaments on the importance and the ubiquitous nature of steroids. The urgency for the syntheses of a wide array of steroids for several intended biomedical applications are found in the chemical and biochemical literatures. Several efforts are underway to achieve this milestone. There have been developments in therapies for the treatment of breast cancer which target the estrogen receptor. In the domain of rational drug design, a three-dimensional model of the CYP19 aromatase incorporating both the haem and the steroid substrate has been proposed.

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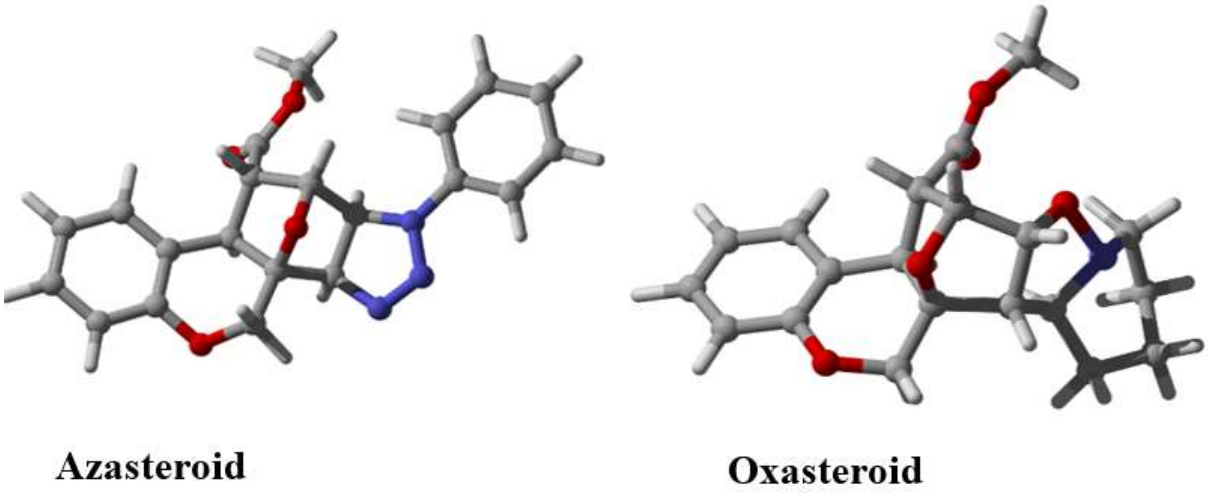
GRAPHICAL ABSTRACT



Editorial

Steroids are hormones produced by the body which aid in the functioning of organs, tissues, and cells. Steroids are associated with the central function of the immune system and hence the overall defense mechanism in living organisms [1–4]. There are reports on the major skeletal types of steroids and their associated range of biological activities [5]. In addition, there are increasing studies in which known non-steroidal pharmacophore are attached to the steroid skeleton with the aim that the latter might provide lipid solubility, receptor selectivity or membrane-binding properties [5]. All these are testaments on the importance and the ubiquitous nature of steroids. The urgency for the syntheses of a wide array of steroids for several intended biomedical applications are found in the chemical and biochemical literatures [6,7]. Several efforts are underway to achieve this milestone [8]. There have been developments in therapies for the treatment of breast cancer which target the estrogen receptor [9]. In the domain of rational drug design, a three-dimensional model of the CYP19 aromatase incorporating both the haem and the steroid substrate has been proposed [10]. There are a number of international conferences on steroids that have published their proceedings including those on aromatase [11], vitamin D [12], and hormonal steroids [13]. There are reviews on oxasteroid [14] and azasteroid [15] chemistry, the enantioselective synthesis of steroids [16], and the addition of extra rings to the tetracyclic steroid skeleton [17]. Epoxidation reactions have played an important role in the partial synthesis of steroids [5]. Despite all the progress, there is still the need for stereochemically efficient and metal-free synthetic methods for the synthesis of steroids. Contemporary organic syntheses aim at the ability to carry out multiple chemical transformations without the need for isolation of intermediates or additional reagents until the final products are obtained. The flexibility to attenuate the stereochemistry of modern-day organic synthesis forms part of the integral objectives. Such chemical reactions enhance synthetic efficiency and hence a likely excellent approach towards steroids syntheses [18]. Tandem sequential cycloaddition reactions

remain elegant in the synthetic toolkit as it meets the objectives of contemporary chemical transformations. The importance of tandem cycloaddition reactions is supported by its extensive use in several studies [19–21]. There are some recent computational studies [22–25] .that shed light on the molecular mechanisms of selected tandem organic reactions.

Tsuge and co-workers reported [26] a metal-free tandem sequential addition reaction between methyl o-(2-furylmethyloxy)- and o-[N-ethyl-N-2-(furylmethyl)amino]cinnamate moieties of methyl (*E*)-3-(2-(furan-2-ylmethoxy)phenyl)acrylate with phenyl azide to form azasteroids [15]. This reaction occur by an initial intramolecular Diels-Alder reaction between methyl o-(2-furylmethyloxy)- and o-[N-ethyl-N-2-(furylmethyl)amino]cinnamate moieties to produce a (4 + 2) adduct. This is followed by an intermolecular 1,3-dipolar cycloaddition reaction between the (4 + 2) adduct and phenyl azide which provided the one-pot [6.6.5]annelation transformation for the formation of polyazasteroid type skeletons with unknown regiochemistry.

In a recent study [27], the regio-, stereo-, and enatio-selectivities of the reaction of methyl o-(2-furylmethyloxy)- and o-[N-ethyl-N-2-(furylmethyl)amino]cinnamate moieties of methyl (*E*)-3-(2-(furan-2-ylmethoxy)phenyl)acrylate with phenyl azide to form azasteroids have been investigated. The answers offered in the said computational study [27] offers an open door for further exploration of this elegant method. In addition, the reactivity of other derivatives of methyl (*E*)-3-(2-(furan-2-ylmethoxy)phenyl)acrylate for the synthesis of various polycyclic-azasteroids were explored. Also, the paper [27] reported a novel synthetic utility of employing nitrones for the formation of oxasteroids [14] that are hitherto unreported and found the reaction favorable. This novel idea prompts the need for further studies on the reactivity of other 1,3-dipoles aimed at synthesizing a wide array of steroids. These mechanistic insights are necessary for rational syntheses and execution of diverse polycyclic steroids of high selectivity and efficiency as well as providing future guidance for correlative experiments. The ability to construct new molecules with potential applications in biomedicine via efficient and selective molecular design and syntheses hinges on thorough understanding of underlying reaction mechanisms. The present knowledge on the pharmaceutical and biological importance of steroids and related heterocyclic compounds makes steroids an ubiquitous natural product and the search for cheap, efficient and toxic-free synthetic methods will continue to be an integral part of future progress in this field.

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