Azasterol as Possible Antifungal and Antiparasitic Drugs

Abstract
The aim of this mini review is to bring together the azasterols of synthetic origin with antifungal and antiparasitic activity. Particular emphasis on those ones have shown to be sterol biosynthesis inhibitors (SBIs).

Keywords: Azasterols; Antiparasitic; Antifungal; Sterols; Eukaryotic microorganisms

Introduction
Sterols are constituents of the cellular membranes that are essential for their normal structure and function [1-3]. In mammalian cells, cholesterol is the main sterol found in the various membranes [1-3]. However, other sterols (e.g. ergosterol) predominate in eukaryotic microorganisms such as fungi and protozoa [4]. Ergosterol biosynthesis is an extremely important area of biochemical difference between eukaryotic microorganisms and their human host that is currently exploited in chemotherapy and in the development of new antifungal agents [5]. Currently, there are several classes of known drugs that interfere with sterol biosynthesis, which are used to treat diseases such as high cholesterol in humans and fungal infections [5-7]. It is worth noting that, all mechanisms are common to the eukaryotic microorganisms and the host and consequently, current drugs are those that are most selective for inhibiting the pathogen. Without complete selectivity, target related side effects occur in the host.

Δ24 - Sterol Methyl Transferase (SMT) in the Synthesis of Membrane Sterols

Fortunately, the metabolic pathway to the synthesis of sterols also involves differentiated steps in both pathogenic microbes and mammalian organisms that may be used for blocking growth of the former without affecting the latter [5,6,8]. One such step refers to the sterol C24-methylations catalyzed by the enzyme Δ24 - sterol methyl transferase (SMT) restricted to plants, protozoa, and fungi [5,6,8]. Together these enzymes are responsible for the formation of ergosterol and more than 200 distinct 24-alkyl side chain structures which act as essential growth factors for these organisms, suggesting an interesting alternative in the search for selective antifungals or antiparasitic drugs. By this rationale, SMT inhibitors should only affect fungal or parasitic cells, without damaging cells from higher eukaryotes, therefore bypassing any undesirable clinical side effect [5,6,8].

Azasterols as Inhibitors of the SMT

In general, the search has been oriented toward steroids with one or more heteroatom in the side chain usually nitrogen to replace either C-24 or C-25 (azasterols), in the hope that they would mimic structurally and electronically the high-energy intermediates (carbocation) generated at C-25 during the methylation reaction and consequently, bind tightly to the SMT [6,8].

Although many side chain azasterols have been synthesized, few have been successful in the inhibition of the SMT or possess any antifungal or antiparasitic activity [9]. Indeed, in the 90’s was reported by the first time the 22,26-azasterol or AZA-I as a SMT inhibitor, an synthetic analogue of solacostigmina a natural product from solanum alkaloids, who caused a significant activity against T. cruzi the causative agent of Chagas disease and Pneumocystis carinii the causative agent of Pneumocystosis [10,11]. This activity was associated with depletion of 24-alkyl sterols of the pathogen agents, showing that they perform essential roles for multiplications in these organisms [10,11]. In view of the important effects displayed by AZA1, other important works were carried out either in different pathogenic organisms, acting singly or in combination with other SBIs [12-16]. These entire results encouraged us to move forward in the structural study and modification of this inhibitor, to improve its activity [17]. These studies showed some structure-activity correlation, that allowed us to synthesize the 22-piperidin-2-il-pregnan-22(S),3ß-diol (AZA-2) and 22-piperidin-3-il-pregnan-22(S),3ß-diol (AZA-3) analogues of AZA-I [18]. AZA-3 was the most active against Paracoccidiodes brasilensis (Y phase) and was also demonstrated that this significant effect was caused by the inhibition of the SMT [19].

Recently, were reported four new sterol-hydrazone derivatives; 20-hydrazone-imidazol-2-yl-5α-pregnan-3ß-ol (H1), 20-hydrazone-pyridin-2-yl-5α-pregnan-3ß-ol (H2), 22-hydrazone-imidazol-2-yl-5-colen-3ß-ol (H3), 22-hydrazone-pyridin-2-yl-5-colen-3ß-ol (H4) and its metal complex derivative with copper(II), gold(II) and platinum(II) as a new SMT inhibitors [20-23]. All of them were tested against leishmania parasites, and pathogenic fungus [20-23]. The results showed that the pathogenic microorganisms were susceptible to the four sterols hydrazones, being H3 the most active and less cytotoxic. The antiproliferative effects were associated to the inhibition of the SMT. Additionally; the metal-H3 complexes were more active than H3 along on the leishmanial parasite and fungal cell [21-23]. The
outcome indicate that our rational strategy has been well oriented to develop new antifungal and antiparasitic drugs.

Conclusion

Although no commercial drugs have evolved over the last 40 years of research on the field of azasteroles as antifungal or antiparasitic, some promising substances have been discovered or developed. In many cases, good to excellent in vitro results have been obtained and even some in vivo data point towards possible therapeutic value. Up to now, azasteroles have not been able to push into the market of the chemically more simple and better known standard antifungals or antiparasitic. However, with the emergence of more and more resistant fungal and parasitic strains, combined with the rising number of patients endangered by parasitic and fungal infections, the need for safe and effective antifungal or antiparasitic will get greater. These new therapeutics could be azasterols or derivatives thereof. The foundations for such an application have been well-aid by the considerable basic research on azasteroles described in this article.

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Conflict of Interest

None.

References