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Comparative molecular modelling of biologically active sterols

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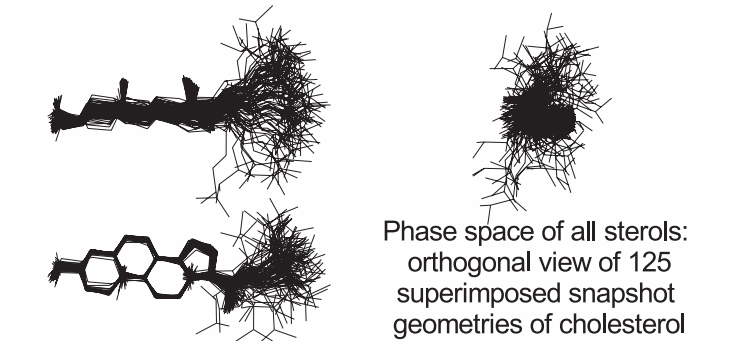
HIGHLIGHTS

- Phase space occupied by six sterols was defined using the molecular dynamics method.
- Statistical analysis of the data obtained was performed for detailed comparison.
- The results show similarity of the conformational spaces of all the tested sterols.
- Differential sterol-drug affinity is not mainly caused by conformational diversity.

GRAPHICAL ABSTRACT



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ABSTRACT

Membrane sterols are targets for a clinically important antifungal agent – amphotericin B. The relatively specific antifungal action of the drug is based on a stronger interaction of amphotericin B with fungal ergosterol than with mammalian cholesterol. Conformational space occupied by six sterols has been defined using the molecular dynamics method to establish if the conformational features correspond to the preferential interaction of amphotericin B with ergosterol as compared with cholesterol. The compounds studied were chosen on the basis of structural features characteristic for cholesterol and ergosterol and on available experimental data on the ability to form complexes with the antibiotic. Statistical analysis of the data obtained has been performed. The results show similarity of the conformational spaces occupied by all the sterols tested. This suggests that the conformational differences of sterol molecules are not the major feature responsible for the differential sterol – drug affinity.

Introduction

Cellular membranes of eukaryotic organisms contain various sterols which potently influence membrane properties (Fig. 1). Cholesterol is found in mammalian cell membranes while ergosterol is a major fungal sterol. It has been evidenced that both these sterols are targets for antifungal polyene macrolide antibiotics like amphotericin B (Fig. 2) [1–5]. The relatively specific antifungal action of amphotericin B is thought to be based on its greater affinity to fungal ergosterol than to mammalian cholesterol. The amphotericin B (AmB) – sterol complex formed causes lethal membrane permeability changes.

Elucidation of molecular mechanisms of selective action of AmB is very important for the rational modification of this valuable antifungal antibiotic towards development of a modified product with diminished animal toxicity.

The only dissimilarities between cholesterol and ergosterol are two additional double bonds located in the ring system and in the side chain and an additional methyl group in the side chain of the latter sterol (Fig. 1). The structural differences between the sterol

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molecules are thus relatively small. To get more information on possible molecular reasons for the differential affinity of amphotericin B to both these sterols we have examined the sizes and ranges of the conformational spaces occupied by cholesterol, ergosterol, and related sterols (Fig. 1). It has been postulated in earlier paper that the preferential binding of amphotericin B to ergosterol might be related to the preferred conformation of the sterol, especially the mutual position of the side chain and the mean plane of the ring system [6]. In the present studies we have focused on the behaviour of side chains of a selected set of sterols taking into account two dihedral angles α, β (Fig. 1) which describe the most mutual position of the chain in relation to the ring system.

All computations have been carried out for the molecules in vacuum. Such calculations are considered to be a reasonable approximation of the lipophilic membrane environment in which sterols are found. They are fast and do not require much computer resources.

We could not make much use of the conformations of cholesterol and, in particular, ergosterol derived from X-ray data. The crystal data in the case of cholesterol indicates a few different conformations present in unit cell [7–9]. In addition, geometry and dynamics of molecules stacked in crystalline state may differ from that of molecules floating freely in water or in biological membranes. Moreover, the X-ray data for ergosterol are of poor quality [10]. Thus, there is no possibility to determine statistically most favourable conformations on the basis of this data.

We selected six various sterols for computations: cholesterol, ergosterol, 7-dehydrocholesterol, dihydrocholesterol, β-sitosterol and stigmasterol (Fig. 1). Their molecular properties were compared. The additional four sterols to be studied were selected on the basis of structural characteristics related to cholesterol or ergosterol and available experimental biophysical data on amphotericin B – sterol interactions [11].

Comparative studies presented in this paper were performed with the use of molecular dynamics methods. It is rather apparent that the ring system of sterols is relatively rigid and takes similar molecular shape in all steroids; consequently we focused only on the conformational spaces occupied by the sterols' side chains which were quantified into subspaces corresponding to several stretched or bent geometries.

Methods

Geometries of ergosterol and cholesterol were obtained from crystallographic data on cholesterol [7–9] and ergosterol [10]. Hydrogen atoms with standard geometry were assigned to X-ray structures. Geometries of the phytosterols were built with the use of SYBYL molecular modelling suit [12]. The structures created have been subsequently refined using the semiempirical AM1 method covered by the MOPAC 2000 package [13]. Except for the hydroxyl protons hydrogen atoms were removed after refinement.

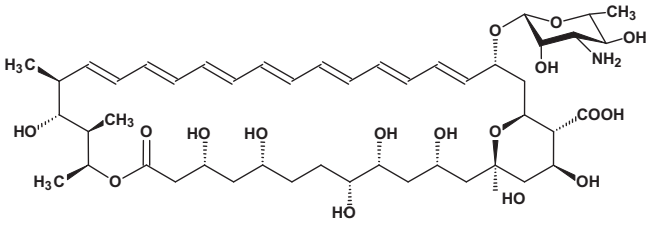

Fig. 2. Structure of amphotericin B.

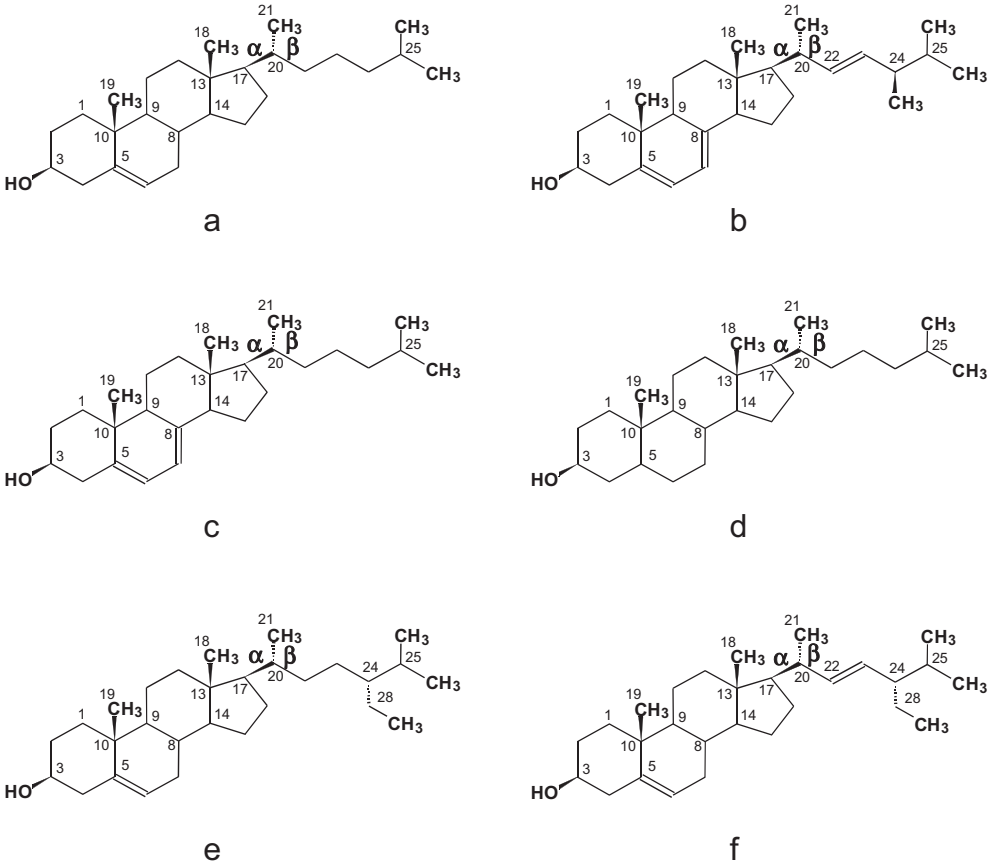

Fig. 1. Chemical structure of cholesterol (a), ergosterol (b), 7-dehydrocholesterol (c), dihydrocholesterol (d), β-sitosterol (e), stigmasterol (f).