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MOLECULAR PROPERTIES RELEVANT TO BIOAVAILABILITY OF TIOCONAZOLE AND ITS DERIVATIVES

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The molecular properties of the active substance have an impact on their pharmacokinetics and bioavailability (1). To simplify proof of bioequivalence of generics with reference to medicinal products various exemption procedures and rules were implemented. One of them is substitution of *in vivo* bioequivalence study by *in vitro* dissolution similarity determination. This makes a base for so called Biopharmaceutical Classification System (BCS) (2-4). The main two properties are considered: solubility and permeability. Experimental determination of these parameters is cumbersome and frequently impossible. Therefore, in our laboratory we suggested use of theoretically derived determinants as a tool for fast chemical substance classification within BCS (5, 6) and it appeared that they are promising tool for fast chemical substance classification within BCS. The water solubility determination can be efficiently made based on free enthalpy of solvation (ΔG), while permeability can be described by the hydrophobic properties in the first approximation. The hydrophobic properties can be established based on solvation energy in solvents with different polarity. In this study we focused on the important from therapeutic view-point antimycotic medicinal products containing the imidazole ring, i.e. for azole antifungal agents, the largest class of synthetic antimycotics. They are frequently used both systemically and topically in the treatment of systemic Candida infections and mycosis (7, 8) and this use is dependent on the properties of particular agent.

RESULTS AND DISCUSSION

At the first stage of calculations, for each molecule the conformational space was searched for the lowest energy state using Monte Carlo approach. The lowest energy conformers were used as an input for further structure optimization with *ab initio* HF methods at the 6-31G level. In such energy minimum for each structure (Figures 1-4) the ΔG values of solvation were computed both in chloroform and in water medium.

The choice of chloroform medium was selected instead of octanol due to a lack of parametrization for

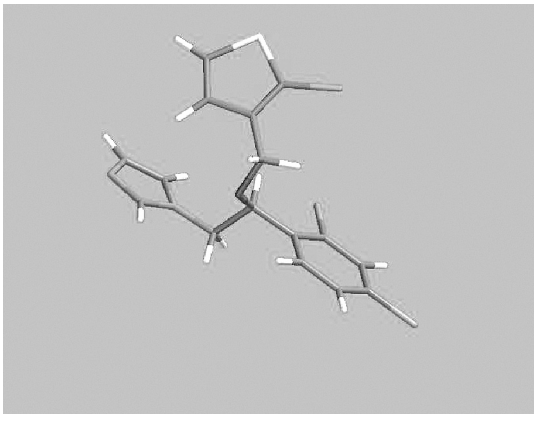

Figure 1. The lowest energy structure of Tioconazole.

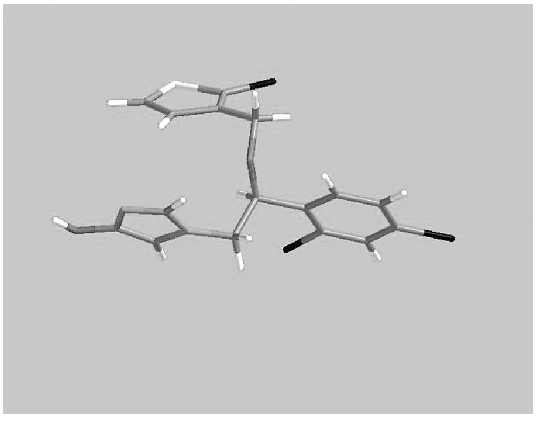

Figure 2. The lowest energy structure of Tioconazole – OH.

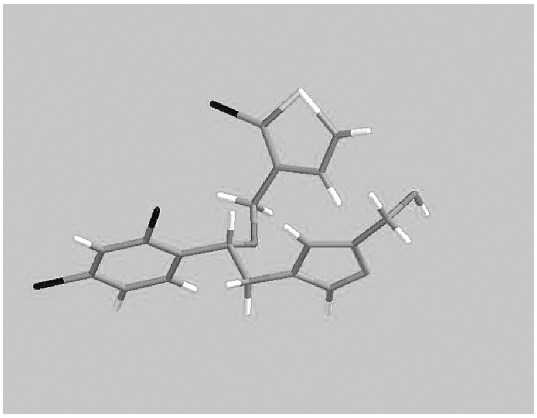

Figure 3. The lowest energy structure of Tioconazole – CH_2OH.

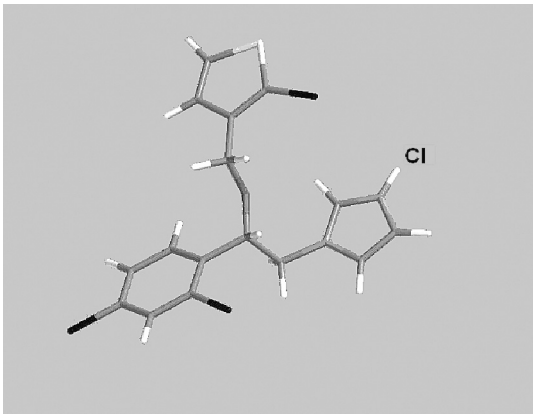

Figure 4. The lowest energy structure of Tioconazole HCl.

octanol within Gaussian package. An additional argument for, was to simulate solvation with the dielectric constant close to that of octanol (4.9 vs. 5.12).

In octanol, however, the hydrogen bonding can contribute to the solvent-solute interaction but in solvation models implemented in Gaussian package the other than electrostatic interactions are not considered. Therefore, the hydrogen bonding properties do not discriminate chloroform and octanol.

The ΔG of solvation by water and chloroform molecules was calculated at the Hartree-Fock 6-31G* level using SCI-PCM model (9, 10). For tioconazole and -OH, $-CH_2OH$ ring derivatives and hydrochloride the values of ΔG of solvation by water molecules appeared discriminative. The -OH and $-CH_2OH$ substituents were selected to separate negative and positive charge of the molecule as a possible source of better interaction with polar medium.

The values are as follows: tioconazole ΔG = -0.51 kcal/mol, -OH in 4 position of imidazole ring ΔG = -3.25 kcal/mol, $-CH_2OH$ in 4 position of imidazole ring ΔG = -1.58 kcal/mol, hydrochloride ΔG = -44.17 kcal/mol. In chloroform, the solvent with dielectric constant similar to octanol, the respective values of ΔG are: -5.25 kcal/mol -2.72 kcal/mol, -3.32 kcal/mol and -27.17 kcal/mol. The analyzed structural changes give hints to synthesis of compounds with better pharmacokinetic properties of antimycotic agents, the -OH substituent appears to be a promising way of parent structure modification.

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