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MOLECULAR PROPERTIES OF OXYCONAZOLE AND TIOCONAZOLE AS THE CRITERIA FOR THEIR BIOAVAILABILITY ESTIMATION

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Abstract: The use of hydration and solvatation free enthalpies (ΔG_h, ΔG_s) as parameters describing water solubility and permeability of drugs was proved to be suitable quantities. The free enthalpies of hydration and solvation by water and chlorobenzene molecules at the Hartree-Fock (6-31G*) level applying PCM model were calculated for oxyconazole and tioconazole. The oxyconazole and tioconazole differ in water and chlorobenzene solubility, what is reflected in calculated ΔG values and electrostatic potential. These characteristics discriminate both compounds with respect to water solubility and permeability. It may be concluded that the ΔG values of hydration and solvation adequately reflect the water solubility and permeability of oxyconazole and tioconazole.

Keywords: oxyconazole, tioconazole, bioavailability

To simplify proof of bioequivalence of generics with reference 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 is a background of the so called Biopharmaceutical Classification System (BCS) (1). In that scheme the main two properties are considered: solubility and permeability. Experimental determination of those parameters is, however, cumbersome and frequently unfeasible. Therefore, in our laboratory we declared theoretically derived determinant as a tool for fast chemical substance classification within BCS (2).

A widely used parameter describing the hydrophobic and at the same time hydrophilic properties of drug molecules is the logarithm of the partition coefficient determined for an octanol/water system (logP) (3). However, we argued that the experimental determination of logP frequently poses many difficulties making this procedure time consuming or simply unfeasible. Especially, it takes place when a solute exhibits inclination to a dimerization in nonpolar phase (octanol) and/or to a dissociation in polar phase (water). Other approach to the logP determination relies on the theoretical calculation by a proper computer program. It is obvious that currently there is the need of searching for some quantity which would be satisfyingly reflecting the lipophilic and/or hydrophilic properties of drug molecules. This can be ΔG of solvation as a quantity which has the adequate properties. Therefore, ΔG can be accepted as the measure of solubility since it is the direct description of the solute-solvent interaction. Additionally, the calculated electrostatic potential around a solute molecule can serve as a supplementary parameter enhancing conclusion derived from ΔG value. We can state that water solubility determination is based on ΔG_h of hydration, whereas a permeability is determined by ΔG_s of solvation in nonpolar solvent.

RESULTS AND DISCUSSION

Here we present results of calculations concerning important from therapeutic view-point antimycotic medicinal products oxyconazole and thioconazole. The free enthalpies of hydration (ΔG_h) and solvation by chlorobenzene (ΔG_s) were calculated for both molecules at the Hartree-Fock (6-31G*) level using PCM model (4, 5).

For oxyconazole and tioconazole these values are: ΔG_h = -2.30 kcal/mol, ΔG_s = 4.84 kcal/mol and ΔG_h = -0.51 kcal/mol, ΔG_s = 5.25 kcal/mol, respectively. These results are referred to the calculated values of electrostatic potential which fall within the range from -53.74 to 34.16 kcal for oxyconazole and from -53.01 to 33.66 kcal. for tioconazole The higher extreme range of potential around the oxyconazole molecule points out that this molecule stronger interacts with water than tioconazole. The obtained results are in full agreement with experi-

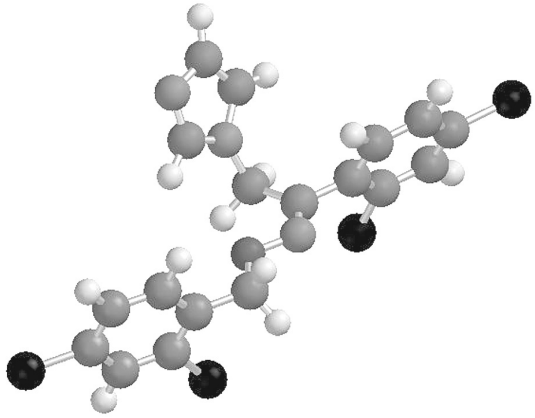

Figure 1. The lowest energy structure of oxyconazole.

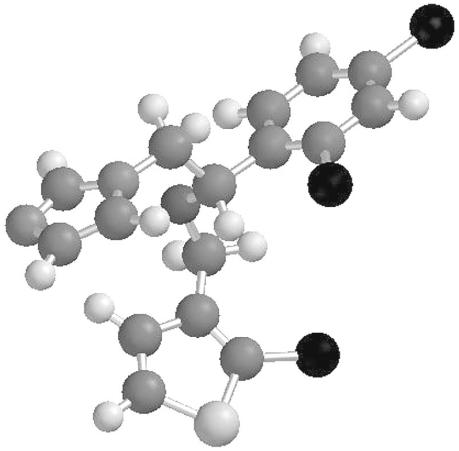

Figure 2. The lowest energy structure of tioconazole.

mental solubility data. The all calculated ΔG values unequivocally point out that solvation free enthalpy is a good determinant of drug solubility and permeability. Thus, ΔG of solvation can be a suitable estimator of logP for drugs of interest. The generalization of this conclusion may concerns other compounds used as active ingredients in medicinal products.

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