The Importance of Keto-Enol Forms of Arylpropanoids Acting as Antifungal Compounds

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Abstract: We report here the importance of a keto-enol equilibrium of an arylpropanoid series acting as antifungal agents. An interesting relationship between ln MIC, ΔE enolization and net atomic charges was found. Two compounds were synthesized and their MIC evaluated in order to prove the above relationship.

Introduction

In the course of our screening program for antifungal activity, we reported that 8.O.4'-neolignans possess a moderate but significant antifungal activity against dermatophytes [1,2]. We performed a systematic study of antifungal properties of arylpropanoids portions and structurally related compounds [3], in order to gain insight into structural requirements for their activity. We found that some arylpropanoids possess strong antifungal effects displaying a biological behaviour similar or better than the currently used antifungal agents such as amphotericin B and ketoconazole.

Structure-activity relationship studies indicated that the C=O group was an indispensable moiety for the antifungal activity of arylpropanoids as well as the apparently necessary α-hydrogen. These results suggest that keto-enol tautomerization could possibly play a role in the bioactivity of antifungal arylpropanoids. The present work reported here has three phases:

1- An exhaustive conformational and electronic study of this series using different levels of theory.

2- A correlation study between antifungal activity and computed parameters (ΔE of enolization and net atomic charges).

3- Synthesis and evaluation of antifungal activity of compounds [a] and [b] to corroborate the results obtained on steps 1 and 2.
Experimental

Chemistry

Compound [a] 2-methyl-2-chloro-1-methylenedioxypripiophenone was synthesized via a chlorination reaction with Cl₂Cu, ClLi in DMF, 16 hs., 120ºC. Compound [b] 1-ethylendioxy-1-methylenedioxyphenyl-2-chloro-propane was prepared from [a] by reaction with ethylene glycol in dry benzene catalyzed by 10-camphorsulfonic acid in a Dean and Stark apparatus, 16 hs.

Calculation Methods

The calculations were performed at semiempirical level, using AM1 from MOPAC 7 program, and \textit{ab initio} levels using the GAUSSIAN 94 program system.

Results and Discussion

From all the methods employed, the keto-forms were computed to be more stable than the enol forms. Also the cis-endo forms of the enol were systematically more stable than the other forms [4]. On the other hand, a correlative trend was observed when the ln [MIC] values were plotted against computed molecular properties, such as $\Delta E$ of enolization and net atomic charges. These results suggest that keto-enol tautomerization may be one of the mechanism of antifungal activity.

In order to corroborate this hypothesis two structurally related compounds, which could not undergo keto-enol tautomerization were synthesized. The experimental results are an additional support for our hypothesis

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References and Notes