

Membrane insertion properties of ketoconazole derivatives: Elucidating the path to fight drug resistant fungal infections

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The addition of a diphenylphosphine or diphenylphosphine oxide motif to the antifungal ketoconazole (**Ke**) resulted in the derivative **KeP** ($\text{Ph}_2\text{PCH}_2\text{-Ke}$) or **KeOP** ($\text{Ph}_2\text{P(O)CH}_2\text{-Ke}$) characterized by improved antifungal activity which could be related with their increased membrane permeabilizing ability. To tackle how these motifs modulate the compounds-membrane interaction, ultimately leading to improved antifungal activity, we studied **4MP** ($\text{Ph}_2\text{PCH}_2\text{-pip-C}_6\text{H}_4\text{-4-OMe}$) and its oxide (**4MOP**) – two structurally simplified analogs of **KeP** and **KeOP** in solution and their interaction with 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) large unilamellar vesicles. The mole fraction membrane/water partition coefficient determined through their intrinsic fluorescence was $(4.29 \pm 0.17) \times 10^4$ and $(5.21 \pm 0.82) \times 10^5$, showing that the interaction of these hydrophobic analogs with the membrane is less favorable than for **KeP** and **KeOP**. Fluorescence quenching by acrylamide, revealed that **4MP** and **4MOP** lie near the surface of the lipid bilayer, in contrast with **Ke**, **KeP**, and **KeOP**. Furthermore, a permeability assay with carboxyfluorescein showed that neither **4MP** nor **4MOP** change markedly the permeability of POPC membranes and that **KeOP** induced the fastest and most extensive membrane leakage. All the results show that the simultaneous presence of **Ke** and the phosphine moiety affords a deep and effective membrane interaction, but the oxygen involved in a P=O bond within the phosphine oxide is crucial to observe significantly increased membrane affinity and permeabilization. The use of fluorescent probes Laurdan and DPH further revealed that **KeOP** enhances water penetration into the hydrophobic core of the POPC bilayer, explaining at the molecular level the highest efficiency of this compound to permeabilize the membrane and antifungal activity, particularly against ketoconazole-resistant strains.

Słowa kluczowe

Drug-membrane interaction, Antifungal agents, Fluorescence spectroscopy, Diphenylphosphinomethyl derivatives, Phospholipid bilayer

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