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New anticandidal Cu(I) complexes with neocuproine and ketoconazole derived diphenyl(aminomethyl)phosphane : luminescence properties for detection in fungal cells.

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Streszczenie

The search for new antifungals is very important because the large genetic variation of pathogenic organisms has resulted in the development of increasingly effective defense mechanisms by microorganisms. Metal complexes as potential drugs are nowadays gaining interest, because they are characterized by accessible redox states of metal centers and a plethora of easily modifiable geometries. In this work we present two new copper(I) iodide or thiocyanide complexes with 2,9-dimethyl-1,10-phenanthroline (dmp) and a diphenylphosphane derivative of ketoconazole (**KeP**), where a ketoconazole acetyl group is replaced by the $–CH_2PPh_2$ unit, [CuI(dmp)**KeP**] (**1-KeP**) and [CuNCS(dmp)**KeP**] (**2-KeP**) – their synthesis and structural characteristics. The analysis of the intrinsic fluorescence of the ketoconazole moiety in the coordinated **KeP** molecule revealed that the copper(I) central atom does not act as a quencher and the observed decrease of fluorescence intensity is a result of a strong inner filter effect caused by the presence of the CuXdmp unit. Moreover, the complexes exhibit a remarkable MLCT (metal–ligand charge transfer) based phosphorescence with the emission maximum at 600–615 nm in aqueous media, which probably results from the formation of dimers and higher order oligomers in the most polar solutions. Both complexes proved to be promising antifungal agents towards *Candida albicans*, showing a relatively high efficiency towards the fluconazole resistant strains with – *CDR1* and *CDR2* or *MDR1* efflux pump overexpression, which suggests that they overcome at least partially these defense mechanisms. Simulations of docking to the cytochrome P450 14α-demethylase (the azoles' primary molecular target) suggested that the compounds studied were rather incapable of competitively inhibiting this enzyme, unlike ketoconazole and the **KeP** ligand. On the other hand, the phosphorescence in aqueous solutions allowed recording the confocal micrographs of the complexes which showed that both of them are situated in spherical structures inside the cells, most likely in the vacuoles.

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