1 CONCLUSIONS

In the context of Medical Mycology today, the development of new more effective antifungal agents is a priority. In fact, there are still only about six drugs in use to treat invasive fungal infections, concretely the polyene amphotericin B (including its new lipidic formulations), the antimetabolite flucytosine, the triazoles fluconazole, itraconazole, and voriconazole, and the echinocandin caspofungin. Simultaneously, the incidence of invasive opportunistic mycoses has been increasing steadily with the increasing number of immunocompromised patients, caused both by HIV (human immunodeficiency virus) infection and AIDS and the development of medical techniques, particularly referring to oncology or transplant patients.

In this setting, the relevance of the development of new antifungal agents and, hence, our work presented here, is easily understandable. The group of the acyloxymethylated incrustoporin derivatives is now in a higher stage of development, after being previously studied concerning structure-antifungal activity relationship and tuning of antifungal activity. Our work has shown the best derivatives from the group, compounds LNO6-22, LNO15-22, and LNO18-22, to have broad spectrum *in vitro* antifungal activity and high potency, inhibiting growth of a variety of pathogenic yeasts and moulds at very low concentrations, including, importantly, fluconazole-resistant strains. Although the differences in activity between the three compounds are quite small, it has also been concluded that LNO18-22 is the most potent of the three. Interestingly, however, the study of the inhibition of filamentation in *C. albicans* at subinhibitory concentrations has shown LNO6-22 to be the strongest inhibitor, yielding results comparable to the ones produced by amphotericin B. Besides that, the flow cytometric studies of LNO18-22 have shown this compound to have a potent fungicidal activity against *C. albicans*. It was found to cause plasmatic membrane depolarization, metabolic activity arrest, and, ultimately, disruption of the plasmatic membrane integrity, either by a direct interaction or by secondary consequences of metabolic impairment, leading to ion channel or pore formation. Simultaneously, the results with the reference drugs amphotericin B and fluconazole confirmed the expected results from the knowledge of their mechanisms of antifungal action.

Regarding the remaining 10 chemical groups of compounds tested, four could be highlighted for producing better results, including compounds with high activity against some of the eight test fungal strains. Concretely, these groups were the quinoline derivatives, the 4-substituted phenylguanidinium salts, the azo dye organotin(IV) compounds, and the quinaldine derivatives, yielding a group of about 10 to 15 compounds overall with very promising potency. The remaining of the chosen groups showed usually moderate activity, justifying their presence in

this report by the potential to yield, after tuning of their antifungal activity, more potent derivatives than the ones obtained so far.

In conclusion, the incrustoporin derivatives are the most promising class of agents, justifying a serious investment in further development. The remaining groups include a series of compounds that require further work in cooperation with the organic chemistry laboratory in order to produce agents with firmer potential.