P05 - SYNTHESIS AND SAR STUDIES OF NEW 3-METHYL-5-(5-PROPYL-1*H*-1-R'-3-PYRAZOLYL)-1*H*-1-R-4-NITROSOPYRAZOLES AS ANTIMICOTIC AGENTS.

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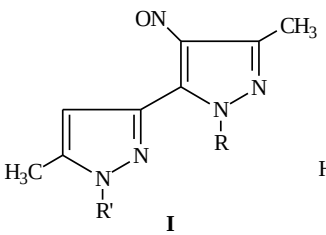
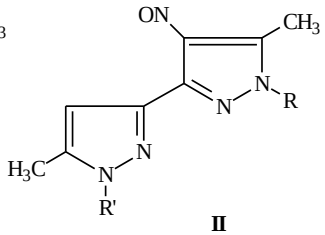
Many ubiquitous yeast are primarily pathogens for immunocompromised patients, individuals with AIDS and organ transplanted are at high risk of cryptococcosis and candidiasis.
In this setting, fungal infections are particularly difficult to treat because antifungal therapy usually does not eradicate the infection and require lifelong treatment with antifungal drugs.
Consequently, the need for novel antifungal agents for opportunistic infections is apparent in light of significant problems associated with current drugs and makes the development of new drug entities all more urgent.
We have reported that some 3-(3-alkyl-4-nitroso-1*H*-5-pyrazolyl)-5-R-isoxazoles [1] and the isomeric 5-(1-alkyl-4-nitroso-1*H*-3-pyrazolyl)-3-R-isoxazoles [2] showed in vitro potent antifungal activity at non cytotoxic concentrations.
This antifungal activity was correlated to: 1) the interaction of the isoxazolic nitrogen with the alkyl group bound to the pyrazolyl nitrogen; 2) the *cis* or *trans* configuration adopted by the nitroso group with respect to the alkyl chain bound to the pyrazolic nitrogen and perpendicularly folded to the molecular plane.
To verify this hypothesis, we synthesized compounds in which the isoxazole was substituted by a pyrazole moiety, leading to the new isomeric series **I** and **II**.



I



II

R':$CH_2CH_2CH_3$; R: a=H, b=CH_3; c=CH_2CH_3

The title compounds tested *in vitro* for antifungal activity against C. Neoformans and C. Krusei, displayed an interesting antifungal activity, in particular compound **Ib** was 2 and 32 fold more potent than Amphotericin B and Fluconazole, respectively, against *C. krusei,* fungus with intrinsic resistance to many of antifungal azoles
These results suggest that, depending on the heterocyclic molecule bound to the 5 position of 1*H*-1-R-4-nitrosopyrazoles, it is possible to modulate the antifungal activity of 4-nitrosopyrazoles.
In vitro metabolism studies and in vivo assay are in progress for all described compounds.

References

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