SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW 1-R-3-(2-PIRIDYL)- 4-NITROSO- 5-CARBOXIETHYL-1*H*-PYRAZOLES.

Stefania Aiello[a] , Carmelo Massimo Maida[b], Fabio Venturella[b], Diego Planeta[c] Marco Giammanco[d], M.Milici[b]

[a] *Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari, Università degli Studi di Palermo*
[b]*Dipartimento di Scienze per la Promozione della Salute G. D' Alessandro, Università degli Studi di Palermo*
[c]*Dipartimento dei Sistemi Agro-Abientali,Università degli Studi di Palermo*
[d] *Dipartimednto di Studi Giuridici, Economici, Biomedici e Psicosociopedagogici delle Scienze Motorie e Sportive, Università degli Studi di Palermo*

Corresponding author: Stefania Aiello, Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy; tel:+39.091 23896802; email: stefania.aiello@unipa.it

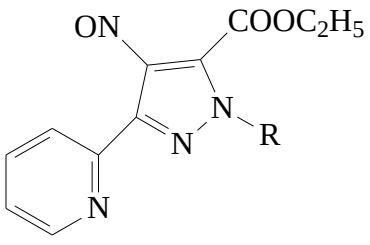
In recent years, epidemiological studies confirm the significant impact on human health by infections caused by pathogenic fungi. In fact, although the Candida genus **is commensal and** a constituent of the normal gut flora, it is responsible for opportunistic infections and can become pathogenic secondary to predisposing factors related to the host, like a comprimised immune system (AIDS, anti-cancer therapy, transplants), excessive prophylaxis with antimicrobial agents, and use of invasive catheters. Large-scale surveillance for fungal infections has demonstrated an increasing incidence of drug-resistant fungal pathogens. As a matter of fact, a significant number of fungi species (especially Candida glabrata and Candida krusei) exhibited primary resistance to Fluconazole or were less susceptible to Amphotericin B.

Furthermore, as a consequence of the toxicity of the currently used polyene antifungal drugs, which leads to interrupt the therapy, and the emergence of *Candida* species resistance to azole-based agents, there is an urgent need for developing alternative drug therapies.

In our previous study we have disclosed the synthesis and antifungal activity of a series of 4-nitrosopyrazoles that mainly displayed *in vitro* potent antifungal activity at no cytotoxic concentrations and that some of these compounds were 4 times more potent than Amphotericine B and Fluconazole respectively against *Cryptococcus neoformans* and *Candida Krusei* [1-4]

As part of our Structure Activity Relationships studies, we were interested in learning the influence of the steric and electronic effects of the substituent in position 5 of the 4-nitrosopyrazoles which had already showed powerful antimycotic activity.

Therefore, we synthetized title compounds and evaluated their antimycotic activity (fig1).



R: **a**=H, **b**= CH_3, **c**=C_2H_5

Fig 1. Synthetized compounds

The 5-carboxiethylester group has made the antimycotic actity dramatically decay, confirming the necessity, for a good antimicotic activity, of derivatives in which the position 5 is free or substituted with little groups as a methyl shown the best antifungal activity.

[1] E. Aiello, S. Aiello, F. Mingoia, A. Bacchi, G. Pelizzi, C. Musiu, M. G. Setzu, A. Pani, P. La Colla and M. E. Marongiu. Synthesis and Antimicrobial activity of New 3-(1-R -3-methyl-4-nitroso-1H-5-pyrazolyl)-5-methylisoxazole derivatives, Bioorganic and Medicinal Chemistry, 2000, 8, 2719-2728

[2] Stefania Aiello; Enrico Aiello, Marica Orioli, Marina Carini, 3-(1-R-3-methyl-4-nitroso-1H-5-pyrazolyl)-5-methylisoxazoles: a new class of antifungal compounds. In vitro metabolism by rat liver:LC and LC-MS studies. Convegno Nazionale, Sorrento 18-22 Settembre 2002.

[3] S. Aiello, E. Aiello and M. Milici: "Synthesis and Antifungal Activity of new 3(5)-methyl-5(3)-(2-thiophenyl) and -(2-quinolyl)-1H-1-R-4-nitrosopyrazoles.Part V". Polish-Austrian-German-Hungarian-Italian Joint Meeting on Medicinal Chemistry, Krakow, October 15-18, 2003

[4] Stefania Aiello, Antonio Macchiarulo, Maria Milici and Enrico Aiello, Sintesi e studi QSAR di nuovi derivati 3(5)-(2-X)-1R-1H-4-nitrosopirazoli: una classe di composti con potente attività antifungina in vitro. Parte VI XVII Convegno Nazionale della Divisione di Chimica Farmaceutica della SCI, Pisa 6-10 settembre 2004.