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Original article

Synthesis, biological evaluation and structure–activity correlation study of a series of imidazol-based compounds as *Candida albicans* inhibitors

Francesca Moraca [d, 1], Daniela De Vita [a, 1], Fabiana Pandolfi [a], Roberto Di Santo [a, b], Roberta Costi [a, b], Roberto Cirilli [e], Felicia Diodata D'Auria [c], Simona Panella [c], Anna Teresa Palamara [c], Giovanna Simonetti [c], Maurizio Botta [d, **], Luigi Scipione [a, *]

[a] Department of "Chimica e Tecnologie del Farmaco", Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185 Rome, Italy
[b] "Istituto Pasteur-Fondazione Cenci Bolognetti", Department of "Chimica e Tecnologie del Farmaco", Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185 Rome, Italy
[c] Department of "Sanità Pubblica e Malattie Infettive", Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185 Rome, Italy
[d] Department of "Biotecnologie, Chimica e Farmacia", "Università degli Studi di Siena", Via A. Moro 2, 53100 Siena, Italy
[e] "Dipartimento del Farmaco", Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy

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ABSTRACT

A new series of 2-(1H-imidazol-1-yl)-1-phenylethanol derivatives was synthesized. The antifungal activity was evaluated *in vitro* against different fungal species. The biological results show that the most active compounds possess an antifungal activity comparable or higher than Fluconazole against *Candida albicans*, non-albicans *Candida* species, *Cryptococcus neoformans* and dermathophytes. Because of their racemic nature, the most active compounds **5f** and **6c** were tested as pure enantiomers. For **6c** the (*R*)-enantiomer resulted more active than the (*S*)-one, otherwise for **5f** the (*S*)-enantiomer resulted the most active. To rationalize the experimental data, a ligand-based computational study was carried out; the results of the modelling study show that (*S*)-**5f** and (*R*)-**6c** perfectly align to the ligand-based model, showing the same relative configuration. Preliminary studies on the human lung adenocarcinoma epithelial cells (A549) have shown that **6c**, **5e** and **5f** possess a low cytotoxicity.

1. Introduction

Fungi infect billions of people every year and millions contract diseases that kill at least as many people as tuberculosis or malaria [1]. The highly fatal fungal systemic infections are supported mainly by *Candida albicans*, *Candida* species non *albicans*, *Cryptococcus neoformans* and *Aspergillus* spp. Superficial mucosal and cutaneous infections are mainly supported by *Candida* spp. and dermatophytes.

Despite the antifungal drugs used in clinical treatments appear to be diverse and numerous, to date few classes of antifungal agents are currently available to treat mucosal or systemic infections [2]. The largest family of antifungal drugs is represented by the azole compounds i.e. imidazoles (Miconazole, Econazole, Clotrimazole, and Ketoconazole) and triazoles (Fluconazole, Itraconazole, and the latest agents, Voriconazole and Posaconazole) (Chart 1) [3–5]. Azoles block fungal membrane ergosterol biosynthesis in the cell by inhibiting the activity of the lanosterol 14α-demethylase, the enzyme necessary to convert lanosterol to ergosterol. The active binding site of lanosterol demethylase contains a heme domain. Azoles bind with a nitrogen atom to the iron atom of the heme, preventing the demethylation of lanosterol [6]. The depletion of ergosterol and accumulation of 14α-methylated sterols disrupt the structure and many functions of fungal membrane leading to inhibition of fungal growth [7].

However, the treatment of invasive fungal diseases still remains unsatisfied as mortality rate, is unacceptable high [8]. Moreover, non-invasive infections, as onychomycoses, are often recurrent, chronic, and generally require long-term treatment with antifungal agents [9]. Hence, there is considerable urgency to discover new antimicrobial agents.

* Corresponding author.
** Corresponding author.
E-mail addresses: maurizio.botta@unisi.it (M. Botta), Luigi.scipione@uniroma1.it, luigi.scipione@fastwebnet.it (L. Scipione).
[1] These authors equally contribute to the work.

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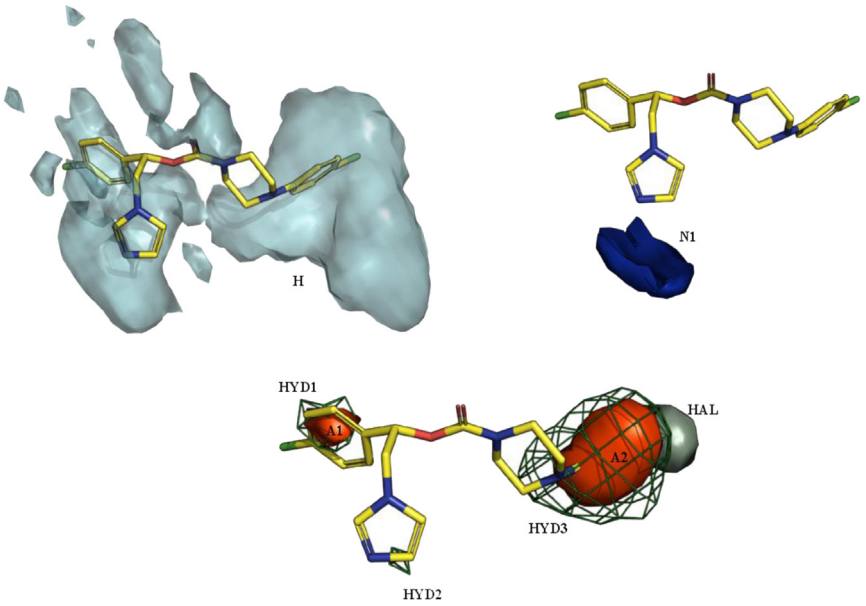

Fig. 1. Contour maps of the ligand-based model generated according to GRID MIFs. A: Cyan surface represents the shape that active compounds should match; B: N1 = blue lone pair nitrogen counter maps; C: HAL1 = grey halogen counter map; A–A2 = orange aromatic counter maps; HYD1–HYD3 = blue marine mesh hydrophobic counter maps. In yellow sticks is represented compound (*S*)-**5f**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

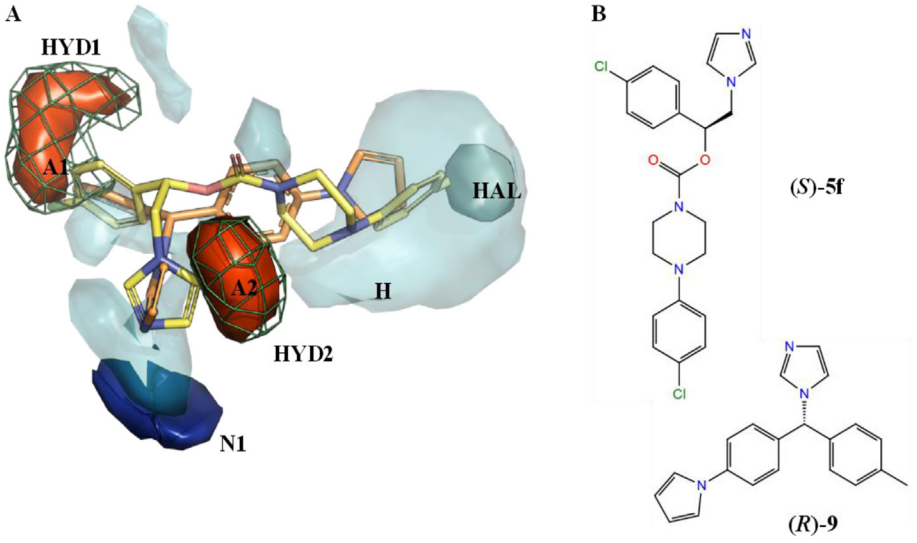

Fig. 2. A; contour maps of the LBM2 model are the same as described in Fig. 1. In yellow stick is represented compound (*S*)-**5f** and in orange stick compound (*R*)-**9**. Non-polar hydrogen atoms are omitted. B; structure of the most active compounds (*S*)-**5f** and (*R*)-**9**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We have previously reported the synthesis and *in vitro* evaluation of antifungal activity of a new series of 2-(1H-imidazol-1-yl)-1-phenylethanol derivatives [10]. Given the azole nature of those compounds, we hypothesized CYP51 as the target and focused on the design and synthesis of new imidazole derivatives, modifying the side chain of 2-(1H-imidazol-1yl)-ethyl carbamates or esters previously reported, in order to improve their antifungal activity [10]. All the new synthetized compounds were tested *in vitro* to evaluate the antifungal activity against different fungal strains and some of them showed high inhibitory activity. Up to date, there is no three dimensional structural information available on *C. albicans* (CACYP51) or other fungal CYP51 enzymes. Therefore, computational techniques were used to rationalize the experimental data. A ligand-based approach helped the discrimination between active and inactive compounds in fully agreement with the *in vitro* data, giving useful information about the functional groups that could be responsible for the antifungal activity.

2. Results and discussion

2.1. Chemistry

The racemic 2-(1*H*-imidazol-1-yl)-1-phenylethanols **1a**–**c**, the esters **2a**,**b** and **3a**–**g** and the carbamates **4a**–**c** were prepared as