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Research paper

Anti-*Candida* activity and cytotoxicity of a large library of new *N*-substituted-1,3-thiazolidin-4-one derivatives

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ABSTRACT

On the basis of the recent findings about the biological properties of thiazolidinones and taking into account the encouraging results about the antifungal activity of some (thiazol-2-yl)hydrazines, new *N*-substituted heterocyclic derivatives were designed combining the thiazolidinone nucleus with the hydrazonic portion. In details, 1,3-thiazolidin-4-ones bearing (cyclo)aliphatic or (hetero)aromatic moieties linked to the N1-hydrazine at C2 were synthesized and classified into three series according to the aromatic or bicyclic rings connected to the lactam nitrogen of the thiazolidinone. These molecules were assayed for their anti-*Candida* effects in reference to the biological activity of the conventional topic (clotrimazole, miconazole, tioconazole) and systemic drugs (fluconazole, ketoconazole, amphotericin B). Finally, we investigated the selectivity against fungal cells by testing the compounds endowed with the best MICs on Hep2 cells in order to assess their cell toxicity (CC_{50}) and we noticed that two derivatives were less cytotoxic than the reference drug clotrimazole. Moreover, a preliminary molecular modelling approach has been performed against lanosterol 14-α demethylase (CYP51A1) to rationalize the activity of the tested compounds and to specify the target protein or enzyme.

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1. Introduction

Opportunistic infections caused by common fungi such as *Candida* species are increasing in the last decades, affecting the lifestyle of the patients in a manner that is proportional to the degree of the infection, which in turn depends on the state of health of the patient [1]. In this regard, apart from the mucocutaneous mycosis with a functional epithelial damage, in patients suffering from serious diseases such as cancer, AIDS, or in those who received transplantation therapy or a broad spectrum antibiotic therapy, the immune system is compromised and this could lead to systemic mycosis [2]. Among fungal infections, recent data showed that there are many cases caused by non-*albicans* species [3–5] such as *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida sakè*. Particularly, candidemia caused by *C. glabrata* is rising [6], but some epidemiologic studies revealed that systemic candidiasis also provoked by *Candida albicans*, *Candida tropicalis* and *C. parapsilosis* is emerging, especially in South America [7–10].

With regard to the therapeutic strategy, the most used drugs belong to the class of azoles because of their good profile in terms of safety and bioavailability, but an increasing incidence of drug resistance occurs, due to the massive use of these azole-based agents [11]. Therefore, it is of primary importance to discover new candidates as antimycotic agents to cope with these alarming data and to manage systemic candidiasis especially in immunocompromised patients. Among novel compounds, thiazolidinones have proven to possess several biological properties, including the antifungal activity [12–16]. Furthermore, in our previous works we reported different scaffolds of [4-(4'-substituted-phenyl)thiazol-2-yl]hydrazine derivatives that have shown to be active as anti-*Candida* agents at very low micromolar concentrations, with low

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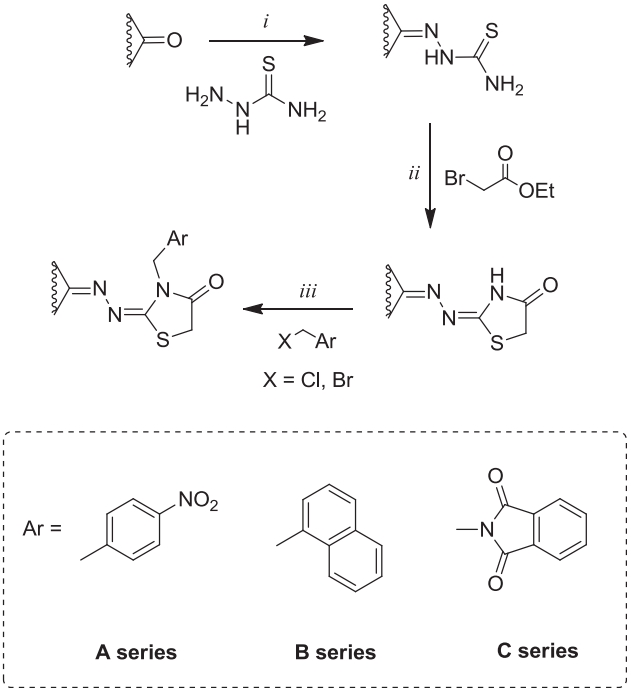
cell toxicity and a synergistic action with clotrimazole (Scheme 1). In detail, compounds containing aliphatic and cycloaliphatic groups at the hydrazonic portion and substituted phenyl rings at C4 of the thiazole showed very low MIC values especially towards *C. albicans* and *C. glabrata*. Similarly, other derivatives with heterocyclic and aromatic substituents at C2 such as furan, thiophene, pyridine, benzodioxole and naphthalene were very active towards *C. albicans* [17–21].

On the basis of these findings about the (thiazol-2-yl)hydrazine scaffold and taking into account the therapeutic importance of thiazolidinone nucleus, especially with regard to its antimycotic activity [22], we developed a large library of new compounds belonging to three different series (**1A**–**26A**, **1B**–**26B**, **1C**–**26C**) as promising anti-*Candida* agents combining three chemically different, but pharmacologically compatible moieties such as a thiazolidinone, a hydrazonic portion and an aromatic or a bicyclic substituent linked at the lactam nitrogen (Scheme 1).

According to the established guidelines of Clinical and Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST), we evaluated the susceptibility of twenty-two clinical *Candida* spp. strains to our compounds by determining their minimum inhibitory concentration (MIC) [23]. Finally, some of the compounds endowed with the best MICs were tested to assess their cell toxicity (CC_{50}) on Hep2 cells in order to evaluate their selectivity against fungal cells and we found that two derivatives were less cytotoxic than the conventional drug clotrimazole.



Scheme 2. Synthesis of the derivatives **1A**–**26A**, **1B**–**26B** and **1C**–**26C**. Reagents and conditions: (*i*) EtOH, acetic acid (cat.), rt; (*ii*) MeOH, CH_3COONa, rt; (*iii*) anhydrous acetone, anhydrous K_2CO_3, reflux.

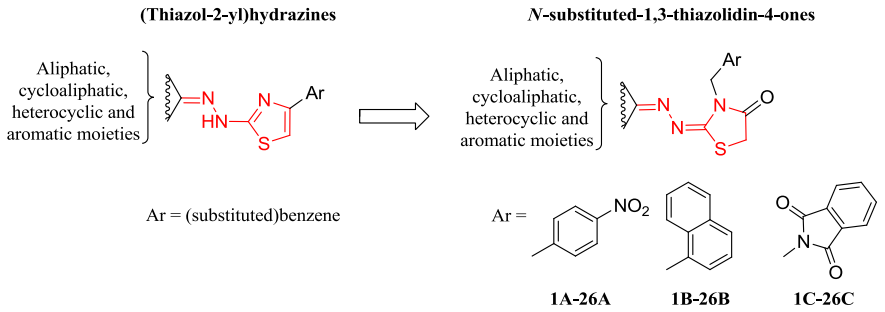
2. Chemistry

We designed novel 1,3-thiazolidin-4-one derivatives in which the portion supported by N1-hydrazine moiety consisted of aliphatic chains (C_3–C_8, linear, branched, unsaturated), cyclic structures, aromatic, bicyclic and (hetero)aromatic rings (furan, thiophene, benzene, pyridine, benzodioxole, and naphthalene), whereas the lactam NH at the 4-thiazolidinone nucleus was functionalized with electrophiles endowed with different steric features obtaining three scaffolds, each of twenty-six compounds, by reaction with 4-nitrobenzyl bromide (**A series**), 1-(chloromethyl) naphthalene (**B series**) and *N*-(chloromethyl)phthalimide (**C series**).

The synthetic strategy is outlined in Scheme 2. Several carbonyl compounds reacted directly with thiosemicarbazide in ethanol using catalytic amounts of acetic acid. The resulting thiosemicarbazones were cyclized with ethyl bromoacetate in methanol and sodium acetate to give the 1,3-thiazolidin-4-one derivatives [24,25]. Finally, by the reaction between the thiazolidinones and 4-nitrobenzyl bromide, 1-(chloromethyl)naphthalene and *N*-(chloromethyl)phthalimide in anhydrous acetone and potassium carbonate we obtained the *N*-functionalized 4-thiazolidinone derivatives (**1A**–**26A**, **1B**–**26B** and **1C**–**26C**). All the synthesized compounds were purified by column chromatography before characterization by spectroscopic methods (Experimental section) and elemental analysis (Supporting information).

3. Antibacterial and anti-*Candida* activity

Derivatives **1A**–**26A**, **1B**–**26B** and **1C**–**26C**, dissolved in dimethylsulfoxide (DMSO), were evaluated for their antibacterial activity. Organisms from routine clinical Gram-positive (*Staphylococcus aureus*, *Staphylococcus warneri*, *Streptococcus faecalis*, *Streptococcus α-hemolyticus*) and Gram-negative isolates (*Escherichia coli*, *Proteus mirabilis*, *Enterobacter* spp., *Klebsiella oxytoca*) from the respiratory tract were collected from specimens of patients at the Hospital 'Azienda Policlinico Umberto I°' (Sapienza University of Rome). The isolates were subcultured on a qualified medium to ensure purity. The isolates were identified by conventional methodologies; all isolates were subcultured to ensure optimal growth. The *in vitro* antibacterial activities of the compounds were determined by the



Scheme 1. Evolution from (thiazol-2-yl)hydrazine to *N*-substituted-1,3-thiazolidin-4-one scaffold.

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