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In vitro screening, homology modeling and molecular docking studies of some pyrazole and imidazole derivatives

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ABSTRACT

A series of synthesized compounds based on pyrazole and imidazole skeletons prepared by palladium catalysts via a one-pot reaction was screened to determine their inhibitory potency against the pathogen fungus *Fusarium oxysporum f.sp. albedinis (F.o.a)* and four bacteria strains namely *Micrococcus luteus*, *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli*. The obtained result showed that these compounds exhibit an efficiency antifungal action. Whereas, they showed a very weak antibacterial activity. The structure-activity relationship (SAR) Analysis and lipophilicity study demonstrates the presence of a strong relation between the structure of the ligands and the antifungal activity. On the other hand, a homology modeling and molecular docking study was carried out on the most active compounds against *F.o.a* fungus, in order to understand and determine the molecular interactions taking place between the ligand and the corresponding receptor of the studied target.

1. Introduction

The design and the discovery of new and different antifungal and antimicrobial agents has become one of the most important tasks of humanity. Much of the research program efforts are directed toward developing new potent drug molecules with low toxicity, high bioavailability and with less side effects. Indeed, recent developments in human and the appearance of resistance phenomena of pathogens to antibiotics constitute necessarily the determining factors in the development of new diseases infectious. Various pathogens (viruses, bacteria, parasites, microscopic fungi, etc.) can affect plants, animals and even humans; and can have serious consequences on the economy or even on human health.

Currently, and concerning the agricultural area, *Fusarium oxysporum* fungi are one of the most important fungal organisms of cultivated soils and they are identified as the most aggressive telluric fungi, causing wilting and rotting on many cultivated plant species [1–3]. In our days, about 80 forms of *Fusarium oxysporum* were identified as pathogenic, which include some special forms such as *Fusarium oxysporum f.sp apii*, which attacks celery and pea crops [4], *Fusarium oxysporum f.sp. cubense* which remains the most destructive diseases of banana worldwide [5]. While *Fusarium oxysporum f.sp. albedinis (F.o.a)* still remains the most dangerous agent among all pathologies of date palms [6]. Actually, *F.o.a*, causing Bayoud disease in date palms in Morocco, represents very serious human, social and economic risks particularly in North Africa. Bayoud has destroyed more than two thirds and still causes death of 4.5–12% of date palm groves in Morocco [7,8]. The fight against this fungus remains always limited to prophylactic measurements. In fact, the disinfection of the soil is very expensive, toxic and difficult; in addition, it is still incomplete due to the induction of resistant strains [9].

At the same time, many bacteria strains become more and more resistant to multiple types or classes of antibiotics currently used, such as *Staphylococcus aureus* and *Escherichia coli* bacteria that developed resistance to a large spectrum of antibiotics including Amikacin, Cephalothin, Cefpirome, Chloramphenicol, Gentamicin, Tetracycline and others [10]. Nowadays, over 70% of pathogenic bacteria that cause infections in hospitals are estimated to be resistant to at least one of the currently available antibiotics normally used to treat them [11]. Actually, this problem of resistance is due principally, in part to the inappropriate use of antibiotics in human medicine and the extensive use in the agricultural industry in the other part [12]. This crisis is a global issue, it is on the rise and some serious infections has become more difficult to treat. For this, new antibiotics that are active against resistant microorganisms are required to address the challenge.

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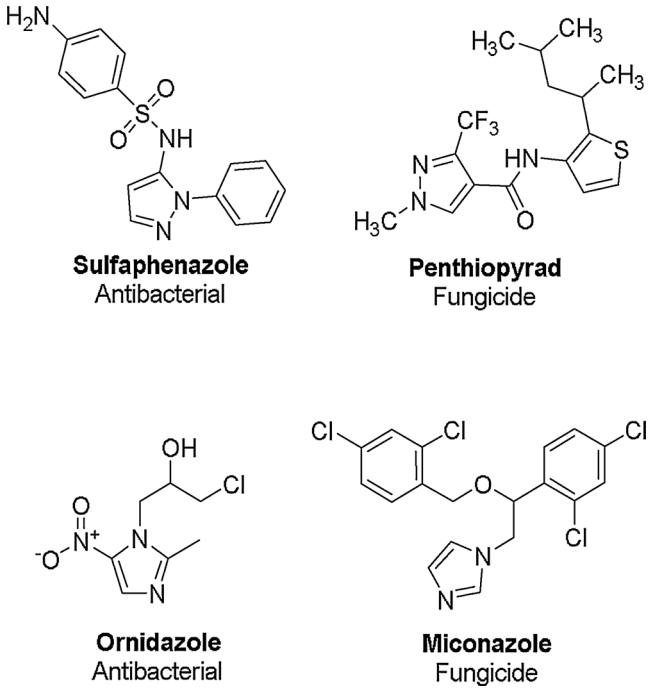

Fig. 1. Examples of bioactive pyrazoles and imidazoles as antibacterial and antifungal agents.

In light of this growing antibiotic resistance and in order to searching for new drugs against bacterial and fungi infections, many heterocyclic compounds have been the subject of extensive research works in the recent past; these include, for example, pyrazole and imidazole that belong to azole heterocyclic, an important group of heterocyclic compounds having a five-membered ring [13–18]. Actually, these scaffolds are an interesting building block in various biomolecules such as histidine (protein constituent), histamine and natural products (caffeine, pilocarpine alkaloid, etc.). In addition, these skeletons have been serving as an important versatile template to synthesize several classes of compounds as potential agents in agrochemicals and pharmaceutical industry such as Sulfaphenazole, Penthiopyrad, Ornidazole and Miconazole [19–22] (Fig. 1).

In particular, 4,5-diarylpyrazoles and 2,5-diarylimidazoles have received an interesting attention during last decades as potential biomolecules in drug discovery area. In fact, these structures have been found to be associated with a wide range of biological and pharmacological properties including antimicrobial, anti-inflammatory, antioxidant, antitumoral, antiparasitic, antidiabetic activities and others [23–28].

Molecular docking has become a powerful tool for structure-based drug discovery. It involves the prediction of ligand conformation and orientation within a targeted protein binding site residues. Currently, this approach has very improved processes used in the early stages of research and development (R & D) of new drugs. In fact, several marketed drugs come from a rational design based on docking strategies [29–32]. Nowadays, many improvements on docking tools have been made in the last years [33]. Today, more than 30 molecular docking software and many servers (commercial or free) is available for use [34]. The most frequently cited are: AutoDock [35], GOLD (Genetic Optimization for Ligand Docking) [36], FlexX [37], DOCK [38], MVD (Virtual Molegro Docker) [39] and MOE (Molecular Operating Environment) [40]. These programs allow rapid screening of large libraries of compounds and rely on specific algorithms using the principle of steric complementarity or molecular interactions to place a ligand in the active site of a target. Their protocol consists of two essential steps Docking/Scoring.

In this paper and in continuation of our research work on design and synthesis of active biological molecules, we report our contribution in this area by testing a series of 4,5-diarylpyrazole and 2,5-diarylimidazole derivatives for their antifungal and antibacterial potential against the growth of fungus: *F. oxysporum f.sp. albedinis* and four bacteria strains *Micrococcus luteus*, *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli*. The study was completed by a homology modeling and a docking study to understand the binding mode of the ligand to the active site of the target protein.

2. Material and methods

2.1. Chemistry

The target compounds were already described in the literature by Takfaoui et al. [41,42]. These compounds were prepared via a palladium-catalyzed C—H bond activation. In fact, this method gives a rapid access to the desired products and with high yields, it is also present important economic and ecological advantages in comparison to other classical cross-couplings such as Suzuki, Negishi, Kumada or Stille reactions [43–47]. Among the compounds that we have selected for this study, four are pyrazole-based (**1a-d**) and two are imidazole-based (**2a** and **2b**) derivatives (Fig. 2). Additionally, these compounds can be classified as symmetrical compounds according to the substitution pattern on the phenyl rings.

2.2. Biological assays

2.2.1. Antifungal activity screening

The agar diffusion method [48] was used to determine the antifungal potential of our compounds after some modifications. Briefly, after isolation and preparation of the *Fusarium* fungus; a sterilized solution (filtration using 0.45 µm millipore filters) of the tested compounds in DMSO as emulsifier at different concentrations (52.5, 105, 210 and 280 µg/mL) was mixed with potato dextrose agar (PDA) medium and put in a Petri plate which left standing for 10 min at room temperature. After that, mycelial discs of 6 mm diameter were taken from the peripheral growth of the pathogen (*F.o.a*) and placed into the middle of new Petri dishes containing PDA before the incubation at 28 °C for 7 days. DMSO- distilled water mixture was used as negative control. The half-maximal inhibitory concentration (IC_{50}) was calculated using a non-linear regression algorithm of the dose (concentration) - response (percentage of inhibition) curve using Graphpad Prism software.

2.2.2. Antibacterial activity screening

The in vitro antibacterial activity for the studied compounds was carried out against three gram-positive bacteria viz. *Micrococcus luteus*, *Bacillus subtilis*, *Staphylococcus aureus* and one gram-negative strain viz. *Escherichia coli* by the disk diffusion method on Muller-Hinton Agar (MHA) according to the methods of the National Committee for Clinical Laboratory Standards (NCCLS) recommended by the World Health Organization (WHO) and the French norm NF-U-47-107 [49,50]. *Micrococcus luteus*, *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus* strains were available in Biochemistry and biotechnology Laboratory of Faculty of Sciences at Mohammed First University, Oujda,

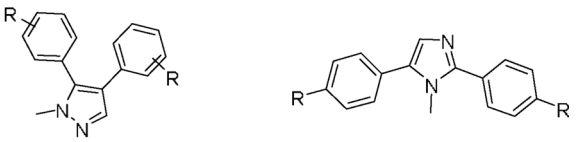

Fig. 2. Structure of the tested compounds.