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Original article

# Synthesis, structure–activity relationships, and in vitro antibacterial and antifungal activity evaluations of novel pyrazole carboxylic and dicarboxylic acid derivatives

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ABSTRACT

A series of pyrazole-3-carboxylic acid and pyrazole-3,4-dicarboxylic acid derivatives were synthesized, the structures were confirmed by their NMR ($^{1}$H and $^{13}$C) and FT-IR spectra, and elemental analyses. The antibacterial and antifungal activities of the compounds against five bacterial and five fungal pathogens were screened using modified agar well diffusion assay. Most of the molecules have inhibitory effects on both standard and clinical *Candida albicans* strains. However, only the molecules **8**, **10**, **21**, and **22** demonstrate some inhibitory effects on *Candida parapsilosis*, *Candida tropicalis*, and *Candida glabrata* strains. The structure–antifungal activity relationships of the compounds on the *C. albicans* strains were investigated by electron-conformational method. The pharmacophores and antipharmacophores responsible for the inhibition and non-inhibition of the *C. albicans* strains were obtained by electronic and geometrical characteristics of the reactive fragments of the molecules. These fragments along with the associated parameters can be used in designing the future more potent antifungal agents. It has been shown that both the positions of electronegative atoms like F and O in the pyrazole substituents and the amount of the associated charges on such atoms are crucial in regulating the strength of antifungal activity for the *C. albicans* strain.



## 1. Introduction

The synthesis of pyrazole derivatives that contain a five-membered heterocyclic organic compound with two adjacent nitrogen atoms has great interest in agrochemical, pharmaceutical, and chemical industries [1]. For example, they possess a wide range of bioactivities [1, 2], including antiviral [3], anti-inflammatory [4], anticonvulsant [5], anticancer [6], insecticidal [7], and antifungal [8, 9] activities. In recent years, several drugs including patented ones are developed from the pyrazole derivatives of five-membered ring. For instance, **celecoxib** demonstrates anti-inflammation effect and inhibits COX-2; **rimonabant** functions as cannabinoid receptor and is utilized in obesity treatment; **fomepizole** inhibits alcohol dehydrogenase; and **sildenafil** inhibits phosphodiesterase (Fig. 1).

Modification of the structural profile by altering the 1-, 3-, or 4-position substituent in pyrazole ring affects some bioactivities remarkably [2,10]. The incorporation of trifluoromethyl groups into organic molecules, including pyrazole derivatives, has a potential to modify the bioactivities [11–15].

In continuation of our research efforts of the discovery of novel pyrazole derivatives [16–18], herein we describe synthesis, antibacterial, and antifungal activities of a series of novel pyrazole carboxylic acid and dicarboxylic acid derivatives. The structure–activity relationships of the *Candida albicans* strains have also been studied in terms of electronic and geometrical characteristics by using electron-conformational method. This comprehensive approach of combining the experimental and quantum chemical studies give a chance to predict and to design further novel derivatives.

Nitro group is known to lower solubility of compounds. Therefore, nitro compounds are rarely considered in bioactivity measurements. Since the polar groups present in the novel pyrazole derivatives counteract the insolubility effect of the nitro group, the

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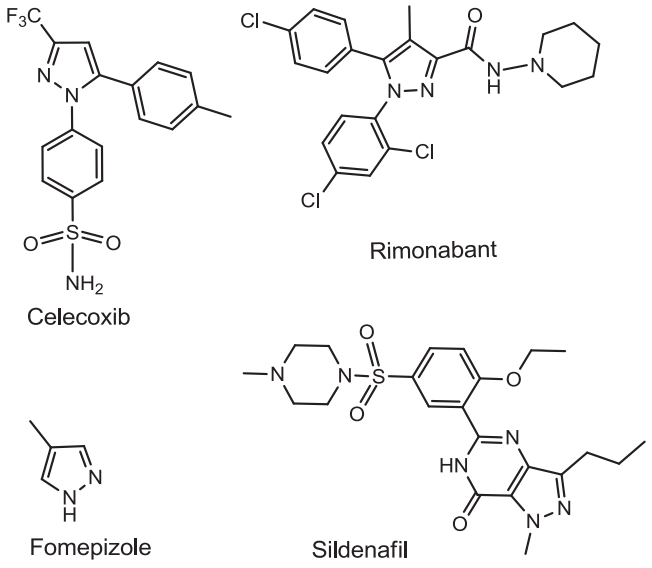



**Fig. 1.** Several drug molecules which include pyrazole scaffold.

present pyrazole derivatives with a nitro group become soluble in DMSO at 25 °C, allowing antifungal and antibacterial activity measurements of the present molecules.

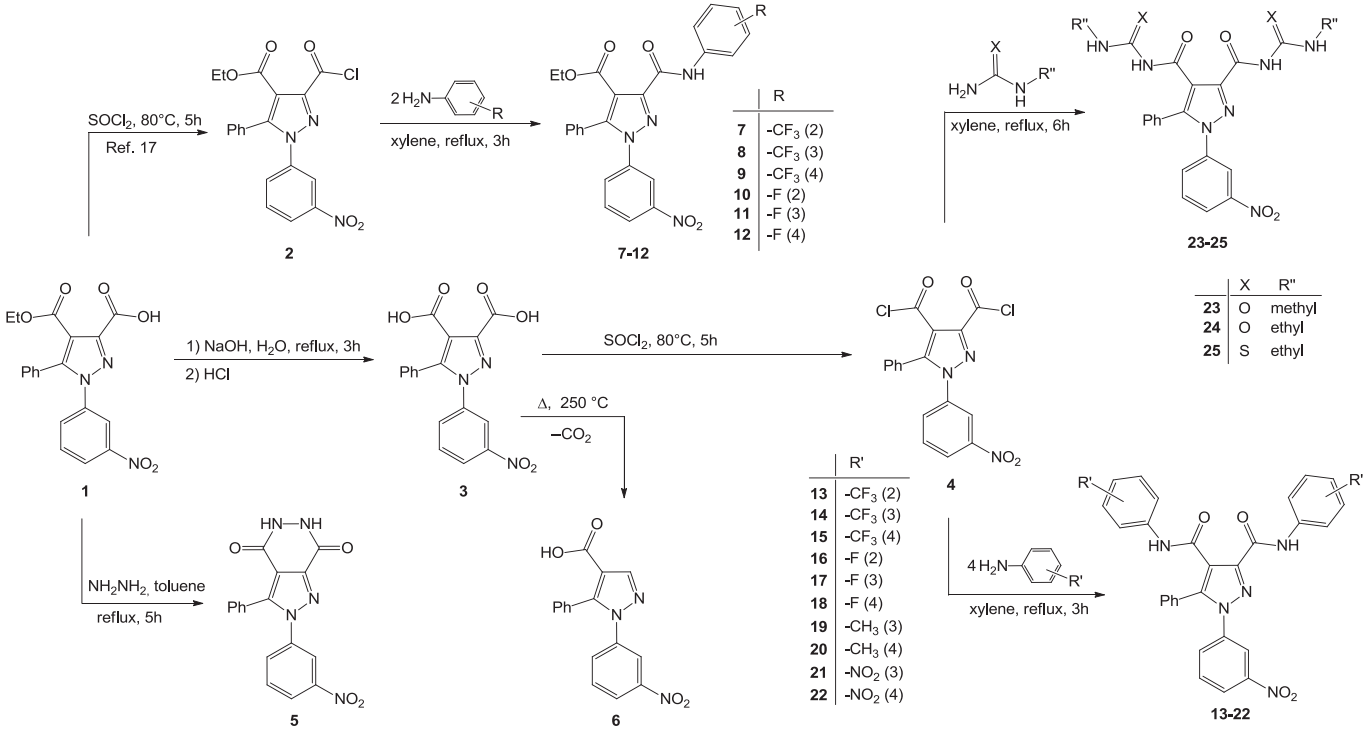
$^{1}H$ and $^{13}C$ NMR spectroscopy were employed for clarifying chemical structures of the derivatives while FT-IR was applied as a complementary technique for determining their structure via monitoring the frequencies of the characteristic functional groups such as (C=O). The molecular weight of the novel molecules were confirmed by elemental analysis. The bioactivity evaluations were done by both standard strains and species obtained from patients.

## 2. Results and discussion

### 2.1. Chemistry

In the current report, the starting compound (**1**) was synthesized via the reaction of furandiones with hydrazones by heating in solventless media [19], and its acid chloride (**2**) was obtained from the reaction with $SOCl_2$ [16]. Then a novel pyrazole-3,4-dicarboxylic acid (**3**) was prepared from the basic hydrolysis of **1** at a high yield (88%). IR spectrum of **3** showed a broad absorption band from 2500 to 3500 $cm^{-1}$ due to OH stretching of −COOH. The absorption bands associated with other functional groups appeared in the expected regions and the absorption values were consistent with our previous reports and literature [16,19]. Pyrazole 3,4-dicarboxylic acid (**3**) was easily converted to its acid chloride (**4**) reacted with excess $SOCl_2$ in solventless media again. The method is easy to perform and gives the product in high yield (82%). Reaction of **1** with anhydrous hydrazine led to the formation of a pyrazolo-pyridazine derivative (**5**) in about 63% yield (See Scheme 1). In this reaction, -$NH_2$ groups of hydrazine attacks to carbonyl carbons of **1** and in the second stage cyclization occurs with the removal of 1 mol water and 1 mol ethanol. Characteristic NH stretching bands are observed at 3361 $cm^{-1}$ and 3380 $cm^{-1}$ for compound **5**. Considering the reactions and the final products in the current study, the important IR peaks are CH (aromatic), C=O (amide), $NH_2$, C=C, C=N. The stretching of aromatic CH groups shows frequencies around 3060 $cm^{-1}$ [20]. Broad bands of the NH stretching indicate downward wave-numbers [21]. The IR signals of C=C and C=N appear as a region rather than single sharp peaks. This is explained by several motions such as in plane vibration of C=N [22].

The $^{1}H$ NMR results depict the successful synthesis of the molecules. In the $^{1}H$ NMR spectrum of the compound **5** the peaks belonging to NH groups are observed as broad singlet at 12.57 ppm. The compound **6** was obtained from the decarboxylation of **3** at




**Scheme 1.** The synthetic route of pyrazole carboxylic acid derivatives.