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Original article

A novel series of thiazolyl–pyrazoline derivatives: Synthesis and evaluation of antifungal activity, cytotoxicity and genotoxicity

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ABSTRACT

In the current work, new thiazolyl–pyrazoline derivatives (**1**–**22**) were synthesized and evaluated for their antifungal effects against pathogenic yeasts and molds using a broth microdilution assay. Ames assay was carried out to determine the genotoxicity of the most effective antifungal derivatives. The cytotoxicity of the compounds (**1**–**22**) was also investigated against A549 human lung adenocarcinoma and NIH/3T3 mouse embryonic fibroblast cells. Among these derivatives, 2-[5-(4-fluorophenyl)-3-(5-methylthiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(4-methylsulfonylphenyl)thiazole (**18**) can be identified as the most promising anticandidal derivative due to its notable inhibitory effect on *Candida zeylanoides* with a MIC value of 250 μg/mL when compared with ketoconazole (MIC = 250 μg/mL), low cytotoxicity against NIH/3T3 cells and non-mutagenic effect. On the other hand, 2-[5-(4-fluorophenyl)-3-(5-chlorothiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(4-bromophenyl)thiazole (**4**) can be considered as the most promising anticancer agent against A549 cancer cells owing to its notable inhibitory effect on A549 cells with an IC_{50} value of 62.5 μg/mL when compared with cisplatin (IC_{50} = 45.88 μg/mL) and low cytotoxicity against NIH/3T3 cells.

1. Introduction

Eukaryotic pathogens such as fungi pose a continuous and serious threat to public health since they share a close evolutionary relationship with their human hosts, limiting the number of drug targets that can be exploited to selectively kill fungal pathogens [1]. In recent years, the acquisition of multiple-drug resistance has resulted in a corresponding increase in demand for new effective antifungal agents with enhanced activity and limited toxicity [2–4]. On the other hand, in the last few decades, cancer has emerged as the second leading cause of death after cardiovascular disorders. The treatment of cancer is often complicated by high toxicity, low tolerability, and development of resistance [5–8].

Medicinal chemists have carried out considerable research on pyrazoline derivatives due to their diverse therapeutic applications extending from central nervous system applications to antimicrobials. The most predominant biological activity is observed for the class of 'antimicrobial agents' [9–11]. Furthermore, a considerable amount of research has reported that pyrazole-based heterocycles show promising activity against cancer cell lines including A549 human lung adenocarcinoma cell lines [12–16].

In terms of medicinal chemistry, thiazoles have also attracted a great deal of interest due to their presence in a large number of biologically active compounds, including natural products and pharmaceutical agents. The clinical efficacy of tiazofurin and its analogs, and bleomycins (BLMs) pointed out the importance of thiazole ring in the field of cancer treatment. Sulfathiazole (antimicrobial drug), abafungin (antifungal drug), and ritonavir (antiviral drug) are other examples of thiazole-based agents. Considerable research on thiazole and thiazolyl–pyrazoline derivatives in relation to their biological activity has been accomplished [17–32].

Prompted by the afore-mentioned findings and in the continuation of our ongoing research in the field of design, synthesis and biological evaluation of thiazolyl–pyrazoline derivatives [33,34], herein we described the synthesis and evaluation of a new series of thiophene substituted thiazolyl–pyrazolines as potential

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antifungal and anticancer agents.

2. Results and discussion

The synthesis of thiazolyl–pyrazoline derivatives (**1**–**22**) followed the general pathway outlined in Scheme 1. Initially, 1-(5-chloro/methylthiophen-2-yl)-3-(4-fluorophenyl)-2-propen-1-ones (**A**/**B**) were synthesized *via* the base-catalyzed Claisen–Schmidt condensation of 2-acetyl-5-chloro/methylthiophene with 4-fluorobenzaldehyde. Secondly, 3-(5-chloro/methylthiophen-2-yl)-5-(4-fluorophenyl)-1-thiocarbamoyl-2-pyrazolines (**C**/**D**) were obtained by the cyclization of chalcones (**A**/**B**) with thiosemicarbazide in the presence of sodium hydroxide. Finally, the ring closure reaction of 3-(5-chloro/methylthiophen-2-yl)-5-(4-fluorophenyl)-1-thiocarbamoyl-2-pyrazolines (**C**/**D**) with phenacyl bromides afforded thiazolyl–pyrazoline derivatives (**1**–**22**).

The structures of the newly synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, and elemental analyses.

In the IR spectra of compounds **C** and **D**, the stretching bands for N–H group were observed in the region 3473–3350 cm^{-1}. C=N, C=C stretching and N–H bending vibrations were observed in the region 1575–1454 cm^{-1}. In the IR spectra of compounds **1**–**22**, C=N, C=C stretching and N–H bending vibrations were observed in the region 1633–1450 cm^{-1}. The aromatic and aliphatic C–H stretching vibrations gave rise to bands at 3140–3016 cm^{-1} and 2987–2839 cm^{-1}, respectively. In the IR spectra of the cyano-substituted compounds, the stretching bands for C≡N group occurred at 2223–2218 cm^{-1}.

In the ^{1}H NMR spectra of the compounds, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 3.14–3.44 ppm (H_A), 3.98–4.04 ppm (H_M). The CH proton appeared as doublet of doublets at δ 5.64–5.72 (H_X) ppm due to vicinal coupling with two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring (J_{AM} = 17.50–18.00 Hz, J_{AX} = 6.50–7.50 Hz, J_{MX} = 11.50–12.00 Hz)

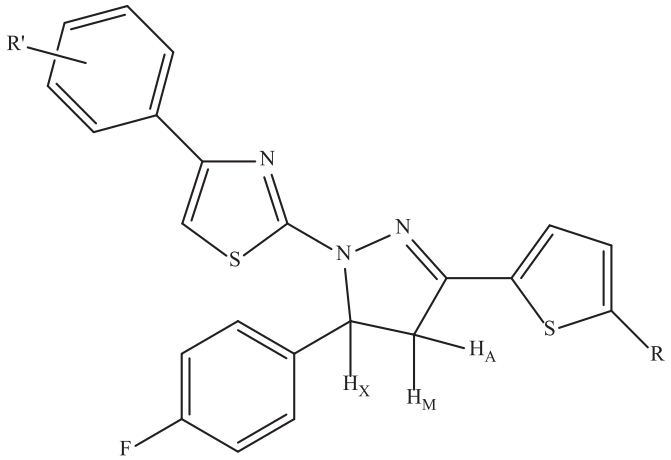


Fig. 1. AMX system of the pyrazoline ring.

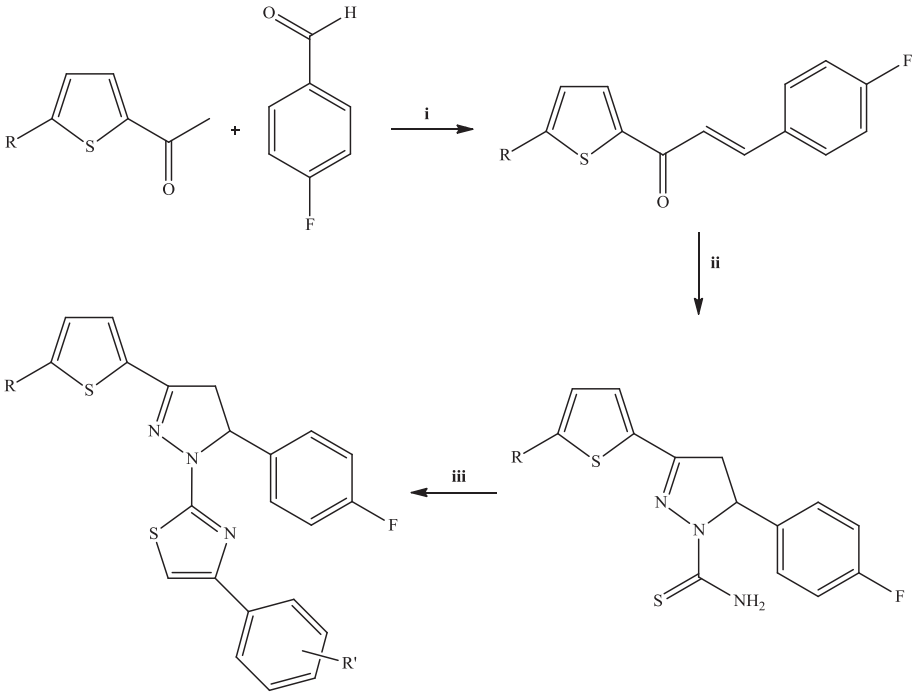
(Fig. 1). All the other aromatic and aliphatic protons were observed at expected regions.

In the ^{13}C NMR spectra of the compounds, the C_3, C_4 and C_5 carbons of the pyrazoline ring were observed at 148–151 ppm, 42–44 ppm and 62–65 ppm, respectively. In the ^{13}C NMR spectra of compounds **C** and **D**, C=S carbon appeared in the region 175–176 ppm. All the other aromatic and aliphatic carbons were observed at expected regions.

All of the synthetic compounds gave satisfactory mass spectroscopic data and elemental analysis, which were in full accordance with their depicted structures.

The synthesized compounds (**1**–**22**) were tested *in vitro* against pathogenic yeasts and molds. As shown in Table 1, the compounds exhibited more significant antifungal activity against yeasts than molds.

Among the pathogenic fungi species, *Candida zeylanoides* was the most susceptible yeast to the tested compounds. Compounds



Scheme 1. The synthetic route for the preparation of thiazolyl–pyrazoline derivatives (**1**–**22**). Reagents and conditions: (i) 10% aqueous sodium hydroxide solution, ethanol, rt, 10 h; (ii) thiosemicarbazide, NaOH, ethanol, reflux, 8 h; (iii) substituted 2-bromoacetophenone, ethanol, reflux, 6 h.