Synthesis, characterization, and antifungal activities of novel ferrocenyl pyrazolines containing sulfonamide moiety

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Abstract: A series of novel ferrocenyl pyrazolines containing sulfonamide moiety was prepared in a two-step reaction. All new derivatives were characterized by NMR spectroscopy and physical data. The antifungal potential of the synthesized ferrocenyl pyrazolines was evaluated on different fungal species, with several compounds exhibiting moderate antifungal effects. Notably, compounds exhibited MIC values in the range of 0.5–2 mg/mL against *Penicillium canescens* and *Candida albicans*, indicating selective antifungal activity and potential for further development as antifungal agents.

Keywords: antifungal activity, ferrocene, pyrazolines, sulfonamides, synthesis

1. Introduction

Pyrazolines are an important class of heterocyclic compounds containing two nitrogen atoms in the five membered ring [1]. Significant number of activities have been directed towards diversely substituted pyrazolines such as antimicrobial [2], antiinflammatory [3], and many more.

The sulfonamide moieties are pharmacophores responsible for the biological response of several clinically significant drugs [4]. They have diverse biological activities, including anticancer [5], antimicrobial [6], and many other.

The ferrocenyl group has been incorporated into the structure of many biologically active molecules, resulting in increased activity. Taking that into account, we decided to prepare new ferrocenyl pyrazolines containing sulfonamide moiety, and investigate their antifungal activity.

2. Material and methods

2.1. Chemistry

All starting chemicals were commercially available and used as received, and the solvents were purified by distillation. NMR spectra: Varian Gemini 200 MHz spectrometer, using $CDCl_3$ as the solvent and TMS as the internal standard. ^1H and ^{13}C NMR chemical shifts were reported in parts per million (ppm). The melting points: MelTemp1000 apparatus.

2.1.1. General procedure for the synthesis of ferrocenyl pyrazolines containing sulfonamide moiety

Croton ferrocene **1** (1.00 mmol) was dissolved in methanol (15 mL). Then, sodium acetate (5 mmol), and hydrazine hydrate (3 mmol) were added, and the solution was refluxed for 4 h. Afterwards, the hot solution was filtered off. Into the cold filtrate, corresponding benzenesulfonyl chloride (1.5 mmol), and triethylamine (0.4 mL) were added, and stirred at room temperature overnight. Afterwards, the solution was poured into cold water, stirred for 5 minutes, and extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. Crude concentrated solution was purified through a short column (stationary phase: silica gel, mobile phase: dichloromethane).

2.1.2. Antifungal activity

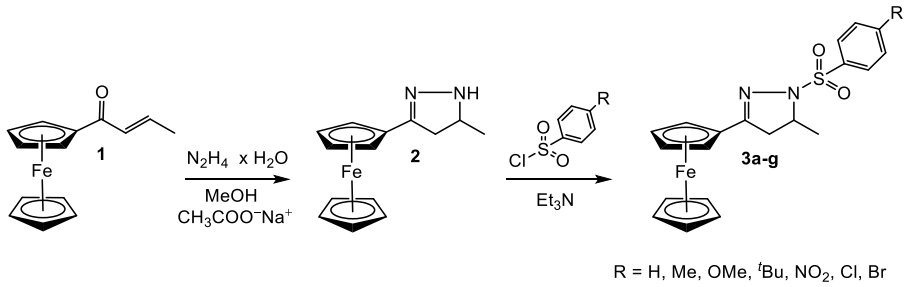
All fungal species were obtained from the Institute of Public Health in Kragujevac and the Laboratory of Microbiology, Department of Biology, Faculty of Science, University of Kragujevac, Serbia. The antifungal potential of the tested compounds was determined using the standard microdilution method, and results were expressed as minimum inhibitory concentrations (MICs) [7].

The antifungal activity of the synthesized compounds was assessed against three filamentous fungi *Penicillium canescens* (FSB 23), *Fusarium oxysporum* (FSB 91), and *Aspergillus brasiliensis* (ATCC 16404) as well as one yeast *Candida albicans* (ATCC 10259) [7]. Fungal cultures were prepared according to NCCLS guidelines [8]. Fungal inocula MICs were assessed visually. Nystatin served as positive controls for antifungal activity.

3. Results and Discussion

3.1. Chemistry

The novel ferrocenyl derivatives were synthesized in two steps (Scheme 1). For the synthesis of intermediate **2**, the cyclization of croton ferrocene **1** was performed using hydrazine monohydrate in the presence of sodium acetate in methanol. Formed compound **2** was not isolated, but used directly for condensation with substituted phenylsulphonyl chloride in the presence of triethylamine. The formed ferrocenyl pyrazolines containing sulfonamide moiety (**3a-g**) were obtained in very good yields (62-85%).



Scheme 1. Synthesis of ferrocenyl pyrazolines containing sulfonamide moiety, **3a-g**

The new ferrocenyl derivatives were obtained in a crystal form and characterized by their spectral data (^{1}H and ^{13}C NMR).

3.2. Antifungal activity

Several compounds showed moderate antifungal activity, particularly against *Penicillium canescens*, with MICs ranging from 0.5 to 1 mg/mL (Table 1).

Table 1. Antifungal activity of synthesized compounds **3a-g**

Compound	*MIC (mg/mL)**			
	Penicillium canescens	*Fusarium oxisporum*	*Aspergillus brasiliensis*	*Candida albicans*
3a	1	1	1	2
3b	0.5	2	2	2
3c	0.5	2	2	1
3d	> 2	> 2	> 2	2
3e	0.5	> 2	> 2	0.5
3f	0.5	> 2	> 2	2
3g	0.5	> 2	> 2	2
Nystatin	2.5	1.25	1.25	0.625

*MIC value for Nystatin is expressed in μg/mL.

The observed selective antifungal activity of the synthesized compounds may be attributed to their unique structural features, including the presence of the ferrocene moiety, the hydrazone linkage, and the sulfonyl group, all of which are known to enhance lipophilicity, redox properties, and hydrogen bonding potential. These characteristics could facilitate stronger interactions with fungal cell membranes or enzyme targets compared to bacterial systems, possibly leading to increased membrane disruption or inhibition of fungal-specific metabolic pathways [9].

4. Conclusions

In this study, seven new ferrocenyl pyrazolines containing sulfonamide moiety were prepared in very good yields, and their structures were characterized by spectral data (^{1}H NMR, and ^{13}C NMR). The antifungal activity of compounds **3a-c** was evaluated, and the results showed that these compounds exhibited moderate activity, particularly against *P. canescens.* On the other hand, compounds **3e-g** demonstrated selective antifungal activity, with moderate inhibition of *P. canescens* and *C. albicans.*

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