



## Original article

# Synthesis and investigation of antimicrobial activities of nitrofurazone analogues containing hydrazide-hydrazone moiety

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## ABSTRACT

In this research we synthesized and tested for *in vitro* antimicrobial activity 21 nitrofurazone analogues. The compounds we obtained were identified on the basis of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy. The *in vitro* screening of antimicrobial properties of synthesized compounds revealed a wide spectrum of antimicrobial activity. Compounds **28**, **29**, **32–43**, and **45–48** showed very high bactericidal effect towards *Staphylococcus* spp. ATTC and *Bacillus* spp. ATTC (MIC = 0.002–7.81 µg/ml and MBC = 0.002–31.25 µg/ml). The levels of activity of several compounds were far better than those of nitrofurantoin, ciprofloxacin or cefuroxime.

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## 1. Introduction

The increasing number of cases of multidrug-resistant infections difficult to diagnose and treat pose a major concern to public health care. To overcome these problems, developing new and safe antimicrobial agents with better effectiveness is required (Coates et al., 2002). One of several routes to find new chemotherapeutic agents is to modify the chemical structure of existing medicines which could result in broadening the spectrum of their activity and reducing their toxicity to human body (Moellering, 2011). In our research we decided to synthesize nitrofurazone analogues, because nitrofurazone is important antibacterial agent (McCalla et al., 1970) and in its structure we found the hydrazide-hydrazone moiety which is of our interest due to its promising biological activity (Fig. 1) (Rollas and Kūçūkgūzel, 2007; Bala et al., 2013).

Recently we have published interesting results concerning antibacterial activity of hydrazide-hydrazone derivatives (Popiołek et al., 2014, 2016a,b; Popiołek and Biernasiuk, 2016a,b). Hydrazide-hydrazones of 3-methoxybenzoic acid showed signifi-

cant antibacterial activity against Gram-positive bacterial strains, especially against *Bacillus* spp. ATTC (Popiołek and Biernasiuk, 2016a). In addition to this we have reported that hydrazide-hydrazones of 2-substituted acetic acid displayed potent bactericidal activity against Gram-positive and Gram-negative bacterial strains (Popiołek and Biernasiuk, 2016b).

It is worth to add that beside antibacterial activity (Kūçūkgūzel et al., 2002, 2003; Özkay et al., 2010; Deep et al., 2010; Rasras et al., 2010; Kumar et al., 2011; Rutkauskas et al., 2013; Pieczonka et al., 2013; Cukurovali and Yilmaz, 2014; Satyanarayana et al., 2014; Morjan et al., 2014; Rambabu et al., 2015), hydrazide-hydrazone derivatives have attracted much attention thanks to their usability as intermediates in organic synthesis (Rollas and Kūçūkgūzel, 2007; Bala et al., 2013) and they display a wide spectrum of such interesting biological properties as antifungal (Loncle et al., 2004; Backes et al., 2014), antitubercular (Koçyiğit-Kaymakçioğlu et al., 2006, 2009; Pavan et al., 2010; Velezheva et al., 2016), antiviral (Şenkardes et al., 2016), anticancer (Kumar et al., 2012; Çıkla et al., 2013; Wardakhan et al., 2013; Nasr et al., 2014; Kūçūkgūzel et al., 2015; He et al., 2016; Mukherjee et al., 2016), anti-inflammatory (Moldovan et al., 2011) and analgesic activity (Mohareb et al., 2010).

Based on the afore mentioned facts, and in an attempt to find new potent antimicrobial agents thanks to this research we synthesized and evaluated for their *in vitro* antimicrobial activity 21 analogues of nitrofurazone and we discovered that they showed very high bactericidal activity, particularly against *Staphylococcus* spp. ATTC and *Bacillus* spp. ATTC.

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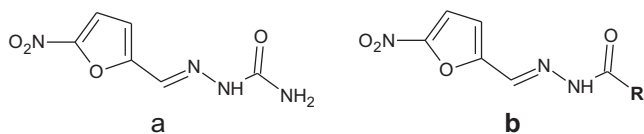


Fig. 1. Chemical structure of nitrofurazone (A) and synthesized analogues (B).

## 2. Materials and methods

### 2.1. Chemistry

Reagents and solvent used in this research were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany) and were used without further purification. Melting points were determined on Fisher-Johns blocks melting point apparatus (Fisher Scientific, Germany) and left uncorrected. The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on the BRUKER AVANCE 300 apparatus (Bruker BioSpin GmbH, Germany) in  $\text{DMSO}-d_6$  with TMS as the internal standard. Chemical shifts are reported in ppm ( $\delta$ ) with the use of TMS as the standard reference. The coupling constants ( $J$ ) are given in Hertz. The progress of the reaction and purity of obtained compounds were monitored by TLC, using pre-coated aluminum sheet 60 F254 plates (Merck Co. USA), in a  $\text{CHCl}_3/\text{C}_2\text{H}_5\text{OH}$  (10:1, v/v) solvent system. The spots were detected by exposure to the UV lamp at 254 nm. The elemental analysis of obtained compounds was carried out with the AMZ 851 CHX analyser (PG, Gdańsk, Poland). The results of elemental analysis (C, H, N) were within  $\pm 0.4\%$  of the calculated values.

#### 2.1.1. Preparation of carboxylic acid hydrazides (9–13, 20)

The compounds **11**, **12**, **13** were prepared using the procedures reported earlier (Popiołek et al., 2016b). Compound **9**, **10**, **20** were synthesized by following procedure: 0.01 mol of appropriate ethyl ester of carboxylic acid was dissolved in ethanol and heated under reflux with 0.011 mol of 100% hydrazine monohydrate for 2 h. After that the solution was cooled to room temperature and the precipitate formed. Then it was filtered off, dried and recrystallized from ethanol.

Physico-chemical and spectral data of compounds **9–13**, **20** are presented in Supplementary Materials.

#### 2.1.2. Preparation of nitrofurazone analogues (28–48)

**2.1.2.1. General procedure.** 0.01 mol of previously obtained carboxylic acid hydrazides (**9–13**, **20**) or commercially available hydrazides (**7**, **8**, **14–19**, **21–27**) were dissolved in 10–20 ml of ethanol and then 0.011 mol of 5-nitro-2-furaldehyde was added. The mixture was heated under reflux for 3 h. After that the solution was allowed to cool at room temperature and then was placed in refrigerator for 12 h. Subsequently the precipitation created was filtered off and recrystallized from ethanol.

Physico-chemical and spectral data of compounds **28–48** are presented in Supplementary Materials.

### 2.2. Microbiology

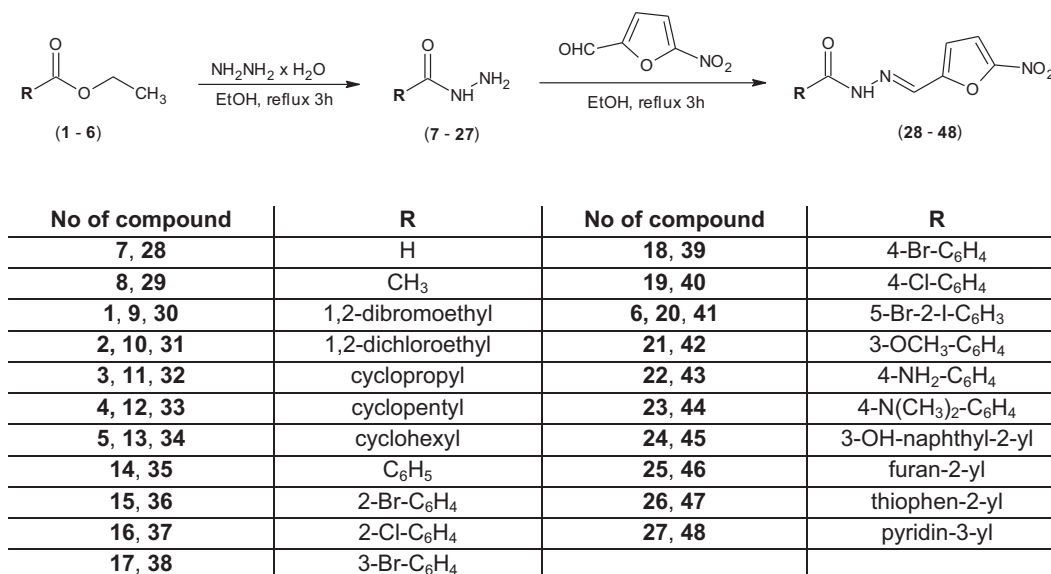
#### 2.2.1. In vitro antimicrobial assay

The examined compounds were screened *in vitro* for antibacterial and antifungal activities using the broth microdilution method based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) (EUCAST discussion document E. Dis 5.1, 2003) and Clinical and Laboratory Standards Institute guidelines (M27-S4, 2012).

In this research a panel of reference and clinical or saprophytic strains of microorganisms was used. This included Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 43300, *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 10876, *Micrococcus luteus* ATCC 10240), Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, *Bordetella bronchiseptica* ATCC 4617, *Salmonella typhimurium* ATCC 14028, *Pseudomonas aeruginosa* ATCC 9027) and fungi belonging to yeasts (*Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019).

The antimicrobial assays were performed like in our previous research concerning *in vitro* screening of hydrazide-hydrazone derivatives (Popiołek and Biernasiuk, 2016a,b). Nitrofurantoin, ciprofloxacin, and cefuroxime (Sigma-Aldrich) were used as reference antibacterial compounds. Fluconazole (Sigma-Aldrich) was used as reference antifungal positive control. All the experiments were repeated three times and representative data were presented.

The MBC/MIC or MFC/MIC ratios were used to determine bactericidal/fungicidal ( $\text{MBC/MIC} \leq 4$ ,  $\text{MFC/MIC} \leq 4$ ) or bacteriostatic/fungistatic ( $\text{MBC/MIC} > 4$ ,  $\text{MFC/MIC} > 4$ ) effect of the tested compounds (Wiegand et al., 2008).



Scheme 1. Synthesis pathway to nitrofurazone analogues (28–48).

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