Synthesis and In Vitro Antibacterial Activity of New 2-(1-Methyl-4-nitro-1H-imidazol-5-ylsulfonfonyl)-1,3,4-thiadiazoles

BAHRAM LETAFAT, NEGAR MOHAMMADHOSSEINI, ALI ASADIPOUR and ALIREZA FOROUHADI

Department of Chemistry, Islamshahr Branch
Islamic Azad University, Tehran, Iran
Department of Medicinal Chemistry
Faculty of Pharmacy and Pharmaceutics Research Center
Kerman University of Medical Sciences, Kerman, Iran
Department of Medicinal Chemistry
Faculty of Pharmacy and Pharmaceutical Sciences Research Center
Tehran University of Medical Sciences, Tehran, Iran
aforouhadi@yahoo.com

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Abstract: In the present study we report the synthesis and antibacterial activity of a new series 2-(1-methyl-4-nitro-1H-imidazol-5-ylsulfonfonyl)-1,3,4-thiadiazoles (6a-c). Compounds 6a-c were tested in vitro by the conventional agar dilution method against a panel of microorganisms including gram-negative and gram-positive bacteria. Compound 6b with 5-(5-nitrofuran-2-yl)-residue on 1,3,4-thiadiazole scaffold have shown promising antibacterial activities against gram-positive bacteria including Staphylococcus aureus, Staphylococcus epidermidis and Bacillus subtilis.

Keywords: Synthesis, Nitroimidazole, 1,3,4-Thiadiazole, Antibacterial activity

Introduction

Nitroimidazoles, such as metronidazole, misonidazole, ornidazole, secnidazole, etanidazole and tinidazole are commonly used as therapeutic agents against a variety of protozoan and bacterial infections of humans and animals. Some nitroimidazole derivatives have become the important agents for a long time for treatment of serious infections caused by anaerobic bacteria and protozoa. As pathogenic bacteria continuously evolve mechanisms of resistance to currently use antibacterial drugs, the discovery of novel and potent antibacterial
agents is the best way to overcome bacterial resistance and develop effective therapies. Moreover, the use of nitroheterocycles as antiviral, anticancer and radio sensitizing agents is well established. In our previous studies, some new compounds containing 5-nitroheterocycles and 1,3,4-thiadiazole with different substituents at the C2-position of the thiadiazole ring were synthesized and evaluated for activity against several bacterial species and H. pylori. In continuation to our ongoing research work on new nitroheterocyclic derivatives, herein, we describe the synthesis and in vitro antibacterial activity of new 5-sulfonyl-1-methyl-4-nitro-1H-imidazoles (6a-c) against a panel of gram-positive and gram-negative bacteria.

Experimental
All starting materials, reagents and solvents were purchased from Merck and Aldrich chemical companies. The purity of the synthesized compounds was confirmed by thin layer chromatography (TLC) using various solvents of different polarities. Merck silica gel 60 F254 plates were used for analytical TLC. Column chromatography was performed on Merck silica gel (70-230 mesh) for purification of intermediate and final compounds. 1H NMR spectra were recorded using a Varian 80 spectrometer and chemical shifts are expressed as δ (ppm) with tetramethylsilane (TMS) as internal standard. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disks). Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

Chemistry
The synthesis of 5-substituted-1-methyl-4-nitro-1H-imidazole derivatives (6a-c) was achieved with an efficient synthetic route outlined in Figure 1. The starting material 4(5)-bromo-5(4)-nitroimidazole (1) was prepared according to the literature method. The reaction of 1 with diazomethane in dry diethyl ether afforded 1-methyl-5-bromo-4-nitro-1H-imidazole 3 as major product. Compound 3 could be also prepared from nitration of 5-bromo-1-methyl-1H-imidazole. Treatment of 3 with appropriate arylthiols in the presence of potassium hydroxide afforded the desired sulfides 5a-c. Oxidation of compounds 5a-c by 3 moles of m-CPBA in dichloromethane gave 1,3,4-thiadiazole sulfones 6a-c.

![Figure 1](image_url)

**Figure 1.** Structure of 5-substituted-1-methyl-4-nitro-1H-imidazoles (6a-c) reagent and condition: (i) CH2N2, dry ether; (ii) KOH, EtOH, reflux (iii) m-CPBA, CH2Cl2
General procedure for the synthesis of 5-substituted 1-methyl-4-nitro-1H-imidazoles (6a-c)

A mixture of 5a-c (1.0 mmol), m-chloroperbenzoic acid (3.0 mmol) and NaHCO$_3$ (3.0 mmol) in 15 mL of dichloromethane was stirred for three days. The reaction mixture was monitored by TLC. After consumption of the starting material, water (15 mL) was added and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2×15 mL). The combined organic phases were washed with water and dried (Na$_2$SO$_4$). Evaporation of the solvent gave a solid which was recrystallized from ethanol.

N-(5-(1-Methyl-4-nitro-1H-imidazol-5-ylsulfonyl)-1,3,4-thiadiazol-2-yl)acetamide (6a)

Yield 83%; m.p. 152-154 °C; IR (KBr, cm$^{-1}$): 1670 (C=O), 1351 (NO$_2$), 1326, 1145 (S=O). $^1$H NMR (80 MHz, CDCl$_3$): δ: 7.82(s, 1H, Imidazole), 3.68(s, 3H, NCH$_3$), 2.05 (s, 3H, COCH$_3$).

2-(1-Methyl-4-nitro-1H-imidazol-5-ylsulfonyl)-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole (6b)

Yield 82%; m.p. 148-150 °C; IR (KBr, cm$^{-1}$): 1555, 1357 (NO$_2$), 1328, 1144 (S=O). $^1$H NMR (80 MHz, CDCl$_3$): δ: 8.05(d, 1H, furyl, J=3.8Hz), 7.59 (s, 1H, imidazole), 7.53(d, 1H, furyl, J=3.8Hz), 4.08 (s, 3H, CH$_3$).

2-(1-Methyl-4-nitro-1H-imidazol-5-ylsulfonyl)-5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazole (6c)

Yield 85%; m.p. 82-84 °C; IR (KBr, cm$^{-1}$): 1550, 1350 (NO$_2$), 1324, 1142 (S=O). $^1$H NMR (80 MHz, CDCl$_3$): δ: 8.13(s, 1H, 5-nitroimidazole), 7.87(s, 1H, 4-nitroimidazole), 3.70, 3.95 (2s, 6H, 2CH$_3$).

Biological activity

Compounds 6a-c were screened for their antibacterial activity against gram-positive (Staphylococcus aureus ATCC 25923, Staphylococcus epidermidis ATCC 14940, Bacillus subtilis ATCC 6051) and gram-negative (Escherichia coli ATCC 25922, Klebsiella pneumoniae ATCC 10031, Enterobacter aerogenes PTCC 1221) bacteria by the conventional agar dilution method$^{12}$. Twofold serial dilutions of the compounds and reference drugs were prepared in muller hinton agar. Drugs (6.4 mg) were dissolved in DMSO (1 mL) and the solution diluted with water (9 mL). Further progressive double dilution with melted muller-Hinton agar was performed to obtain the required concentrations of 64, 32, 16, 8, 4, 2, 1 and 0.5 µg/mL. Petri dishes were inoculated with 1-5×10$^4$ colony-forming units (cfu) and incubated at 37 °C for 18 h. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the test compound, which resulted in no visible growth on the plate. To insure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

Results and Discussion

The synthesized compounds 6a-c were assessed for their antibacterial activity against a panel of gram-positive (Staphylococcus aureus, Staphylococcus epidermidis and Bacillus subtilis) and gram-negative (Klebsiella pneumoniae, Escherichia coli and Enterobacter aerogenes) bacteria using a conventional agar-dilution method. The MIC values (µg/mL) obtained for compounds 6a-c are presented in Table 1. MIC values of the tested derivatives indicate that compounds 6b and 6c showed a higher antibacterial activity against gram-positive rather than gram-negative bacteria. Compounds 6b and 6c had respectable in vitro activity.
against *Staphylococci* and *B. subtilis*, but were less active than the reference drug norfloxacin. Compound 6a showed no significant activity against gram-positive and gram-negative bacteria.

**Table 1. In vitro antibacterial activities of compounds 6a-c against selected bacteria**

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**Conclusion**

We have synthesized and evaluated the antibacterial activities of a series of 1-methyl-4-nitro-1H-imidazoles containing different arylthio or arylsulfonyl groups at the 5-position. Compound 6b with 5-(5-nitrofuran-2-yl)- residue on 1,3,4-thiadiazole scaffold have shown promising antibacterial activities against gram-positive bacteria including *Staphylococcus aureus, Staphylococcus epidermidis* and *Bacillus subtilis*. The structure-activity relationship observed from this series of compounds can be used to further optimize the structures to obtain potent novel antimicrobial drugs.

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**References**
