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Antimicrobial activity screening of some sulfonamide derivatives on some *Nocardia* species and isolates

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Summary

Nocardia are aerobic, catalase-positive, Gram-positive microorganisms and typically acid-alcohol fast at some stage of the growth cycle. The genus *Nocardia*, a member of Mycolata group, is clinically important because it is an opportunistic pathogen. The sulfonamide derivative medicines are prefered to cure infection caused by *Nocardia*, such as nocardiaosis and mycetoma.

Antimicrobial activities of seven sulfonamide derivatives have been investigated against some *Nocardia* species and isolates using the disk diffusion method on Sensitest agar medium (Oxoid). Thirty-six organisms, which consisted of 10 soil isolates selected from different clusters of Aymen study (2003), six clinical isolates provided by Ege University, Medical School, Microbiology and Clinical Microbiology Department, four reference strains, 15 type strains and a control strain of *Staphylococcus aureus* ATCC 43300 were tested. The strongest inhibition was observed in the cases of **IV** [*N*-(2-hydroxy-4-nitro-phenyl)-4-methyl-benzensulfonamid], **V** [*N*-(2-hydroxy-5-nitro-phenyl)-4-methyl-benzensulfonamid] and **III** [*N*-(2-Hydroxy-phenyl)-4-methyl-benzene-sulfonamide] against *Nocardia*. Introducing a hydroxyl group into the *ortho* position on the ring increased the antimicrobial activity. Substitution of the electron withdrawing groups such as a nitro group increased the antimicrobial activity remarkably.

Introduction

Among the actinomycetes, *Nocardia* species are soilborne, Gram-positive and partially acid-alcohol fast at some stage of the growth cycle. They cause primary pulmonary or cutaneous infection in humans, and the microorganisms can eventually disseminate through the central nervous system route to any other organ/soft tissues (Lerner, 1996; Boiron et al., 1998). The antimicrobial therapy for infections with *Nocardia* species often includes

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sulphonamides which are used to cure nocardiaosis and mycetoma. Due to this treatment, the fatality rate has been reduced substantially (Boiron et al., 1992; Saubolle, 1993; Wortman, 1993; Lerner, 1996; Boiron et al., 1998). However, in many cases, the use of these drugs may run the risk of developing bacterial resistance, side effects or poor patient response to the treatment, including relapses, which have been reported in some previous and recent studies (Welsh et al., 1987; Welsh, 1991; McNeil and Brown, 1994; McNeil et al., 1995; Burget, 1999; Torres et al., 2000; Saubolle, 2002; Matulionyte et al., 2004). Therefore, this not only requires the use of alternative therapeutic regimens but it also underscores the importance of in vitro susceptibility testing of nocardia species to improve the therapeutic outcome (Brown and McNeil, 2003; Saubolle and Sussland, 2003). Considering this background, the objective of this study is to present and evaluate the data on the antimicrobial susceptibility of 35 nocardia consisting of 15 type strains, four reference strains, six clinical and 10 soil isolates against seven sulfanomide derivatives and some other antimicrobials.

Materials and methods

Preparation of the sulfonamides

General procedure for preparation of the sulfonamides is as follows (Vogel, 1989). For a typical run; 0.06 mol substituted aniline was dissolved in 30 ml benzene. 0.06 mol *p*-toluenesulfonylchloride in 20 ml benzene was added into the solution. 0.06 mol dry pyridine was added into 20 ml benzene slowly and it was refluxed for 4 h, so the solvent was removed and a solid was obtained. The solid was dissolved in 10% (w/v) NaOH solution and extracted with $CHCl_3$. Aqueous solution was acidified with HCl to obtain raw sulfonamide. Recrystallization of ethanol–water mixture from raw sulfonamide resulted in corresponding sulfonamide in pure form (Celik, 1999). Some physical and spectral data of the synthesized sulfonamides were summarized below:

4-Methyl-N-phenyl-benzenesulfonamide **(I)** m.p.100–101 °C. ^{1}H NMR ($CDCl_3$), δ (ppm) 2.4 (s,3H), 6.8 (s,1H), 7.10 (m,3H), 7.24 (m,4H), 7.65 (m,2H); IR(KBr), 3245 (NH), 3056, 2971, 2898, 1598, 1486, 1415, 1336 (SO_2 asym.), 1224, 1160 (SO_2 sym.) cm^{-1} (Deng et al., 2005).

4-Methyl-N-(4-nitro-phenyl)-benzenesulfonamide **(II)** m.p.190–191 °C. ^{1}H NMR (acetone-d_6), δ (ppm) 2.35 (s,3H), 3.0 (s,1H), 7.37 (d,2H), 7.45 (dd,2H), 7.80 (d,2H), 8.14 (dd,2H); IR(KBr), 3336 (NH), 3083, 2923, 2852, 1594, 1521 (NO_2 asym.), 1324 (SO_2 asym.), 1162 (SO_2 sym.) cm^{-1} (Bunce et al., 2004).

N-(2-Hydroxy-phenyl)-4-methyl-benzenesulfonamide **(III)** m.p. 137–138 °C. ^{1}H NMR (acetone-d_6), δ (ppm) 2.36 (s,3H), 3.12 (s,1H), 6.90 (m,3H), 7.20 (m,3H), 7.69 (d,2H), 8.99 (broad,1H); IR (KBr) 3434 (OH), 3299 (NH), 1473, 1419, 1324 (SO_2 asym.), 1229, 1188 and 1160 (SO_2 sym.) cm^{-1} (Kondo et al., 2005).

N-(2-Hydroxy-4-nitro-phenyl)-4-methyl-benzenesulfonamide **(IV)** m.p. 181–182 °C. ^{1}H NMR (acetone-d_6), δ (ppm) 2.23 (s,3H), 3.37 (s,1H), 7.34 (d,2H), 7.63 (d,2H), 7.71 (dd,1H), 7.82 (d,2H), 8.65 (s,1H), 10.99 (s,1H); IR (KBr) 3608 (OH), 3270 (NH), 3079 (Ar–H), 2920, 1596, 1525 (NO_2 asym.), 1446, 1402, (SO_2 asym.), 1336 (NO_2 sym.), 1270, 1162, 1128 (SO_2 sym.) cm^{-1} (Andersen et al., 1991).

N-(2-Hydroxy-5-nitro-phenyl)-4-methyl-benzenesulfonamide **(V)** m.p. 208–209 °C. ^{1}H NMR (acetone-d_6), δ (ppm) 2.32 (s,3H), 3.60 (broad,1H,–NH), 6.97 (d,1H), 7.31 (d,2H), 7.75 (d,2H), 7.87 (dd,1H), 8.33 (d,1H), 8.55 (broad, 1H,–OH); IR (KBr) 3407 (OH), 3280 (NH), 3085 (Ar–H), 2930, 1596, 1523 (NO_2 asym.), 1454, (SO_2 asym.), 1342 (NO_2 sym.), 1164 (SO_2 sym.) cm^{-1} (Bartsch et al., 1993).

N-(5-Chloro-2-hydroxy-phenyl)-4-methyl-benzenesulfonamide **(VI)** m.p. 189–190 °C. ^{1}H NMR (acetone-d_6), δ (ppm) 2.35 (s,3H), 3.55 (broad,1H,–NH), 6.79 (d,1H), 6.92 (dd,1H), 7.31 (d,2H), 7.36 (d,1H), 7.71 (d,2H), 8.62 (broad, 1H,–OH); IR (KBr) 3450 (OH), 3259 (NH), 3080, 2930, 1602, 1504, 1440, 1384, 1319 (SO_2 asym.), 1216, 1170 (SO_2 sym.) cm^{-1} (Andersen et al., 1991).

N-(2-Hydroxy-5-methyl-phenyl)-4-methyl-benzenesulfonamide **(VII)**) m.p. 142–143 °C. ^{1}H NMR (acetone-d_6), δ (ppm) 2.14 (s,3H), 2.33 (s,3H), 3.47 (broad,1H,–NH), 6.67 (d,1H), 6.74 (dd,1H), 7.13 (s,1H), 7.27 (d,2H), 7.67 (d,2H), 8.46 (broad,1H,–OH); IR (KBr) 3370 (OH), 3247 (NH), 3039, 2917, 1596, 1517, 1446, 1390, 1321 (SO_2 asym.), 1290, 1245, 1187, 1162, 1112 (SO_2 sym.) cm^{-1} (Andersen et al., 1991).

Bacterial strains and inoculum preparation

A total of 36 test organisms, which consists of 10 soil isolates selected from different cluster of Aymen soil isolates (2003), six clinical isolates