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Original Article

Antibacterial activity of novel 2-(substituted sulfonamido) benzoic acid derivatives☆

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ABSTRACT

Objectives: Sulfonamides were the first chemotherapeutic agents to be used in human, systemically for the treatment of bacterial infection. Though, varieties of sulfonamides are currently available, bacteria have developed resistance to them. This prompted to search for the novel sulfonamide based antibacterials.

Methods: Novel 2-(substituted sulfonamido) benzoic acid derivatives were tested for their antibacterial activity against 19 Gram −ve and 2 Gram +ve pathogenic bacteria and MIC values were determined by agar dilution method.

Results: The tested compounds showed moderate to good antibacterial activity against tested bacteria. Compounds, A5, A12, A15, A18 and A19 were showed moderate antibacterial activity against atypical *Escherichia coli*. Compounds, A13 and A14 showed good antibacterial activity (MIC = 183.81 μg/ml) against *Plesiomonas shigelloides* and atypical *E. coli*, respectively.

Conclusion: This study concludes that further structural optimization of 2-(substituted sulfonamido) benzoic acid series would bring more potent useful agents to treat infections caused by range of bacteria.

1. Introduction

The importance of sulfonamide moiety in medicinal chemistry cannot be ignored, as it constitutes an important class of drugs used extensively as pharmaceutical and agricultural agents. Diverse biological properties viz. antibacterial, antithyroid, antidiabetics, diuretics, carbonic anhydrase (CA) inhibitors etc., are obtained from the sulphonamide structure as lead. Recently, sulfonamides have also been reported for their matrix metalloproteinase (MMP) inhibitory activity.[1–4] Sulfonamides were the first chemotherapeutic agents to be used in human, systemically for the treatment of bacterial infections. In 1938,

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Domagk was awarded the Nobel Prize in medicine for discovering chemotherapeutic value of prontosil (**1**) (Fig. 1).[5] Sulfonamides exhibit antibacterial activity by competitively inhibiting folic acid synthesis. Sulphadiazine (**2**), sulphamethoxazole (**3**) and sulphacetamide (**4**) are commonly used sulfonamides. When administered with trimethoprim, sulphamethoxazole shows synergetic action.

Though varieties of sulfonamides are currently available, bacteria have developed resistance to them. Recently, New Delhi metallo-β-lactamase 1 (NDM-1) has been identified in Gram −ve *Enterobacteriaceae* which is resistance to carbapenam.[6] This prompted us to syntheses a novel series of sulfonamides based on anthranilic acid (A1-A19). The newly synthesized compounds were characterized by using IR, ^{1}H NMR, ^{13}CNMR and Mass Spectrometry (unpublished data). This article documents *in vitro* antibacterial activity of the synthesized compounds against 19 Gram −ve and 2 Gram +ve (*Staphylococcus aureus* ATCC25923 and *Enterococcus faecalis*) pathogenic bacteria, and the minimum inhibitory concentration (MIC) determined by agar dilution method.

2. Experimental

2.1. Synthesis of 2-(substituted sulfonamido) benzoic acid derivatives

2-(substituted sulfonamido) benzoic acid derivatives (A1-A19) were synthesized by reacting 2-aminobenzoic acid (anthranilic acid) with different alkyl, aryl and substituted aryl sulfonyl chlorides. IR, NMR and MS data of synthesized compounds are in agreement with their structures (unpublished data).

2.2. Determination of MIC by agar dilution method

Determination of MIC for the synthesized compounds was carried out as described by Wiegand et al using Mueller–Hinton agar medium against 19 Gram −ve and 2 Gram +ve organisms.[7] About 50 mg/ml solutions of test compounds (A1-A19) as well as sulphamethoxazole were prepared in DMSO. From these stock solutions, serial dilutions of the compounds (50,000, 25,000 − 781.25 μg/ml) were prepared. Then, 16 ml of agar medium (at 50 °C) was added to bring the final concentrations in the range of 2941, 1470.5 − 45.95 μg/ml and transferred into petri dishes. Suspensions of each microorganism were prepared to contain approximately 10^{6} colony forming units per ml and applied to plates containing serially diluted compounds to be tested; and incubated at 37 °C for overnight (approx. 18–20 h). At the end of the incubation period, the MIC values were determined. All determinations were done in triplicates and average was taken as final reading. Sulphamethoxazole was used as positive control, and DMSO as negative control.

3. Results and discussion

Minimum inhibitory concentration (MIC) is defined as the lowest concentration that inhibits the visual growth of a microorganism. MIC values of the tested compounds are presented in Table 1. To our knowledge, this is the first report on the antibacterial activity of the novel series of 2-(substituted sulfonamido) benzoic acid. The negative control, DMSO, used for the preparation of test and standard solution did not show any inhibition against the tested organisms. MIC values of the standard against different microorganisms were presented in Table 1, and they are comparable with the values published by Pandeya et al.[8] Tested compounds showed mild to moderate antibacterial activity against tested organisms. Compounds, A5, A12, A15, A18 and A19 were showed moderate antibacterial activity against atypical *Escherichia coli*. Whereas, compounds with *p*-chloro (A14, Fig. 2) and *p*-fluoro (A17) phenyl substitutions showed good antibacterial activity with MIC values 183.81 μg/ml and 367.625 μg/ml, respectively, against atypical *E. coli* when compared with the standard sulphamethoxazole (MIC = 2941 μg/ml). Compounds, A12, A13, A18 and A19 were showed moderate activity against *Vibrio parahaemolyticus*. Good antibacterial activity against *Plesiomonas shigelloides* were showed by compounds, 2-(3-nitrophenylsulfonamido) benzoic acid (A12), 2-(4-nitrophenylsulfonamido) benzoic acid (A13, Fig. 2) and 2-(4-bromophenylsulfonamido) benzoic acid (A15) with MIC values 367.625 μg/ml, 183.81 μg/ml and 367.625 μg/ml, respectively. Bulky substitution in the phenyl ring (A8 and A9) is detrimental for the antibacterial activity. This may be due to the steric hindrance of the bulky

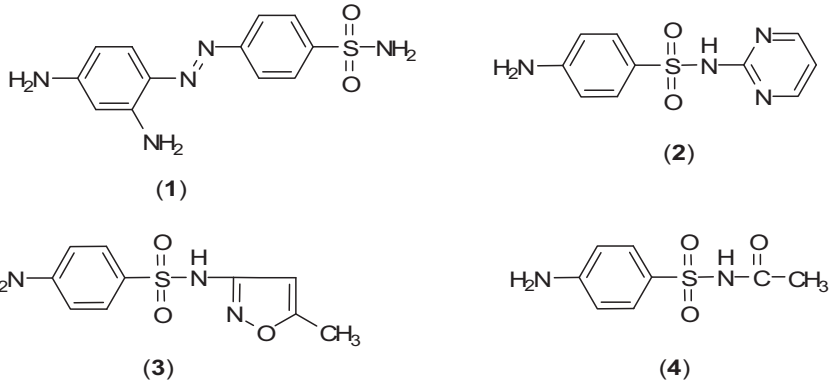

Fig. 1 − (1) Prontosil; (2) Sulphadiazine; (3) Sulphamethoxazole; (4) Sulphacetamide.