SYNTHESIS OF SOME NEW ANTIMICROBIAL THIADIAZOLYL AND OXADIAZOLYL QUINOLINE DERIVATIVES

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Abstract. Two series of substituted thiadiazoyl and oxadiazoylquinolines (3a-h, 4a-h, 7a-f, 8a-f and 9) were synthesized and screened for their antimicrobial activity. Some of the tested compounds showed promising activity. Compound 4b exhibited bactericidal activity against S. aureus at 31.25 µg/ml. While compound 8a showed distinct antifungal activity against C. albicans (MIC at 31.25 µg/ml). The detailed synthesis, spectroscopic and biological data are reported.

The quinoline nucleus was reported to exhibit various biological activities such as antiamoebic 1, antimalarial 2,3, antiviral 4,5 as well as anti-inflammatory activity 6,7. In addition, the discovery of nalidixic acid, a urinary tract antimicrobial drug 8, prompted the synthesis of many quinolone and quinoline derivatives and examination of their antimicrobial activity 9-11. Norfloxacin, ofloxacin, and ciprofloxacin (nalidixic acid analogs) were marketed as active antimicrobial medications 12. Besides, oxadiazole and thiadiazole rings are important examples of the heteroazoles that by themselves or in combination with other ring systems possess antimicrobial activity 13-15. In view of these facts and as a continuation of a research program carried out in our laboratory 16-19 two series of substituted thiadiazoyl and oxadiazoylquinolines have been synthesized to investigate their antimicrobial activity.

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Chemistry

The synthetic pathway depicted to obtain the new compounds (3-9) is outlined in schemes 1-3. The starting materials, 2-substituted cinchonicin acids 1a-c were prepared according to Pfitzinger reaction\(^{20,21}\). While, 2-amino-5-alkyl (or aralkyl) thio-1,3,4-thiadiazoles 2a-c, were obtained by refluxing a mixture of thiosemicarbazide, carbon disulfide and anhydrous sodium carbonate in absolute ethanol, followed by S-alkylation using either dialkylsulfates or aralkyl halides\(^{22}\). Condensation of the appropriate cinchonicin acid 1a-c with the selected aminothiadiazole 2a-c in the presence of DCC furnished the proposed 1,3,4-thiadiazol-2-yl-quinoline-4-carboxamides 3a-h (Scheme 1, Table 1). Oxidation of the aforementioned compounds 3a-h to the corresponding sulfonyl analogs 4a-h was carried out using potassium permanganate in glacial acetic acid (Scheme 1, Table 1). On the other hand, the key intermediates 2-substituted cinchonicin acid hydrazides 5a,b (Scheme 2) were obtained by following the reported procedure\(^{23}\). Treatment of the acid hydrazides 5a,b with carbon disulfide in alkaline medium afforded the expected 5-thioxo-1,3,4-oxadiazolylquinolines 6a &b\(^{24}\) (Scheme 2, Table 2). These thiol 6a,b were then alkylated to their corresponding alkyl or aralkyl thio analogs 7a-f (Scheme 2, Table 2). Oxidation of 7b,d,e,f was performed by potassium permanganate in glacial acetic acid at room temperature to afford the corresponding sulfonyl derivatives 8b,d,e,f (Scheme 3, Table 2). While using the same conditions for compounds 7a,c, both gave one and the same product, 2-methyl-4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinoline 9 (Scheme 3). Formation of this compound could be a result of further oxidation of the sulfones first formed. Thus, oxidation of 7a and 7c was repeated at 0-5°C to yield the expected sulfonyl products 8a,c (Scheme 3, Table 2) as proved by interpreting their microanalytical and spectral data.

Results and Discussion

The newly prepared compounds were preliminarily evaluated for their in vitro antibacterial activity against Staphylococcus aureus (ATCC 6538p) as an example of Gram-positive bacteria and Escherichia coli (NCTC 10418), Pseudomonas aeruginosa (ATCC 9027) as representative examples of Gram-negative bacteria. They were evaluated for their in vitro antifungal activity against Candida albicans (ATCC