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Preliminary communication

3-(1,3,4-Thiadiazole-2-yl)quinoline derivatives: Synthesis, characterization and anti-microbial activity

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ABSTRACT

A new series of thiadiazoles and intermediate thiosemicarbazones were synthesized from the chloroquinone molecule, with an aim to explore their effect on *in vitro* growth of microorganisms causing microbial infection. The chemical structures of the compound were elucidated by elemental analysis, FTIR, 1H and 13C NMR and ESI-MS spectral data. *In vitro* anti-microbial activity was performed against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella typhimurium*, and *Escherichia coli*. The MIC was detected using the double dilution method. The results were compared by calculating percent inhibit area/μg of the compounds and the standard "amoxicillin". The selected compounds were tested for cytotoxic results using MTT assay H9c2 cardiac myoblasts cell line and the results showed that all the compounds offered remarkable >80% viability to a concentration of 200 μg/mL.

1. Introduction

The innovative research for antibiotics has improved mankind's health status by confining life threatening infections. However, the emergence and spread of bacterial resistance represent a severe global problem [1]. Multidrug-resistant gram-positive pathogens, such as methicillin-resistant *Staphylococci aureus* (MRSA), penicillin resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *enterrococci* (VRE), compounded problems in the therapeutics [2–4]. Heterocyclic thiadiazoles are widely exposed to therapeutic world, because of their known anti-HIV [5], anti-inflammatory [6–8], anti-cancer [9], anti-tuberculosis [10,11], anti-convulsant [12] and anti-hypertensive [13,14] activities. Nitroheteroaryl-1,3,4-thiadiazole derivatives have shown impressive anti-microbial and antiparasitic activity particularly against *Trypanosomatid protozoa* [15]. Thiadiazole derivative, 2-(4-chloropheny1amino)-5-(4-aminophenyl)-1,3,4-thiadiazole showed 57% inhibition against *Mycobacterium tuberculosis* [16].

Quinolines have been of great interest as antibacterial and antiviral compounds for several decades, starting from the introduction of nalidixic acid in 1962 for the urinary tract infections. Various successful attempts have been made to produce the potent therapeutic agents such as torvafloxin [17], moxifloxacin [18], gemifloxacin [19] and gatifloxacin [20] etc. from quinoline. The incidence of gram-positive bacterial resistance to these antibacterial agents is growing and will be of major concern in near future [21,22]. Therefore, there is an urgent need for novel chemical entities that are particularly effective against gram-positive pathogens. In continuation of our efforts in developing heterocycles of biological interest [23–25] and considering the significant role of thiadiazoles [26–28] and quinolines in biological applications, we wish to report here the synthesis of a new series of quinoline-thiadiazole derivatives and their anti-microbial activities.

2. Result and discussion

2.1. Chemistry

The synthetic route of compounds (**1B**–**24B**) is shown in Fig. 1. Compounds were obtained from a starting material of 2,8-substituted-quinoline-3-carbaldehyde. The synthesized thiosemicarbazones (Fig. 1, Table 1) of substituted-quinoline were cyclized in presence of acetic anhydride to get the final thiadiazole compounds. All the reactions were monitored by TLC (aluminum sheet, silica gel 60 F_{254}, Merck). The precursor, thiosemicarbazone (**1A**–**24A**) and the final compounds (**1B**–**24B**) were purified by column chromatography using silica gel (pore size 60 Å, 200–400

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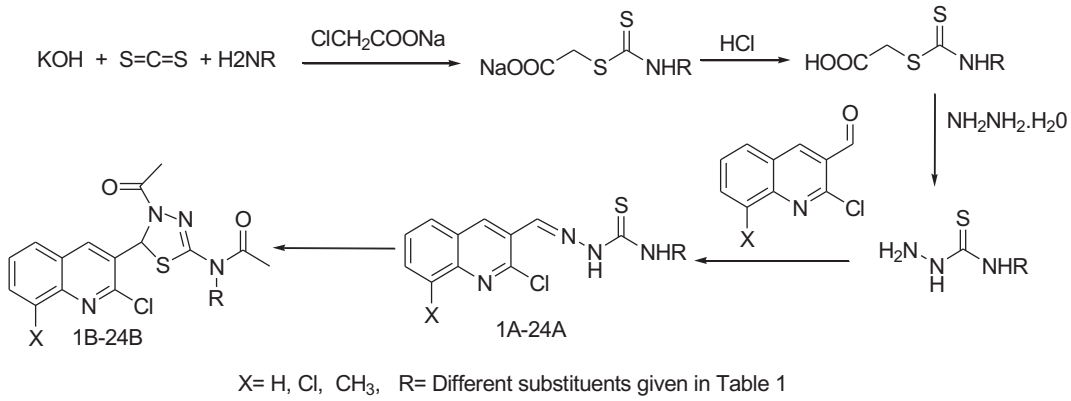
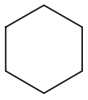
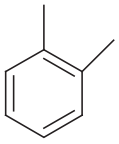
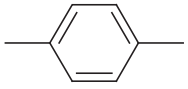
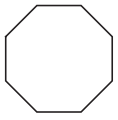
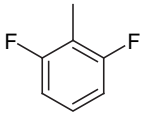
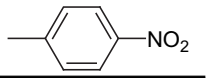


Fig. 1. Schematic Representation of the Synthetic route adopted for the synthesis N-4-acetyl-5-(2,8-substitutedquinolin-3-yl)-4,5-dihydro-1,3,4-thiadiazole-2-yl)acetamide derivatives.

mesh) and eluted with proper solvent ($CHCl_3$:CH_3OH) system. The elutants were concentrated *in vacuo* and crystallized at 4 °C using chloroform hexane mixture to obtain a pure compound. The purity of the compounds was decided on the basis of melting points and elemental data analysis.

All the compounds were characterized using the ^{1}H NMR, IR and mass spectrophotometry. Some of the compounds were analyzed by using ^{13}C NMR. Almost all the compounds showed the molecular ion signal at M + 1, however in some cases [M + Na] signal was found. In ^{1}H NMR, the characterize signal around 7.28–6.72 ppm (CH=N) shows the condensation of substituted-quinoline-3-carbaldehyde and the different thiosemicarbazides. Other signals were found in accordance to the established structures. When the thiosemicarbazides were condensed in excess of acetic anhydride, the corresponding singlet shows an up-field shift from 7.28–6.72 ppm to 5.69–4.93 ppm range. The proton shift showed the change in status of carbon from unsaturated to saturated one. The cyclization was confirmed by the disappearance of NH signals and the appearance of a new singlet signal due to the six proton ($-CH_3$) around 2.13–3.10 ppm. To confirm the results, some molecules were analyzed by ^{13}C NMR. The ^{13}C NMR spectra of thiadiazoles showed some prominent signals, such as signals in 50–60 ppm, and around 22–26 ppm range, which were absent in corresponding thiosemicarbazones. These signals represent the change in carbon environment and were attributed to CH(NS) carbon and alkyl carbon, as the inclusion of two methyl groups was expected in the process of cyclization.

Table 1
Different substituent's "X" and "R" as indicated in Fig. 1.

Compound	X	R
1A, 1B	Cl	H
9A, 9B	H	
17A, 17B	CH_3	
3A, 3B	Cl	
11A, 11B	H	
19A, 19B	CH_3	
5A, 5B	Cl	
13A, 13B	H	
21A, 21B	CH_3	
7A, 7B	Cl	
15A, 15B	H	
23A, 23B	CH_3	
2A, 2B	Cl	
10A, 10B	H	
18A, 18B	CH_3	
4A, 4B	Cl	
12A, 12B	H	
20A, 20B	CH_3	
6A, 6B	Cl	
14A, 14B	H	
22A, 22B	CH_3	
8A, 8B	Cl	
16A, 16B	H	
24A, 24B	CH_3	

The structures were further confirmed by the appearance and disappearance of a band around 3400 cm^{-1} in the thiosemicarbazones and thiadiazoles, respectively. This suggests that the NH group had reacted in the process of cyclization. Besides the other characteristic signals for aromatic rings and C=N, a strong signal around 2930–2965 cm^{-1} indicates the presence of aliphatic methyl groups. The signal appeared as a new signal in the compound (**1B**–**24B**). The existence of a strong band in the region 1102–1133 cm^{-1} due to C=S and the absence of any band in the region 2500–2600 cm^{-1} due to C–SH suggest that all thiosemicarbazones retains the thione nature. In the compounds (**1B**–**24B**), two sharp carbonyl peaks were observed, backing inclusion of two acetyl groups to the newly cyclized thiadiazoles at the two different positions. Carbonyl group stretching frequency corresponded to esteric carbonyl stretching and amidic carbonyl stretching were observed at 1640–1678 cm^{-1}.

2.2. Pharmacology

2.2.1. In vitro evaluation of antibacterial activity against gram-positive and gram-negative bacteria

All the synthesized thiosemicarbazones (**1A**–**24A**) and their thiadiazole derivatives (**1B**–**24B**) were screened for their antimicrobial activity using the gram-positive and gram-negative bacteria. Four different cultures, two each of gram-negative (*Escherichia coli* and *Salmonella typhimurium*) and gram-positive (*Staphylococcus aureus* and *Staphylococcus pyogenes*) were treated