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Synthesis and Antimicrobial Activity of Some Novel 7-Chloro-4-aminoquinoline Derivatives

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Abstract—A number of novel 7-chloro-4-aminoquinoline derivatives have been efficiently synthesized by nucleophilic aromatic substitution reaction of 4,7-dichloroquinoline with α,ω-diaminoalkanes of variable carbon-chain length. Treatment of the intermediates with substituted aromatic/heteroaromatic aldehydes has led to the corresponding Schiff bases. Structures of the products have been elucidated from FTIR, ^{1}H, and ^{13}C NMR, and mass spectra. Antimicrobial tests of the compounds have indicated that the most active ones displayed MIC values in the range of 1.5 to 12.5 μg/mL, however they displayed no antifungal activity. According to the accumulated data, length of the carbon-chain linker and electronic properties of the compounds are decisive for their biological activity. Molecular docking studies have supported the above relationships.

Keywords: 7-chloro-4-aminoquinolines, Schiff base, antimicrobial activity, molecular docking, ADMET studies

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INTRODUCTION

4-Aminoquinoline nucleus have been found ubiquitously in nature (4-AQ) [1–6] and therefore are used in designing of bioactive compounds displaying anti-virulence [7], antimalarial [8, 9], anti-leishmanial [10], anti-platelet aggregation [11], anti-viral [12], anti-inflammatory, immune-modulatory, and anticancer [1] activities.

The Schiff bases derivatives have been well-established for biocidal activity [13]. A series of 4-oxothiazolidin-2-ylidenehydrazide derivatives have been designed and evaluated for their antibacterial potential [14]. N-(Salicylidene)-2-hydroxyaniline was quoted as a typical example of a compound efficient against *Mycobacterium tuberculosis* (H37Rv) with MIC value as low as 8 μg/mL [15], and various bis-Schiff-base derivatives of isatin demonstrated significant antibacterial, antifungal and antiviral activities [16].

The overlaps in geographical manifestation between malaria and non-malarial infectious diseases led to the idea of possible use of amino-quinoline moiety in development of new antimicrobial agents.

Therefore, some compounds containing Schiff-bases of 7-chloro-4-aminoquinolines with high antimicrobial potential were designed and synthesized as presented below.

RESULTS AND DISCUSSION

Novel derivatives of 7-chloro-4-aminoquinoline **5**–**12** were synthesized in a two-step reaction *via* nucleophilic aromatic substitution (Scheme 1). FTIR spectra of the synthesized derivatives demonstrated characteristic bands of N=C bond at 1505–1610 cm^{-1} [17]. ^{1}H NMR spectra of the compounds exhibited a singlet in the range of 8.98–8.92 ppm attributed to the secondary amino group and a triplet in the range of 8.24–8.10 ppm characteristic to the imine group.

Due to the fact that one of modes of action of ciprofloxacin involve the enzyme, DNA topoisomerase, it was used as the target (DNA topoisomerase IV, PBD ID 3FV5) for estimating molecular interactions with the synthesized ligand molecules, presumably responsible for antimicrobial potential of the products. Another bacterial protein, the Penicillin Binding Protein 1a (PBP1a, PDB ID 3UDI) was also selected to dock the synthesized ligand molecular structures for determining their binding ability. The target protein PBP1a plays a key role in resistance development to the existing drugs. The binding