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A novel templates of piperazinyl-1,2-dihydroquinoline-3-carboxylates: Synthesis, anti-microbial evaluation and molecular docking studies

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ABSTRACT

A series of piperazinyl-1,2-dihydroquinoline carboxylates were synthesized by the reaction of ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylates with various piperazines and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis. All the synthesized compounds were screened for their *in vitro* antimicrobial activities. Further, the *in silico* molecular docking studies of the active compounds was performed to explore the binding interactions between piperazinyl-1,2-dihydroquinoline carboxylate derivatives and the active site of the Staphylococcus aureus (CrtM) dehydrosqualene synthase (PDB ID: 2ZCQ). The docking studies revealed that the synthesized derivatives showed high binding energies and strong H-bond interactions with the dehydrosqualene synthase validating the observed antimicrobial activity data. Based on antimicrobial activity and docking studies, the compounds **9b** and **10c** were identified as promising antimicrobial lead molecules. This study might provide insights to identify new drug candidates that target the S. aureus virulence factor, dehydrosqualene synthase.

N-Heterocyclic compounds remain an attractive topic from both fundamental organic chemistry and medicinal chemistry point of view. Among all heterocycles, the synthesis of quinolones has received much attention from medicinal chemists due to a wide variety of pharmacological properties attributed to this compound class itself. They have been reported to show typical antibacterial activity, and also displayed a typical diverse biological profiles such as anti-tumor, anti-tubercular, anti-HIV, antibacterial, anti-malarial activities, and the biological properties continue to expand[1–4] as shown in Fig. 1. The majority of quinolones in clinical use are fluoroquinolones which are one of the most useful and versatile antibacterial agents, where several candidates are already in clinical use such as Ciprofloxacin, Norfloxacin and Ofloxacin.[5] They have emerged as one of the dominant classes of chemotherapeutic drugs for the treatment of various bacterial infections in both community and hospital settings.[6] However, since these compounds became available for clinical use, resistance among Methicillin-resistant *Staphylococcus aureus* has been observed in different parts of the world.[7–9] Molecular hybridization, which is based on the incorporation of two or more pharmacophores into a single molecule, may provide novel candidates having complimentary activities and/or multiple pharmacological targets and/or one part can counterbalance the side effects caused by another part.[10] Modifications in the basic structure of quinolones[11] have increased their antibacterial spectrum and potency, as well as improving bioavailability, making quinolones useful agents for the treatment of urinary, systemic and respiratory tract infections. Obviously, this strategy represents an encouraging approach on the development of new agents with potential therapeutic application (Fig. 2).[12–18]

As a part of our efforts to develop new biologically active molecules,[19] we describe the synthesis and antimicrobial evaluation of quinolones bearing piperazines at C-4 position as shown in Scheme 1. All the derivatives were further screened for *in vitro* antimicrobial activities. In this context, we herein report the synthesis of piperazine linked 1,2-dihydroquinoline carboxylate hybrids in good to excellent yields as depicted in Fig. 3.

Synthesis of intermediates and target compounds was accomplished according to the steps illustrated in Scheme 1. The first synthetic step involved *N*-alkylation of isatoic anhydride with iodoalkanes to obtain the corresponding *N*-alkyl isatoic anhydrides **2** and **3**. Condensation of diethyl malonate and *N*-alkyl isatoic

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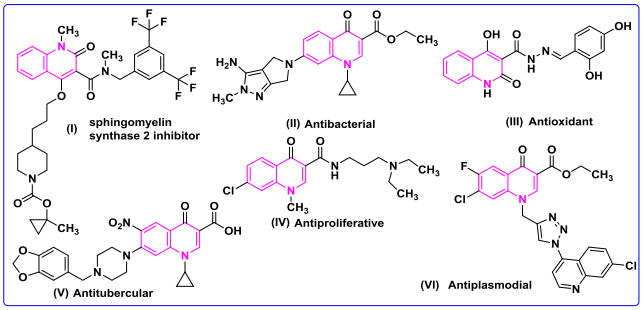


Fig. 1. Representative examples of biologically active quinolone-based compounds.

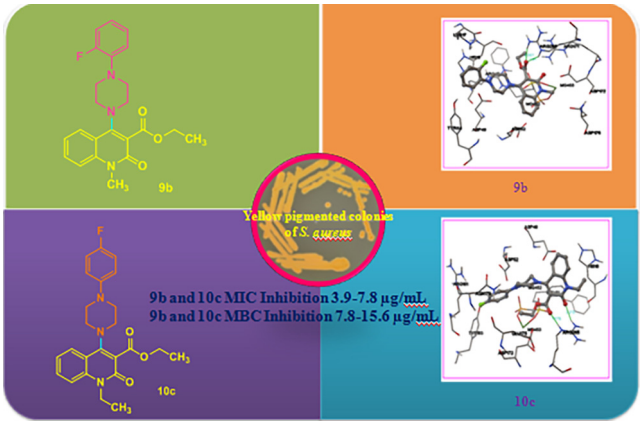
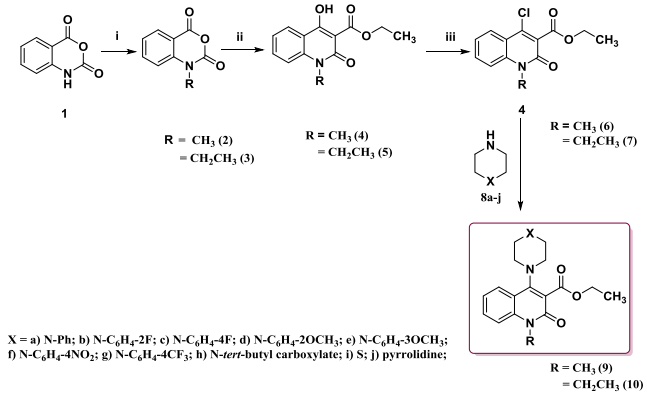


Fig. 2. Design strategy for ethyl-2-oxo-4-(piperazin-1-yl)-1,2-dihydroquinoline-3-carboxylate hybrids.



Scheme 1. Synthesis of ethyl-2-oxo-4-(piperazin-1-yl)-1,2-dihydroquinoline-3-carboxylate hybrids **9a–j** and **10a–j**. *Reagents and conditions:* i) RI, NaH, dry DMF, 0 °C-RT, 5 h ii) Diethyl malonate, NaH, dry DMF, 120 °C, reflux, 16 h, iii) $POCl_3$, reflux, 3 h.

anhydrides in the presence of sodium hydride in dry dimethylformamide led to compounds **4** and **5** in good yields (78%–72%).[20] The corresponding **4** and **5** were further converted into chloro derivatives using phosphoryl chloride under thermal condition for 3 h under inert atmosphere.[21] (Scheme 1).

All the synthesized compounds (**9a–j** and **10a–j**) were characterized by using ^{1}H NMR, ^{13}C NMR, HR-Mass and IR spectroscopic methods. Spectral data of all synthesized compounds were in good agreement with the proposed structures. In ^{1}H NMR spectra, the characteristic triplet signals appeared for piperazine protons at δ

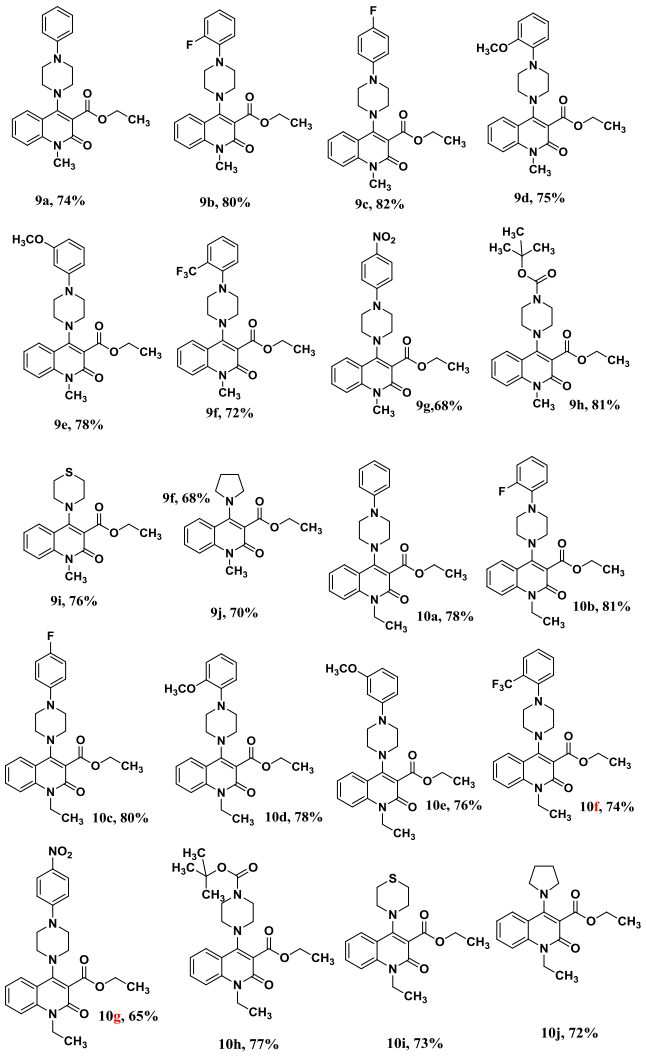


Fig. 3. Newly synthesized ethyl-2-oxo-4-(piperazin-1-yl)-1,2-dihydroquinoline-3-carboxylatederivatives **9a–j** and **10a–j.**

3.10–3.85 ppm. The structures for all these compounds were further confirmed by HRMS analysis. For instance, **9a** displayed a molecular ion peak at *m/z* 392.19687 $[M+H]^+$ suggesting the molecular formula of $C_{23}H_{25}N_3O_3$. Additionally, the IR spectra for the target compounds **9a–j** and **10a–j** exhibited characteristic absorption bands at 1635–1648 cm^{-1}, 1080–1360 cm^{-1} and 2924–2982 cm^{-1} which corresponded to C═O, C—N and C—H_3 respectively (Fig. 4).

The synthesized hybrids **9a–j** and **10a–j** were evaluated for their *in vitro* antimicrobial activity against Gram positive bacterial strains such as *Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 96, *Staphylococcus aureus* MLS-16 MTCC 2940, *Micrococcus luteus* MTCC 2470, Gram-negative bacterial strains such as *Escherichia coli* MTCC 739, *Klebsiella planticola* MTCC 530, *Pseudomonas aeruginosa* MTCC 2453 and a fungal strain *Candida albicans* MTCC 3017, and the results to this regard are tabulated in Table 1. Ciprofloxacin and Miconazole were used as standard controls for the bacterial and fungal strains, respectively. The compounds **9b** and **10c** exhibited promising and broad spectrum antimicrobial activity against all the test pathogens except for *Klebsiella planticola* MTCC 530 and *Pseudomonas aeruginosa* MTCC 2453 with MIC values ranging from 3.9 to 7.8 µg/mL. Further, the compounds **9b** and **10c** exhibited a MIC value of 3.9 µg/mL against *Candida albicans*