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Derivatives (halogen, nitro and amino) of 8-hydroxyquinoline with highly potent antimicrobial and antioxidant activities

Rungrot Cherdtrakulkiat [a], Somchai Boonpangrak [b], Nujarin Sinthupoom [a], Supaluk Prachayasittikul [c,*], Somsak Ruchirawat [d,e], Virapong Prachayasittikul [a,*]

[a] Department of Clinical Microbiology and Applied Technology, Faculty of Medical Technology, Mahidol University, Bangkok 10700, Thailand
[b] Center for Innovation Development and Technology Transfer, Faculty of Medical Technology, Mahidol University, Bangkok 10700, Thailand
[c] Center of Data Mining and Biomedical Informatics, Faculty of Medical Technology, Mahidol University, Bangkok 10700, Thailand
[d] Laboratory of Medicinal Chemistry, Chulabhorn Research Institute and Program in Chemical Biology, Chulabhorn Graduate Institute, Bangkok 10210, Thailand
[e] Center of Excellence on Environmental Health and Toxicology, Commission on Higher Education (CHE), Ministry of Education, Thailand

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ABSTRACT

8-Hydroxyquinoline (8HQ) compounds have been reported to possess diverse bioactivities. In recent years, drug repositioning has gained considerable attention in drug discovery and development. Herein, 8HQ (**1**) and its derivatives (**2–9**) bearing various substituents (amino, nitro, cyano and halogen) were investigated for their antimicrobial against 27 microorganisms (agar dilution method) and antioxidant (DPPH method) activities. The parent 8HQ (**1**) exerted a highly potent antimicrobial activity against Gram-positive bacteria including diploid fungi and yeast with MIC values in the range of 3.44–13.78 μM. Moreover, the halogenated 8HQ, especially 7-bromo-8HQ (**4**) and clioquinol (**6**), displayed a high antigrowth activity against Gram-negative bacteria compared with the parent compound (**1**). Apparently, the derivatives with a relatively high safely index, e.g., nitroxoline (**2**), exhibited strong antibacterial activity against *Aeromonas hydrophila* (MIC = 5.26 μM) and selectively inhibited the growth of *P. aeruginosa* with the MIC value of 84.14 μM; cloxyquin (**3**) showed a strong activity against *Listseria monocytogenes* and *Plesiomonas shigelloides* with MIC values of 5.57 and 11.14 μM, respectively. Most compounds displayed an antioxidant activity. Specifically, 5-amino-8HQ (**8**) was shown to be the most potent antioxidant (IC_{50} = 8.70 μM) compared with the positive control (α-tocopherol) with IC_{50} of 13.47 μM. The findings reveal that 8HQ derivatives are potential candidates to be further developed as antimicrobial and antioxidant agents.

1. Introduction

Nitrogen heterocycles constitute a large group of compounds with a vast array of pharmacological activities [1–3]. Specifically, quinoline is a privileged structure that is found in a variety of natural products and therapeutics. 8-Hydroxyquinoline (8HQ), a derivative of quinoline, has a strong metal chelating property [4]. The derivatives of 8HQ have been reported to have multifunctional uses as antimicrobial, antioxidant, anticancer, antiinflammatory and antineurodegenerative agents [5–8]. The halogenated 8HQs, such as cloxyquin (5-chloro-8HQ), clioquinol (5-chloro-7-iodo-8HQ or CQ), 7-bromo-8HQ and iodoquinol (5,7-diiodo-8HQ), have been synthesized and are commercially available [9]. The cloxyquin was reported to show good antitubercular and antiamoebic activities [10]. CQ was also used for several years as an antidiarrheal agent to treat amoebic infection. Then, it was banned from oral consumption in the 1960s because it can cause subacute myelo-optic neuropathy (SMON) [11]. However, the neurotoxicity of CQ can be solved by the recommended dosage control and vitamin supplementation. Nitroxoline (5-nitro-8HQ or NQ) has been used for the treatment and prophylaxis of acute and recurrent urinary tract infection [7]. In addition, NQ has been approved by the Food and Drug Administration (FDA), and is widely used as an anti-neurodegenerative drug to treat Alzheimer's disease and cancer in humans [6]. Moreover, metal complexes in 8HQ have been reported to enhance 8HQ bioactivities [12]. The search for novel potent lead compounds and repositioning of the well-known compounds/drugs for therapeutic applications are the main challenges [13–16]. In recent years, drug repositioning or repurposing has attracted pharmaceutical companies because the possibility of using the approved or investigational drug in a new therapeutic area avoids the expensive and time-consuming pharmacokinetic and toxicity tests that are required for new drug candidates [17]. Currently, diverse bioactivities of the 8HQ derivatives have not been fully explored. Therefore, 8HQ and its derivatives that bear substituents (amino, halogen, nitro) at positions

* Corresponding authors.
E-mail addresses: supaluk@swu.ac.th (S. Prachayasittikul), virapong.pra@mahidol.ac.th (V. Prachayasittikul).

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5 and/or 7 as well as a cyano group at 2-position were investigated for their antimicrobial and antioxidant activities as well as cytotoxic effect.

2. Materials and methods

2.1. Compounds and chemical reagents

Nine tested compounds (**1**–**9**, Fig. 1) are commercially available. Specifically, 8HQ (**1**), NQ (**2**), cloxyquin (**3**), 7-bromo-8HQ (**4**), CQ (**6**), iodoquinol (**7**), and 5-amino-8HQ (**8**) were purchased from Sigma, USA. Compounds 5,7-dichloro-8HQ (**5**) and 8HQ-2-carbonitrile (2-CN-8HQ, **9**) were purchased from Acros Organics.

α-Tocopherol (vitamin E), 2,2-diphenyl-1-picrylhydrazyl (DPPH), Dulbecco's Modified Eagle's Medium (DMEM), fetal bovine serum (FBS), penicillin-streptomycin, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were supplied by Sigma, USA. Dimethyl sulfoxide (DMSO) was purchased from Merck, Germany.

2.2. Antimicrobial activity assay

Antimicrobial activity of 8HQ and its derivatives (**1**–**9**) was performed using the agar dilution method, as previously described [2]. Briefly, the tested compound was dissolved in DMSO and, then, was mixed with the Müeller Hinton (MH) broth. The compound solution was two-fold diluted, and 1 mL of each dilution was mixed into the MH agar to obtain the final concentration range of 0.25–256 μg/mL. DMSO (0.5%) was added into the MH agar and was used as a reagent control. The microorganisms were cultured in the MH broth at 37 °C overnight and were diluted with a normal saline solution until the cell density was 0.5 McFarland standard (1.5×10^8 CFU/mL). The microorganisms were inoculated onto the agar plates and were incubated at 37 °C for 24–48 h. A minimum inhibitory concentration (MIC) of the compounds was determined. Twenty-seven strains of the tested microorganisms were Gram-negative bacteria: *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Serratia marcescens* ATCC 8100, *Salmonella* Typhimurium ATCC 13311, *Salmonella* Choleraesuis ATCC 10708, *Salmonella* Enteritidis, *Shigella dysenteriae*, *Morganella morganii*, *Citrobacter freundii*, *Plesiomonas shigelloides*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa* ATCC 27853, *Pseudomonas stutzeri* ATCC 17587, *Shewanella putrefaciens* ATCC 8071, *Achromobacter xylosoxidans* ATCC 27061; Gram-positive bacteria: *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 29213, *Staphylococcus epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 10240, *Enterococcus faecalis* ATCC 29212, *Enterococcus faecalis* ATCC 33186, *Corynebacterium diphtheriae* NCTC 10356, *Bacillus subtilis* ATCC 6633, *Listeria monocytogenes*, *Bacillus cereus*; and diploid fungi and yeast: *Candida albicans* ATCC 90028 and *Saccharomyces cerevisiae* ATCC 2601.

2.3. Antioxidant activity assay

Compounds (**1**–**9**) were determined for their antioxidant properties using the DPPH assay [18]. DPPH (a stable purple color radical) reacts with an antioxidant to form a light-yellow diphenylpicrylhydrazine, which is the reduced product that can be detected using a spectrophotometer. The assay was initiated by adding a 1 mL solution of DPPH in methanol (0.1 mM) to a sample solution (0.45 mL, 1 mg/mL dissolved in DMSO). The reaction mixture was incubated for 30 min in a dark room. The absorbance at 517 nm was measured using a UV–visible spectrophotometer (UV-1610, Shimadzu), and the percentage of radical scavenging activity (RSA) was calculated using the following equation:

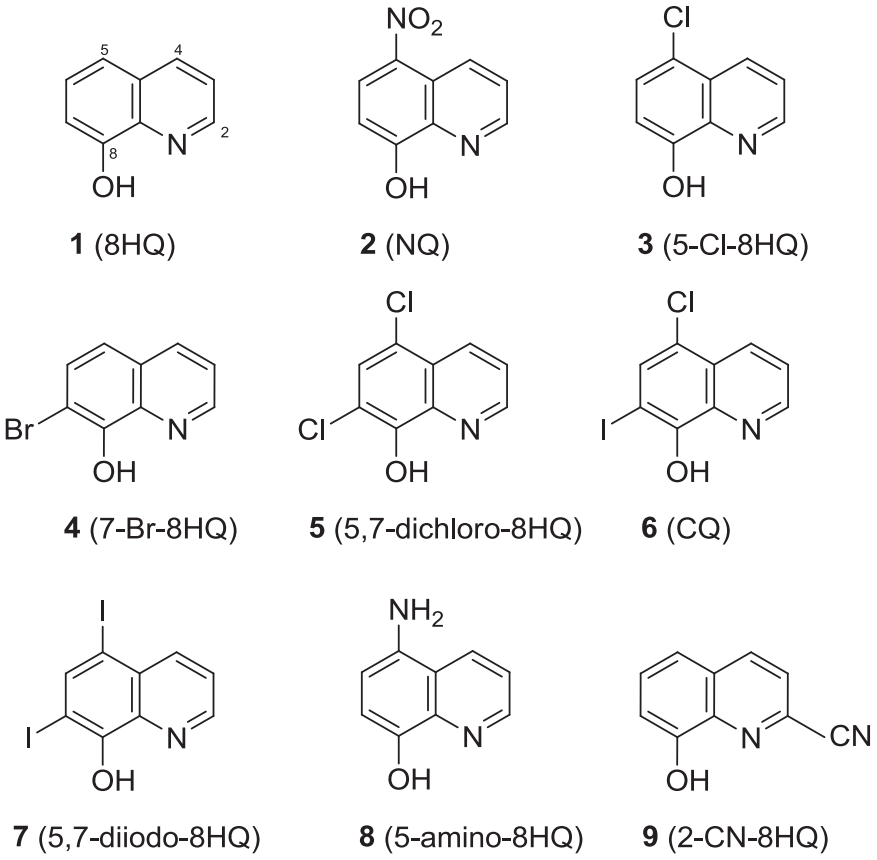

Fig. 1. Chemical structures of 8HQ and its derivatives (**1**–**9**).