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Synthesis, Characterization and Biological Activity of Some Novel 5-((4-Alkyl piperazin-1-yl) methyl) quinolin-8-ol Derivatives

Mohamed El Faydy [1], Naoufal Dahaief [2], Mohamed Rbaa [1], Khadija Ounine [2], Brahim Lakhrissi [1]*

[1]*Laboratory of Agricultural Resources, Polymers and Process Engineering, IbnTofail University, Department of chemistry, B.P. 133, Kenitra, Morocco*

[2]*Laboratory of Nutrition, Health and Environment, IbnTofail University, Department of biology, B.P. 133, Kenitra, Morocco*

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**Corresponding author. E-mail: b.lakhrissi2012@gmail.com*

Abstract

A series of new 5-((4-Alkyl piperazin-1-yl) methyl) quinolin-8-ol derivatives were synthesized starting from the properly substituted 4-piperazine, by condensation with 5-chloromethyl-8-quinolinol in the presence of triethylamine. The structures of all the compounds were identified by ^{1}H NMR and ^{13}C NMR. The 5-Chloromethyl-8-Quinolinol hydrochloride (CMQ) was also characterized by IR spectra. The antibacterial activity of the newly synthesized compounds was evaluated and screened "in vitro" using the disc diffusion technique against Gram-positive and Gram-negative bacterial strains .The antibacterial screening results revealed that among the fourth compounds screened, three of them, showed a very good antibacterial activity compared to the standard antibiotic.

Keywords: Quinolinol; piperazine; synthesis; characterization; antibacterial activity

1. Introduction:

Among the by-products of the quinoline, we can quote Hydroxyquinoline derivatives, which are used due to their biological activity as inhibitors of catechol *O*-methyltransferase inhibitors [1], of HIF-1a prolyl hydroxylase [2]. Styrylquinoline derivatives have gained strong attention recently due to their activity as perspective HIV integrase inhibitors [3], antibacterial [4-5], antimalarial [6], antitumor agents [7-9], antifungal and herbicidal activities [10], protein tyrosine kinase inhibitors [11] and protozoal–retroviral co-infections [12]. In addition, some of the investigated quinoline derivatives also showed antineoplastic activity [13]. However, because of its poor solubility, cosolvents and surfactants must be used for its formulation in water or organic solvents. Some of 8-quinolinol derivatives and their complexes with transition metals were reported to be active against some bacteria and DNA [14-15]. The compounds containing quinolin-8-ol pharmacophore seem especially interesting. According to the results reported recently, the 8-hydroxyquinoline derivatives are also potent agents for neuroprotection in Alzheimer's, Parkinson's, and other neurodegenerative diseases [16]. The heterocyclic compounds containing a piperazine ring have shown potent pharmacological activities including antimicrobial and the substituted piperazines are important pharmacophores found in the field of medicinal chemistry [17-18].

In the present study, we have synthesized a series of some quinolin-8-ol derivatives containing a 4-substituted piperazine moiety. The synthesized compounds were characterized by ^{1}H and ^{13}C NMR and tested against Gram-positive and Gram-negative bacteria.

2. Experimental Section

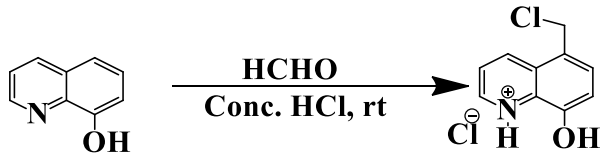
2.1. General Information

All chemicals products were purchased from Aldrich or Acros (France or Spain).Infrared spectra were recorded in a FT-IR Nicolet 400D Spectrophotometer using KBr pellets. NMR spectra were recorded on a model Bruker Avance (300 MHz) for solutions in Me_2SO-d_6. The progress of the reaction was followed by Thin-Layer Chromatography (TLC) using silica gel 60 F254 (E. Merck) plates with visualization by UV light (254 nm). Silica gel with 0.040–0.063 mm particle size was used as a support in every flash chromatography purification procedure.

2.2. Chemical synthesis

2.2.1. Synthesis of 5-Chloromethyl-8-Quinolinol hydrochloride (CMQ)

5-Chloromethyl-8-hydroxyquinoline hydrochloride (**I**) was synthesized according to the method described by Burckhalter [19], which consists to the reaction of 8-hydroxyquinoline with formaldehyde and concentrated hydrochloric acid (scheme 1). NMR ^1H spectroscopy and IR were used for the characterization and confirmation of the product structure.



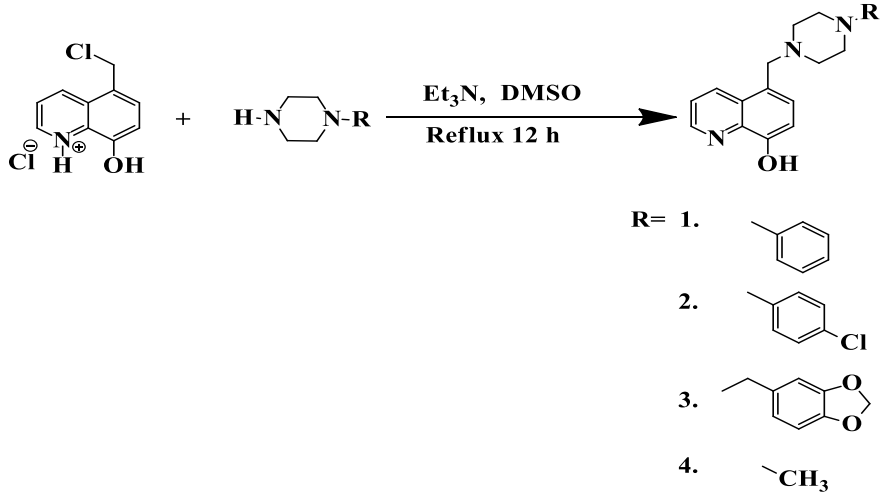
(I)

Scheme 1: Synthesis of 5-Chloromethyl-8-hydroxyquinoline hydrochloride (**CMQ**)

A mixture of 10.0 g (68 mmol) of 8-hydroxyquinoline, 11 mL of concentrated hydrochloric acid (36 %, 11.65 N), and 11 mL (397 mmol) of formalin **(**37 **%** formaldehyde and 12 % methanol), was treated with hydrogen chloride gas and stirred for 6 h. The solution was allowed to stand at room temperature for 2 h without stirring. The yellow solid obtained was collected on a filter, washed three times in acetone and dried under vacuum to afford 5-chloromethyl-8-hydroxyquinoline hydrochloride as a yellow solid (7.0 g, 70 %) without further purification, m.p. : 282 °C, R_f Value: 0.52 (n-hexane/acetone: 4/6), NMR ^1H (300 MHz, Me_2SO-d_6), δ_{ppm} = 9.21-9.10 (m, 2H, aromatic), 7.47-8.09 (m, 3H, aromatic), 5,31 (s, 2H ,CH_2-Cl); IR (KBr cm^{-1}): 1600 (C=C aromatic), 2850 - 3000 (C-H aromatic), 3219 (NH^+), 1410-1330 (O-H), 1470-1490 (CH_2-Cl).

2.2.2. Synthesis of 5-((4-Alkyl piperazin-1-yl) methyl) quinolin-8-ol

The condensations of 5-chloromethyl-8-hydroxyquinoline hydrochloride with an appropriate secondary amines in the presence of triethylamine give the corresponding 5-substituted products (Scheme 2).



Scheme 2: Synthesis of 5-((4-alkyl piperazin-1-yl)-methyl) quinolin-8-ol

General procedure:
To a stirred solution of 5-chloromethyl-8-hydroxyquinoline hydrochloride (**I**) (5.74 mmol) and triethylamine (8.5 mmol) in dimethyl sulfoxide (20 mL), the appropriate piperazine (5.74 mmol) was added and the resulting mixture was heated at 80 °C for 12 h. The reaction was monitored by thin layer chromatography (TLC). After completion and cooling to room temperature, Water (50 mL) was subsequently added and the product extracted with ethyl acetate (EtOAc) (3×80 mL). The combined organic phases were combined**,** dried over anhydrous sodium sulfate, filtered and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography with hexane/acetone (6:4) to furnish the desired product as clear brown oil.

2.2.3. Synthesis of 5-((4-phenylpiperazin-1-yl) methyl) quinolin-8-ol (PPMQ)
It was synthesized from 1-phenyl piperazine and 5-(chloromethyl) quinolin-8-ol following the general procedure Yield 80 %, brown oil, R_f Value: 0.25 (n-hexane/acetone: 4/6).
^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.96-7.28 (m, 5H, benzene), 7.30-8.83 (m, 5H, quinoline), 5.03 (s, 1H, OH), 3.42 (s, 2H, aromatic-CH_2-N), 2.05 (m, 4H, -CH_2-N), 2.87 (m, 4H, -CH_2-N).
^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 40.81, 42.54, 45.10, 48.96 (N-$\underline{C}H_2$-C), 61.35 (quinoline-$\underline{C}H_2$-piperazine), 110.18, 111.55, 118.07, 121.71, 122.21, 127.86, 129.09, 134.22, 136.42, 148.17, 153.72 (quinoline and phenyl).

2.2.4. Synthesis of 5-(4-(4-chlorophenyl) piperrazin-yl) methylquinolin-8-ol (CPMQ)
It was synthesized from 1(4-chlorophenyl) piperazine and 5-(chloromethyl) quinolin-8-ol following the general procedure. Yield 75 %, brown oil, R_f Value: 0.3 (n-hexane/acetone: 4/6)
^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.71-7.30 (m, 4H, benzene), 7.10-8.02 (m, 5H, quinoline), 5.95 (s, 1H, OH), 3.37 (s, 2H, aromatic-CH_2-N), 2.48 (m, 4H, -CH_2-N), 2.97 (m, 4H, -CH_2-N).
^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 52.89, 56.30 (N-$\underline{C}H_2$-C), 62.15 (quinoline-$\underline{C}H_2$-piperazine), 110.28, 112.79, 116.76, 108.27, 109.06, 109.47, 122.35, 129.04, 147.63 (quinoline and 4-chlorophenyl).

2.2.5. Synthesis of 5-((4-benzo-[1, 3]-dioxo-5-ylmethyl) piperazinyl) methylquinolin-8-ol (BPMQ)
It was synthesized from 1-(benzo-[1.3]-dioxo-5-ylmethyl) piperazine and 5-(chloromethyl) quinolin-8-ol following the general procedure. Yield 60 %, brown oil, R_f Value: 0.4 (n-hexane/acetone: 4/6):

^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 7.01-8.82 (m, 8H, aromatic), 3.05 (s, 2H, aromatic-CH_2-N), 2.48 (s, 8H, -CH_2-piperazine), 3.76 (s, 2H, piperazine-CH_2-phenyl), 6.97-7.11 (m, 3H, -CH-), 6.07 (s, 2H, O-CH_2-O)5.39 (s, 1H, OH group).
^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 48.92, 52.89 (N-$\underline{C}H_2$-C), 62.15 (quinoline-$\underline{C}H_2$-piperazine), 64.27 (N-$\underline{C}H_2$-1-(benzo-[1.3]-dioxole), 101.20, 102.79, 106.76, 108.27, 109.06, 109.47, 122.35, 129.63, 147.63 (quinoline and benzo-[1.3]-dioxole).

2.2.6. Synthesis of 5-(4-methylpiperrazinyl)-methylquinolin-8-ol (MPMQ)
It was synthesized from 1-methylpiperazine and 5-chloromethylquinolin-8-ol following the general procedure **A**. Yield 85 %, brown oil, R_f Value: 0.2 (n-hexane/acetone: 4/6)
^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.48-8.05 (m, 8H, aromatic), 3.39 (s, 2H, aromatic-CH_2-N), 2.06 (s, 3H, -CH_3), 2.52 (m, 4H, CH_2 group), 2.97 (m, 4H, CH_2 group), 3.39 (s, 1H, OH group).
^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 45.07 ($\underline{C}H_3$), 48.78, 49.04, 49.91, 51.04 (N-$\underline{C}H_2$-C), 61.35 (quinoline-$\underline{C}H_2$-piperazine), 112.43, 116.73, 120.02, 129.39, 129.45, 151.33 (quinoline).
The examination of these reactions shows that the yields are generally greater than 60 per cent and may reach 80 per cent; the comparison between the synthesized compounds reveals a decrease in yield by replacing the methyl carried by piperazine, by *p*-chlorophenyl or 4-(benzo-[1,3]-dioxo-5-yl)methyl or 4-chlorophenyl more bulky groups. This could be explained by steric hindrance**.**

3. Antimicrobial activity

3.1. Microorganisms

The antimicrobial activity of the synthesized compounds was tested towards four different microorganisms. Bacteria selected for this study are *Escherichia coli* and *Staphylococcus aureus* that are opportunists and pathogenic responsible for poisonings food and infections, *Enterobacter ludwigii* is regarded as an emerging opportunistic human pathogen; the choice of *Bacillus subtilis* is based on the fact that it presents a sporulation character. They are found in the environment, food and in the intestines of animals as well as humans and they are associated with human infection. They were all supplied by laboratory of nutrition, health and environment. Each bacterium was inoculated on the culture medium Mueller-Hinton agar [20-21].

3.2. Antibacterial assay

Antibacterial activity was determined using the disc diffusion assay. Overnight culture was streaked on the surface of Muller-Hinton agar plate. Sterile filter paper disc was saturated with 10 µL of 0.5 µL/mL v/v solution of the newly synthesized compounds under investigation in dimethyl sulfoxyde (DMSO). The plates and discs were then incubated at 37 °C for 24 h and the developing inhibition zones were compared with those of reference discs (Figures 1 & 2). Antibiotic penicillin G was used as a reference for bacteria.

4. Results and discussion

All the compounds are synthesized by a simple nucleophilic substitution reaction of piperazine derivatives and 5-chloromethyl-8-quinolinol hydrochloride in dimethyl sulfoxide as solvent. We have tried to focus on introducing new functionality on the piperazine ring to achieve a better antimicrobial profile, Since according to the results of the literature, the compounds 1-But-2-enyl-4 methylpiperazine and 1-isobutyl-4-(2-methoxyphenyl) piperazine showed significant activity against antibacterial strains. On the other hand, the piperazine bearing alkyls groups which have electron-withdrawing substituents (like halogen) displayed weaker activity against Gram-positive and Gram-negative bacteria than those having electron-donating substituents (such as ethyl and chlorophenyl), which suggested that substituent group can affect the inhibitory activity, and the compounds with electron-donating substituents exhibited better inhibitory activities than those with electron-withdrawing substituents, also according to Patel and coworkers, who have reported that the incorporating of monohalo (fluoro, chloro)-substituted phenyl ring of piperazine entity bridged to triazine core, displayed good inhibition effect [22-25]. For all the compounds tested, the pH is between 7.5 and 8.0. The results of the antimicrobial activity with standard antibiotic penicillin G are shown in Table 1.

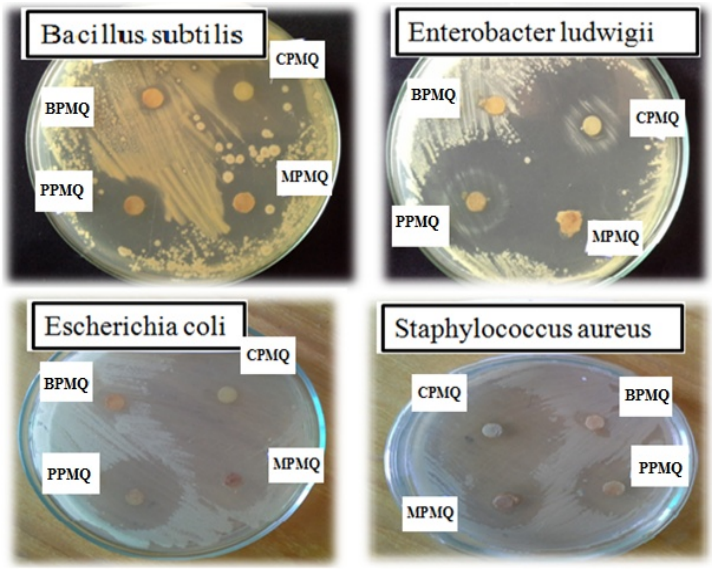


Figure 1: Antibacterial activity of the synthesized compounds against bacteria after 24 h.

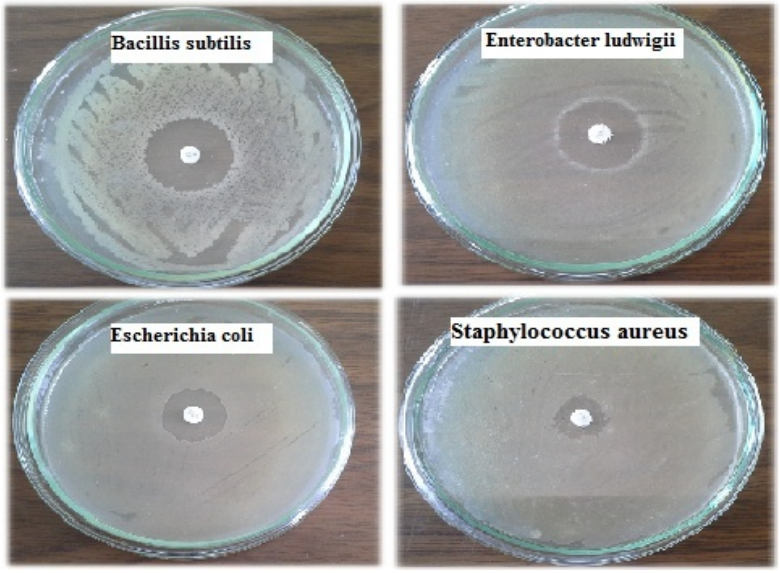


Figure 2: Antibacterial activity of the reference standard Penicillin G against bacteria after 24 h

Table 1: The inhibition zone (mm) of the synthesized compounds and standard Penicillin G against bacteria

Compounds	Inhibition zone diameter (mm)			
	Gram positive bacteria		Gram negative bacteria	
	B. subtilis	*S. aureus*	*E. coli*	*E. ludwigii*
CPMQ	40	25	50	45
BPMQ	25	25	30	27
MPMQ	25	25	30	27
PPMQ	0	No zone	0	No zone
Penicillin G	27	17	24	19

There was considerable variability in the size of zone of inhibition with the different compounds. It is observed that all the compounds exhibited strong activities against bacterial microorganisms in the exception of BPMQ product.

CPMQ compound is highly active against all the bacterial cultures. **PPMQ** and **MPMQ** compounds are moderately active against all the bacterial cultures, but the **BPMQ** compound is inactive against all bacterial cultures.

All products have an almost similar structure; they differ only by substituent at 4-position of the piperazine moiety. The findings of the present study revealed that the considerable variation of these effects were seen with each structural change, the possible electronic effects induced by the group bound to the 4-position of the piperazine moiety are responsible for the inhibitory actions of the studied bacteria.

Conclusion

According to the results, we conclude that anti-bacterial activities screening clearly indicate that the nature of the 4-position substituent of the piperazine moiety, affected the "*in vitro*" antibacterial activity significantly. The antimicrobial screening of the synthesized compounds showed moderate to good activity compared to the antibiotic penicillin G, and can be further developed for application as effective antimicrobial and antifungal agents.

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