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Synthesis and antibacterial activity of ethyl 2-amino-6-methyl-5-oxo-4-aryl-5,6-dihydro-4*H*-pyrano[3,2-c]quinoline-3-carboxylate

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ABSTRACT

The three-component reaction of 4-hydroxy-1-methyl-2(1*H*)-quinolinone, aromatic aldehydes and ethyl cyanoacetate was carried out in the presence of a catalytic amount of 4-dimethyl aminopyridine (DMAP) in aqueous ethanol. The reactions result in the formation of pyranoquinoline derivatives in excellent yields. Antibacterial activity has been evaluated against Gram positive and Gram negative bacteria for some of the synthesized compounds. The results indicated that these compounds are moderately effective against bacterial growth and their effectiveness is highest against *Pseudomonas aeruginosa*.

1. Introduction

Pyranoquinoline derivatives are known to be present in many natural alkaloids [1–4], and possess various pharmacological and biological activities such as antimalarial [5], antiseptic [6], antihypertensive [7], antiviral effect and act as H_1-antihistamines [8,9]. Several quinolone derivatives have been reported as antimicrobial agents in the treatment of many infections [10,11]. They are widely used as synthetic precursors for the construction of many natural polycyclic molecules [12]. Thus, several methods have been described for the synthesis of pyranoquinoline derivatives [13–16]. Among available methods, intramolecular cyclization *via* multicomponent reaction is an efficient protocol for constructing these heterocyclic compounds [17–21]. Moreover, employing appropriate routes to enhance the efficiency of the reactions is a subject of interest. Besides various other reaction parameters, the nature of the catalyst and solvent has significant impact on the reaction [22–25].

Thus, in continuation to our studies in the synthesis of new heterocycles [26–30], we report an efficient synthesis of pyranoquinoline derivatives **4** which are obtained through three-component reactions of 4-hydroxy-1-methyl-2(1*H*)-quinolinone **1**, aromatic aldehydes **2** and ethyl cyanoacetate **3** catalyzed by 4-dimethyl aminopyridine (DMAP) in H_2O/EtOH (1:1) (Scheme 1). Also, some of the selected products were evaluated for their antibacterial activity against Gram positive and Gram negative bacteria.

2. Experimental

Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. NMR spectra were recorded on a BRUCKER DRX-400 AVANCE spectrometer (at 400.1 for ^{1}H and 100.6 MHz for ^{13}C) with $CDCl_3$ as solvent. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a FT-IR, Brucker, VECTOR 22 spectrometer.

2.1. General procedure for the synthesis of compound **4** (exemplified by **4a**)

A mixture of 4-nitrobenzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) in H_2O/EtOH (1:1) (5 mL) was treated with DMAP (10 mol%) at room temperature. After the consumption of starting aldehyde as indicated by TLC analysis (30 min), 4-hydroxy-1-methyl-2(1*H*)-quinolinone (1 mmol) was added to the reaction mixture and the mixture was heated to reflux condition for 2 h. After the completion of the reaction, the reaction mixture was brought to room temperature and the solid precipitate was collected by filtration. The desired product **4a** was obtained as a yellow powder.

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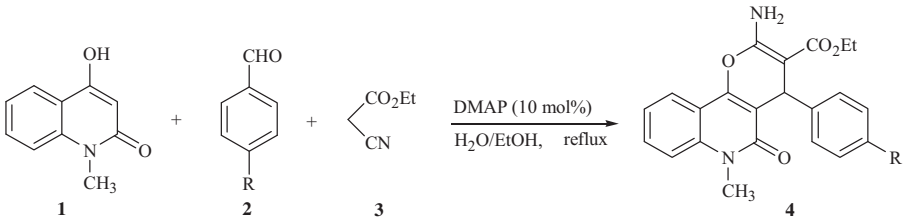

Scheme 1. Synthesis of pyranoquinoline derivatives **4a–i**.

2.2. General procedure for evaluation of antibacterial activity

The *in vitro* biocidal screening, antibacterial activity of compounds **4a**, **4c**, **4d**, **4f** and **4g** was assayed using the Kirby–Bauer disc diffusion method where a filter disc was impregnated with the compounds and placed on the surface of inoculated agar plates. The synthesized compounds were dissolved in DMSO to make a 20 mg mL^{-1} solution then filtered through a sterilized 0.22 μm Ministart (Sartorius) filter. The antibacterial activity of the products was investigated against four bacterial species. Test organisms included *Escherichia coli* PTCC 1330, *Pseudomonas aeruginosa* PTCC 1074, *Staphylococcus aureus* ATCC 35923 and *Bacillus subtilis* PTCC 1023. Late exponential phase of the bacteria was prepared by inoculating 1% (v/v) of the cultures into a fresh Muller–Hinton broth (Merck) and incubating on an orbital shaker at 37 °C and 100 rpm overnight. Before using the cultures, they were standardized with a final cell density of approximately 10^8 cfu mL^{-1}. Muller–Hinton agar (Merck) was prepared and inoculated from the standardized cultures of the test organisms then spread as uniformly as possible throughout the entire media. Sterile paper discs (6 mm diameter, Padtan, Iran) were impregnated with 20 μL of the compound solution then allowed to dry. The impregnated disc was introduced on the upper layer of the seeded agar plate and incubated at 37 °C for 24 h. The antibacterial activity of the products was compared with known antibiotic gentamicin (10 μg/disc) and chloramphenicol (30 μg/disc) as positive controls and DMSO (20 μL/disc) as negative control. Antibacterial activity was evaluated by measuring the diameter of the inhibition zone (mm) on the surface of the plates and the results were reported as mean ± SD after three repeats.

3. Results and discussion

3.1. Chemistry

Initially, we investigated different conditions including catalysts and solvents to optimize the reaction. As a model reaction, a mixture of 4-nitrobenzaldehyde, ethyl cyanoacetate and 4-hydroxy-1-methyl-2(1*H*)-quinolinone was treated in the absence of any catalyst in which trace amount of the product **4a** was obtained. Then, the model reaction was performed in the presence of various amounts of DMAP and hexamethylenetetramine (HMT). It was noted that 10 mol% of DMAP provided the best result in terms of yield and time. Using HMT instead of DMAP, the reaction proceeded with a decreased yield (Table 1).

The model reaction was optimized using various solvents to obtain the best yield of **4a**. Among different solvents, the best results were obtained using H_2O/EtOH (1:1) and DMF. Thus, we preferred to carry out the reactions using H_2O/EtOH (1:1) as an ecofriendly and safe medium. The results are summarized in Table 2.

With the optimal reaction conditions, the reactions of some other aromatic aldehydes were carried out with ethyl cyanoacetate and 4-hydroxy-1-methyl-2(1*H*)-quinolinone and resulted in products **4b–i** in excellent yields (Table 3).

A plausible rationalization for the reaction mechanism is shown in Scheme 2. Presumably, compound **5** is formed *via* Knoevenagel condensation between aldehyde **2** and ethyl cyanoacetate **3** in the presence of a catalytic amount of DMAP. Then, the enolate **6**, which is obtained from the reaction between quinolinone **1** and DMAP, performs the Michael addition to intermediate **5** to generate the intermediate **7**. This intermediate enolizes to produce **8**, which subsequently undergoes an intramolecular cyclization reaction to form **9**. Then, intermediate **9** undergoes a 1,3-proton shift to afford the product **4** exclusively.

The structures of compounds **4a–i** were consistent with their ^{1}H NMR, ^{13}C NMR, IR and mass spectra and elemental analysis.

Table 1
The effects of different catalytic amounts of DMAP and HMT on the reaction of 4-nitrobenzaldehyde, ethyl cyanoacetate and 4-hydroxy-1-methyl-2(1*H*)-quinolinone in H_2O/EtOH (1:1) under reflux.

Entry	Catalyst	Mol (%)	Time (h)	Yield of **4a** (%)
1	DMAP	30	2	90
2	DMAP	20	2	90
3	DMAP	10	2.5	87
4	DMAP	5	2.5	70
5	DMAP	3	2.5	60
6	DMAP	0	7	Trace
7	HMT	30	2	80
8	HMT	20	2	75

Table 2
The effects of different solvents on the reaction of 4-nitrobenzaldehyde, ethyl cyanoacetate and 4-hydroxy-1-methyl-2(1*H*)-quinolinone using DMAP (10 mol%) under reflux condition.

Entry	Solvent	Yield of **4a** (%)
1	H_2O/EtOH (1:1)	90
2	DMF	90
3	Acetone	85
4	H_2O	20

Table 3
Synthesis of dihydropyrano[3,2-c]quinoline derivatives catalyzed by DMAP (10 mol%) in H_2O/EtOH (1:1) under reflux condition.

Entry	Product	R	Yield (%)
1	**4a**	NO_2	96
2	**4b**	H	88
3	**4c**	CN	92
4	**4d**	Cl	90
5	**4e**	Br	87
6	**4f**	CH_3	92
7	**4g**	OCH_3	94
8	**4h**	Furyl	70
9	**4i**	Biphenyl	65