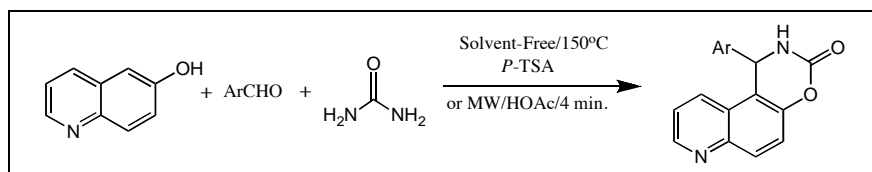


Gazaleh Imani Shakibaei, Hamid Reza Khavasi, Peiman Mirzaei, and Ayoob Bazgir\*

Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran 1983963113, Iran,  
E-mail: [a\\_bazgir@sbu.ac.ir](mailto:a_bazgir@sbu.ac.ir)  
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Oxazino[5,6-*f*]quinolin-3-one derivatives have been synthesized in a one-pot, and efficient process by condensation of 6-quinolinol, aromatic aldehydes and urea under microwave-assisted and thermal solvent-free conditions.

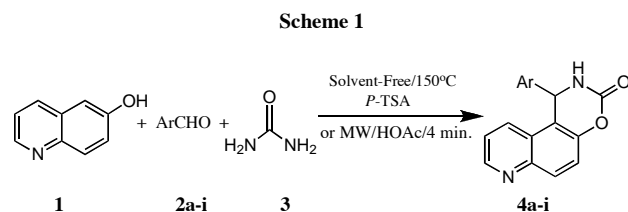
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## INTRODUCTION

The quinoline nucleus is the back-bone of many natural products and pharmacologically significant compounds displaying a broad range of biological activity [1]. Many functionalized quinolines are widely used as antimalarial, antiasthmatic, anti-inflammatory agents, antibacterial, antihypertensive and tyrosine kinase PDGF-RTK inhibiting agents [2,3].

Oxazinone derivatives have received considerable attention due to the interesting pharmacological properties associated with this heterocyclic scaffold [4]. For example, naphthoxazinone derivatives have been reported to act as antibacterial agents [5], or Efavirenz (Sustiva), a benzoxazinone derivative, is a nonnucleoside reverse transcriptase inhibitor that has been approved by the FDA in 1998 and is presently in clinical use for the treatment of AIDS [6]. Therefore, numerous methods for the synthesis of aromatic oxazinone derivatives exist in the literature [7-10].

Very recently, we reported a novel method for the synthesis of naphthoxazinone derivatives by the condensation of  $\beta$ -naphthol, aldehydes and urea [11]. To expand this type of tandem process, herein, we utilized 6-quinolinol (**1**) to produce novel oxazino[5,6-*f*]quinolin-3-one derivatives **4**. Therefore, the reaction of 6-quinolinol (**1**), aryl aldehyde **2** and urea (**3**) in the presence of a catalytic amount of *p*-toluene sulfonic acid (*p*-TSA) at 150 °C under solvent-free conditions were examined (Scheme 1).



## RESULTS AND DISCUSSION

To the best of our knowledge, there are no reports in the literature for the preparation of 1,2-dihydro-1-aryl-[1,3]oxazino[5,6-*f*]quinolin-3-one derivatives **4** via condensation of 6-quinolinol (**1**), aldehyde **2** and urea (**3**).

First, in order to find the best conditions for the synthesis of the quinoline-condensed oxazinone derivatives, the reaction of 6-quinolinol **1**, 4-chlorobenzaldehyde (**2b**) and urea (**3**) was carried out in the different conditions. As indicated in Table 1, the best yield was achieved in the presence of *p*-TSA at 150 °C under solvent-free conditions (Table 1).

**Table 1**  
Condition Effect on the Reaction [a]

Entry	Conditions	Yields %
<b>1</b>	Solvent-free/120 °C/ <i>p</i> -TSA	< 30
<b>2</b>	Solvent-free/150 °C/ <i>p</i> -TSA	77
<b>3</b>	Solvent-free/170 °C/ <i>p</i> -TSA	72
<b>4</b>	Solvent-free/150 °C	< 20
<b>5</b>	EtOH (Reflux)/ <i>p</i> -TSA	< 20
<b>6</b>	DMF (Reflux)/ <i>p</i> -TSA	< 30

[a] 4-Chlorobenzaldehyde (**2b**) (1 mmol), urea **3** (1.5 mmol), 6-quinolinol (**1**) (1 mmol) and Cat. (0.3 mmol), Time= 2.5 h.

Then several aromatic aldehydes **2a-i** with 6-quinolinol (**1**) and urea (**3**) under solvent-free conditions using *p*-TSA at 150 °C reacted to afford the corresponding products in good yields (Table 2). High yields were obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents.

Under the same conditions, with aliphatic aldehydes the yields of the reaction notably decreased (i.e., 20%, with butanal or hexanal), probably due to the possible aldol condensation side reaction. In the absence of *p*-TSA, the

**Table 2**

Reaction of 6-Quinolinol **1**, aldehydes **2** and urea **3** under solvent-free (I) and microwave-assisted conditions (II) [a].

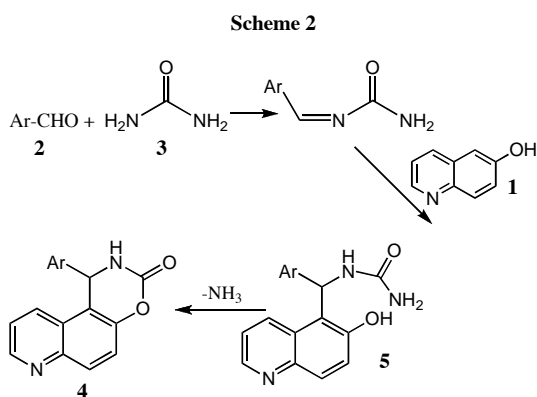
<b>2</b> (Ar =)	Products <b>4</b>	Yields %/ Time h	
		I	II
C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	<b>4a</b>	65/2	60
4-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	<b>4b</b>	77/2.5	75
4-F-C <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	<b>4c</b>	60/2	55
4-Br-C <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	<b>4d</b>	68/2	65
2-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	<b>4e</b>	63/2	58
3-Br-C <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	<b>4f</b>	71/2	69
2-MeO-C <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	<b>4g</b>	66/2	60
4-MeO-C <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	<b>4h</b>	65/2.5	64
4-Me-C <sub>6</sub> H <sub>4</sub> ( <b>2i</b> )	<b>4i</b>	64/2.5	59

[a] With power of 700 W, time= 4 min.

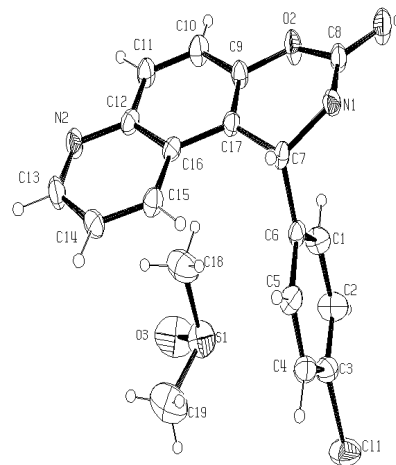
products were obtained in low yields (<20%), when the reactions were carried out in solvent-free conditions at 150 °C (Table 1, entry 4).

In order to decrease the reaction time, microwave irradiation in the absence or in the presence of different catalyst such as *p*-TSA, HOAc, FeCl<sub>3</sub>, ZnCl<sub>2</sub>, SnCl<sub>2</sub> was used. In the course of this study it was found that HOAc is the most effective catalyst in terms of yield. It is clear from Table 2, using microwave irradiation the reaction time decreased from 2-2.5 h to 4 min in the presence of catalytic amount of HOAc. In addition to decrease of reaction time, the yields in all cases are reasonable (Table 2).

According to the results, and as in numerous classical multi-component reaction classic [12], the reaction can be mechanistically considered to proceed through the acylimine intermediate formed *in situ* by condensation reaction of the aldehyde with urea. The subsequent addition of the 6-quinolinol (**1**) to the acylimine, followed by cyclization of the intermediate **5** afforded the corresponding products **4a-i** and ammonia (Scheme 2).



The structures of the products **4a-i** were characterized by ir, <sup>1</sup>H nmr, <sup>13</sup>C nmr and ms spectra. Finally the structure of **4b** was confirmed by a single-crystal X-ray analysis (Figure 1) [15].



**Figure 1.** ORTEP diagram of **4b**.

In summary, we have described an efficient one-pot synthesis for the preparation of 1,2-dihydro-1-aryl-[1,3]oxazino[5,6-f]quinolin-3-one derivatives **4** in three-component cyclo-condensation reaction of 6-quinolinol **1**, aromatic aldehydes and urea under solvent-free and microwave-assisted conditions.

## EXPERIMENTAL

Melting points were measured on an Elecrtothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using an FTIR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. The microwave oven was a domestic National model NN-6653 with select power levels. The reflections for X-ray diffraction analysis were collected on a STOE IPDSII two-circle diffractometer.

**General procedure for preparation of 2-dihydro-1-aryl-[1,3]oxazino[5,6-f]quinolin-3-one under solvent-free conditions (4a-i).** A mixture of 6-quinolinol **1** (1 mmol), aldehyde **2** (1 mmol), urea (1.5 mmol) and *p*-TSA (0.1 g) was heated at 150 °C for appropriate times. After cooling, the reaction mixture was washed with water and then recrystallized from EtOAc/Hexane (1:3) to afford the pure product **4-i** (Table 2).

**General procedure for preparation of 2-dihydro-1-aryl-[1,3]oxazino[5,6-f]quinolin-3-one under microwave irradiation (4a-i).** A mixture of 6-quinolinol **1** (1 mmol), aldehyde **2** (1 mmol), urea (1.5 mmol) and HOAc (0.3 mmol) were finely mixed together. The reaction mixture was placed in a Pyrex test tube and irradiated for 4 min with a power of 700 W. After cooling, the reaction mixture was washed with water and then recrystallized from EtOAc/Hexane (1:3) to afford the pure product **4a-i** (Table 2).

**1,2-Dihydro-1-phenyl-[1,3]oxazino[5,6-f]quinolin-3-one (4a).** White powder, mp 242° dec.; ir: 3415, 3129, 1741 cm<sup>-1</sup>; <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 6.26 (1H, s, CH), 7.31-8.81 (10H, m, arom.), 8.94 (1H, s, NH); <sup>13</sup>C nmr (DMSO-d<sub>6</sub>): 53.87, 114.90, 120.92,

122.56, 124.60, 127.39, 128.62, 129.49, 131.65, 132.01, 143.12, 145.64, 147.76, 149.46, 149.87; ms: m/z 276 ( $M^+$ , 54), 232 (100). *Anal. calcd.* For  $C_{17}H_{12}N_2O_2$ : C, 73.90; H, 4.38; N, 10.14. Found: C, 73.96; H, 4.33; N, 10.17.

**1,2-Dihydro-1-(4-chlorophenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4b).** White powder, mp 210° dec.; ir: 3412, 3128, 1739  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  6.31 (s, 1H, CH), 7.31-8.82 (m, 9H, arom), 8.99 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  53.07, 114.40, 120.98, 122.68, 124.51, 129.36, 129.52, 131.84, 131.96, 133.23, 141.97, 145.62, 147.79, 149.31, 149.98; ms: m/z 310 ( $M^+$ , 15), 266 (100), 232 (96). *Anal. calcd.* for  $C_{17}H_{11}ClN_2O_2$ : C, 65.71; H, 3.57; N, 9.02. Found: C, 65.77; H, 3.61; N, 9.09.

**1,2-Dihydro-1-(4-fluorophenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4c).** White powder, mp 203° dec.; ir: 3413, 1737  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  6.31 (s, 1H, CH), 7.16-8.81 (m, 9H, arom), 8.97 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  53.02, 114.68, 116.23, 120.97, 122.63, 124.51, 129.57, 131.46, 131.97, 139.37, 145.64, 147.73, 149.35, 149.94, 163.28; ms: m/z 294 ( $M^+$ , 42), 250 (100), 232 (100). *Anal. calcd.* for  $C_{17}H_{11}FN_2O_2$ : C, 69.38; H, 3.77; N, 9.52. Found: C, 69.31; H, 3.71; N, 9.57.

**1,2-Dihydro-1-(4-bromophenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4d).** White powder, mp 226° dec.; ir: 3413, 3135, 1740  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  6.28 (s, 1H, CH), 7.24-8.80 (m, 9H, arom), 8.97 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  52.63, 113.84, 120.48, 121.33, 122.19, 123.99, 129.17, 131.34, 131.46, 131.96, 141.87, 145.11, 147.28, 148.81, 149.48; ms: m/z 354 ( $M^+$ , 32), 310 (100), 232 (100). *Anal. calcd.* for  $C_{17}H_{11}BrN_2O_2$ : C, 57.49; H, 3.12; N, 7.89. Found: C, 57.41; H, 3.07; N, 7.82.

**1,2-Dihydro-1-(2-chlorophenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4e).** White powder, mp 271° dec.; ir: 3422, 3113, 1737  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  6.57 (s, 1H, CH), 7.30-8.80 (m, 9H, arom), 8.94 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  52.29, 113.01, 120.92, 122.72, 124.52, 128.83, 130.71, 131.23, 132.04, 132.17, 139.62, 145.64, 148.18, 148.77, 149.84; ms: m/z 310 ( $M^+$ , 10), 266 (20), 232 (100). *Anal. calcd.* for  $C_{17}H_{11}ClN_2O_2$ : C, 65.71; H, 3.57; N, 9.02. Found: C, 65.72; H, 3.60; N, 9.10.

**1,2-Dihydro-1-(3-bromophenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4f).** White powder, mp 274° dec.; ir: 3452, 3112, 1741  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  6.32 (s, 1H, CH), 7.24-8.84 (m, 9H, arom), 8.99 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  53.15, 114.12, 120.99, 122.53, 122.76, 124.52, 126.27, 130.40, 131.58, 131.89, 131.94, 145.53, 145.63, 147.91, 149.28, 150.03; ms: m/z 354 ( $M^+$ , 7), 312 (18), 232 (100). *Anal. calcd.* for  $C_{17}H_{11}BrN_2O_2$ : C, 57.49; H, 3.12; N, 7.89. Found: C, 57.84; H, 3.15; N, 7.80.

**1,2-Dihydro-1-(2-methoxyphenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4g).** White powder, mp 264° dec.; ir: 3440, 3127, 1732  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  3.77 (s, 3H, OCH<sub>3</sub>), 6.36 (s, 1H, CH), 6.87-8.58 (m, 9H, arom), 8.78 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  50.58, 56.05, 112.46, 113.79, 120.72, 121.20, 122.45, 124.75, 129.33, 130.24, 130.47, 131.30, 131.60, 145.49, 148.02, 149.55, 149.67, 157.01; ms: m/z 306 ( $M^+$ , 13), 248 (21), 232 (100). *Anal. calcd.* for  $C_{17}H_{14}N_2O_3$ : C, 70.58; H, 4.61; N, 9.15. Found: C, 70.51; H, 4.65; N, 9.09.

**1,2-Dihydro-1-(4-methoxyphenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4h).** White powder, mp 249° dec.; ir: 3413, 3128, 1740  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  3.67 (s, 3H, OCH<sub>3</sub>), 6.22 (s, 1H, CH), 6.86-8.81 (m, 9H, arom), 8.89 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  53.29, 53.53, 114.76, 115.14, 120.91, 122.51, 124.57, 128.66, 131.51, 132.06, 135.29, 145.64, 147.61, 149.48, 149.83, 159.37; ms: m/z 306 ( $M^+$ , 37), 262 (100), 232 (100). *Anal. calcd.* for  $C_{18}H_{14}N_2O_3$ : C, 70.58; H, 4.61; N, 9.15. Found: C, 70.64; H, 4.61; N, 9.21.

**1,2-Dihydro-1-(4-methylphenyl)-[1,3]oxazino[5,6-f]quinolin-3-one (4i).** White powder, mp 270° dec.; ir: 3446, 3138, 1739  $cm^{-1}$ ;  $^1H$  nmr (DMSO- $d_6$ ):  $\delta$  2.20 (s, 3H, CH<sub>3</sub>), 6.21 (s, 1H, CH), 7.12-8.80 (m, 9H, arom), 8.90 (s, 1H, NH);  $^{13}C$  nmr (DMSO- $d_6$ ):  $\delta$  21.05, 53.58, 115.01, 120.89, 122.51, 124.57, 127.28, 129.97, 131.53, 132.02, 137.93, 140.25, 145.60, 147.65, 149.47, 149.82; ms: m/z 290 ( $M^+$ , 35), 232 (100), 202 (20). *Anal. calcd.* for  $C_{18}H_{14}N_2O_2$ : C, 74.47; H, 4.86; N, 9.65. Found: C, 74.39; H, 4.81; N, 9.58.

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Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 664117, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail:

deposit@ccdc.cam.ac.uk.

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