Synthesis of 2-(hetero)arylquinazolinones in aqueous media

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Abstract

Mechanochemical treatment of \textit{N}-unsubstituted or \textit{N}-methyl anthranilamide with benzaldehyde yielded their Schiff bases derivatives which could be easily cyclized to the corresponding 2-phenyl-2,3-dihydroquinazolinones \textit{via} thermal rearrangement in water. On the basis of the above findings, an eco-friendly method was applied to prepare quinazolin-4(1H)-one derivatives from anthranilamides and a number of (hetero)aryl aldehydes. Heating the aqueous mixture of starting compounds to 90 °C resulted in the products in 81–94% yields. All products precipitated from the reaction mixture and were isolated by simply filtration. No further work-up or purification was necessary.

Keywords: Environmentally friendly methods, aqueous, mechanochemical, ball-milling reactions, chromatography-free

Introduction

2,3-Dihydroquinazolines (DHQZ) are effective substances in medicinal chemistry that possess a broad spectrum of biological activities, including MAO-A\textsuperscript{1} and Shiga toxin\textsuperscript{2} inhibitor, diuretic\textsuperscript{3} or anti-inflammatory\textsuperscript{4} activities. Among the various DHQZ derivatives, 2-aryl quinazolinone hybrids have been found to be good candidates for the inhibition of both tubulin polymerization and the binding of colchicine to tubulin.\textsuperscript{5} Incorporation of a pyrazole moiety at position 2 of the quinazolinone heterocycle gives safer and potent antioxidant\textsuperscript{6} and insecticidal\textsuperscript{7} (Spodoptera frugiperda) agents. Some 2-spirooxindole dihydroquinazolinones demonstrate anti-bacterial activity \textit{in vitro}.\textsuperscript{8}

Several methods have been reported for the preparation of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones, based mainly on the cyclocondensation of anthranil(onitrile)amides with aldehydes in the presence of various catalysts such as cyanuric chloride,\textsuperscript{9} citric acid\textsuperscript{10}, ZnCl\textsubscript{2},\textsuperscript{11} p-TSA\textsuperscript{12} and sulfamic acid\textsuperscript{13}. Moreover, many of these protocols
are associated with the application of exotic catalyst systems, extended reaction times and tedious work-up procedures. For example, some classical and modern methods reported in the literature for the synthesis of 2-phenyl-2,3-dihydroquinazolin-4-(1H)-one (4a) via the reaction of anthranilamide (1a) and benzaldehyde (2a) are outlined in Table 1.

**Table 1. Synthesis of 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (4a)**

<table>
<thead>
<tr>
<th></th>
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</thead>
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<tr>
<td>1</td>
<td>PEG</td>
<td>25</td>
<td>0.25</td>
<td>MCM-41-dtz-Ni Fe3O4/Cu(II)-Schiff base</td>
<td>1</td>
<td>98&lt;sup&gt;e,rc&lt;/sup&gt;</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>ethanol</td>
<td>78</td>
<td>1</td>
<td>Indion-Ina 225 H</td>
<td>1</td>
<td>99&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
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<tr>
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<td>methanol</td>
<td>25</td>
<td>2</td>
<td>Indion-Ina 225 H</td>
<td>1</td>
<td>98&lt;sup&gt;ch&lt;/sup&gt;</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>110</td>
<td>18</td>
<td>–</td>
<td>1</td>
<td>100&lt;sup&gt;-&lt;/sup&gt;</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>water</td>
<td>120</td>
<td>16</td>
<td>–</td>
<td>1</td>
<td>100&lt;sup&gt;e,ch&lt;/sup&gt;</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>ethanol</td>
<td>78</td>
<td>0.83</td>
<td>Boehmite SSA</td>
<td>1</td>
<td>96&lt;sup&gt;e,rc&lt;/sup&gt;</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>acetonitrile</td>
<td>25</td>
<td>0.33</td>
<td>L-proline nitrate</td>
<td>1</td>
<td>96&lt;sup&gt;e&lt;/sup&gt;</td>
<td>20</td>
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<tr>
<td>8</td>
<td>water</td>
<td>25</td>
<td>0.03</td>
<td>1-&lt;i&gt;i&lt;/i&gt;-Pr-1,2,4-triazol.HOTf</td>
<td>1</td>
<td>96&lt;sup&gt;e&lt;/sup&gt;</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>–</td>
<td>MW</td>
<td>0.17</td>
<td>Co-CNTs</td>
<td>1</td>
<td>98&lt;sup&gt;W,rc&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>dichloromethane</td>
<td>40</td>
<td>48–72</td>
<td>–</td>
<td>1.3</td>
<td>98&lt;sup&gt;-&lt;/sup&gt;</td>
<td>23</td>
</tr>
<tr>
<td>11</td>
<td>water</td>
<td>70</td>
<td>0.58</td>
<td>MNPs-PSA</td>
<td>1</td>
<td>97&lt;sup&gt;e,rc&lt;/sup&gt;</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>water</td>
<td>25</td>
<td>0.33</td>
<td>Graphene Oxide</td>
<td>1</td>
<td>94&lt;sup&gt;e&lt;/sup&gt;</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>ethanol</td>
<td>25</td>
<td>1.5</td>
<td>Y(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.91</td>
<td>93&lt;sup&gt;e&lt;/sup&gt;</td>
<td>26</td>
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<tr>
<td>14</td>
<td>water</td>
<td>70</td>
<td>1</td>
<td>SuSa</td>
<td>1</td>
<td>94&lt;sup&gt;e&lt;/sup&gt;</td>
<td>27</td>
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<tr>
<td>15</td>
<td>water</td>
<td>25</td>
<td>0.3</td>
<td>&lt;i&gt;p&lt;/i&gt;-SAC</td>
<td>1</td>
<td>94&lt;sup&gt;e&lt;/sup&gt;</td>
<td>28</td>
</tr>
<tr>
<td>16</td>
<td>water</td>
<td>50</td>
<td>0.42</td>
<td>β-CD-SO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>1</td>
<td>96&lt;sup&gt;e&lt;/sup&gt;</td>
<td>29</td>
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Table 1 (continued)

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<tbody>
<tr>
<td>17</td>
<td>water</td>
<td>90</td>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>18*</td>
<td>water</td>
<td>90</td>
<td>1</td>
<td>–</td>
<td>91</td>
</tr>
</tbody>
</table>

ch column chromatography; e extraction; rc recrystallization; w washing with organic solvent; * from Schiff base 3a

We have previously described eco-friendly methods for the preparation of quinazolin-4(1H)-ones in aqueous[30] or solventless medium from 1a[31] or 2-amino-benzhydrazides[32] and a number of aldehydes[33] and ketones.[34] Inspired by the excellent results of the mechanochemical and in/on water syntheses, we decided to extend the ring closure of 1a and 2-amino-N-methylbenzamide (1b) with the reactions of a number of (hetero)aromatic aldehydes under either aqueous or ball-milling conditions.

Results and Discussion

We initially studied the influence of solventless and catalyst-free conditions in the reaction of anthranilamides 1a and 1b with benzaldehyde (2a) as model reaction. The liquid–solid condensations of 1a and 1b with 2a were carried out in a mixing ball-mill. The reactants in a stoichiometric ratio were placed in a stainless-steel jar with two stainless-steel balls, the vessel was closed, and milling was started at rt at 25 Hz. After a 1-h milling only 10% of the starting compounds remained unconsumed (monitored by TLC). Milling was continued for an additional 1 h, during which eutectic melt products were obtained. 1H NMR spectroscopy of crude products demonstrated that the yields of melt-like compounds were nearly quantitative. Interestingly, under this reaction condition, mixtures both of kinetic (3a, 3b) and thermodynamic (4a, 5a) products were formed (Table 2, Entry 1 and 2). Successful separation of the material in the jar was achieved when the reaction mixtures were dissolved in methanol. After evaporation of methanolic solution to small volume under reduced pressure at rt, followed by the addition of a mixture of Et,O–n-hexane, crystalline imines 3a and 3b were separated out, characterized by FT-IR and 1H NMR analysis. The 13C NMR data on 3a and 3b were described by the utilization of 2D HSQC and HMBC NMR spectra because of the quick intramolecular cyclization of Schiff bases to 4a and 5a on standing in d6-DMSO.

Rao et al. reported that intramolecular cyclization of 3b to 5a is facile and apparently an irreversible process, both in free-state and in acetic acid.[36] In view of above observation, we decided to investigate the rearrangement of 3a and 3b in aqueous medium. After stirring for 1 h at 90 °C, precipitated 4a and 5a were isolated by simple filtration in a yield of 91–93% and high
purity (97–99%). Compounds were obtained as pale yellow solids, their physical and spectroscopic data were in good agreement with the literature.\textsuperscript{21,38}

In order to test our in/on water protocol, we first explored cyclization of a stoichiometric amount of 1a and 1b with 2a at rt. After stirring for 6 h a mixture of 3a/4a or 3b/5a precipitating was filtered off and dried. The ratio of inseparable mixture of constitutional isomers was determined by \textsuperscript{1}H MNR spectroscopy (Table 2, Entry 3 and 4).

Table 2. Condensation of anthranilamides with benzaldehyde under various conditions

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1*</td>
<td>H</td>
<td>-</td>
<td>25</td>
<td>2</td>
<td>3a : 4a (95 : 5)\textsuperscript{a}</td>
<td>98\textsuperscript{b}/68(3a)\textsuperscript{b}</td>
<td>163–165\textsuperscript{b} (217)\textsuperscript{35}</td>
</tr>
<tr>
<td>2*</td>
<td>Me</td>
<td>-</td>
<td>25</td>
<td>2</td>
<td>3b : 5a (91 : 9)\textsuperscript{a}</td>
<td>97\textsuperscript{b}/61(3b)\textsuperscript{b}</td>
<td>124–126\textsuperscript{b} (76)\textsuperscript{36}</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>water</td>
<td>25</td>
<td>6</td>
<td>3a : 4a (79 : 21)\textsuperscript{a}</td>
<td>83\textsuperscript{c}</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>water</td>
<td>25</td>
<td>6</td>
<td>3b : 5a (30 : 70)\textsuperscript{a}</td>
<td>80\textsuperscript{c}</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>water</td>
<td>90</td>
<td>2</td>
<td>4a</td>
<td>88\textsuperscript{c}</td>
<td>224–226\textsuperscript{c} (225–227)\textsuperscript{37} (168–170)\textsuperscript{38}</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>water</td>
<td>90</td>
<td>2</td>
<td>5a</td>
<td>90\textsuperscript{c}</td>
<td>(159–161)\textsuperscript{38}</td>
</tr>
</tbody>
</table>

*Ball-milling at 25 Hz for 2 h; \textsuperscript{a} On the basis of \textsuperscript{1}H NMR; \textsuperscript{b} From MeOH/Et\textsubscript{2}O/n-hexane; \textsuperscript{c} From aqueous suspension.

To optimize the catalyst-free reaction conditions, in addition to the variation in temperature and reaction time, stirring the starting compounds in water and heating (90 °C, 2 h) were found to afford the corresponding 4a and 5a in excellent yields and purity (96–98%, Entry 5 and 6).

With a successful procedure available, we further examined the aqueous condensation of 1a with aldehydes 2b–2j. The mixture of 4 mmol of 1a and 1 equivalent of 4b–4j in 10 ml of water was stirred at 90 °C for 2–4 h. Cyclic products 4a–4e and 4h–4j were isolated by filtration. Under
neutral conditions, the corresponding quinazolinones were obtained in 85-94% yields (Table 3). The poorly water-soluble 2g gave an excellent product yield of 4g only under reflux in a mixture of ethanol/water (1:2). With slight modification, the reaction of 1a with 2f was complete in the presence of 1 ml of 1% I2/KI (Lugol’s solution)\textsuperscript{34} (Entry 6 and 5).

Table 3. Syntheses of 2-(hetero)aryl-2,3-dihydroquinazolin-4(1H)-ones (4b–4j) in aqueous media

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Het)Ar</th>
<th>Time [h]</th>
<th>Product</th>
<th>Yield [%]\textsuperscript{a}</th>
<th>Mp  [°C]\textsuperscript{b} (lit.)\textsuperscript{ref}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>3</td>
<td>4b</td>
<td>85</td>
<td>229–232 (232–234)\textsuperscript{27}</td>
</tr>
<tr>
<td>2</td>
<td>4-FC\textsubscript{6}H\textsubscript{4}</td>
<td>3</td>
<td>4c</td>
<td>92</td>
<td>205–207 (203–204)\textsuperscript{22}</td>
</tr>
<tr>
<td>3</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>2</td>
<td>4d</td>
<td>89</td>
<td>209–212 (206–208)\textsuperscript{20}</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>3</td>
<td>4e</td>
<td>91</td>
<td>202–205 (198–199)\textsuperscript{20}</td>
</tr>
<tr>
<td>5</td>
<td>4-CNC\textsubscript{6}H\textsubscript{4}</td>
<td>4</td>
<td>4f</td>
<td>88\textsuperscript{c}</td>
<td>Mp &gt; 320 (350–351)\textsuperscript{40}</td>
</tr>
<tr>
<td>6</td>
<td>4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>2</td>
<td>4g</td>
<td>90\textsuperscript{d}</td>
<td>194–198 (199–201)\textsuperscript{39}</td>
</tr>
<tr>
<td>7</td>
<td>2-naphthyl</td>
<td>3</td>
<td>4h</td>
<td>94</td>
<td>223–226 (225–226)\textsuperscript{22}</td>
</tr>
<tr>
<td>8</td>
<td>2-furyl</td>
<td>3</td>
<td>4i</td>
<td>86</td>
<td>167–170 (167–168)\textsuperscript{20}</td>
</tr>
<tr>
<td>9</td>
<td>3-piridyl</td>
<td>2</td>
<td>4j</td>
<td>93</td>
<td>230–233 (225–227)\textsuperscript{41}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yields; \textsuperscript{b} from aqueous suspension; \textsuperscript{c} 1 mol% I2/KI; \textsuperscript{d} from EtOH–H\textsubscript{2}O (1:2);

The products were characterized by their spectral data and melting points. \textsuperscript{1}H NMR data of the crude reaction products correlated well with literature values. Inspired by the successful attempt with 1a, we extended the aqueous cyclocondensation of 2b–2j with 2-amino-\textit{N}-methylbenzamide (1 b). All of these reactions were carried out essentially under the same conditions as described above, except that reaction times were shorter for 5f and 5h (Table 4, Entry 5 and 7). In the green procedure, \textit{N}-methyl-quinazolinones 5b–5j were obtained in
good to excellent yields (81–93%). Products 5b, 5d and 5g were characterized by comparion of their spectral data and melting points with those reported in the literature. Although 5e can be found as a known chemical substance its physical and spectroscopic properties have not been fully studied. In this work we report characterization of 5c, 5e, 5f and 5h–j in the Experimental Section.

**Table 4.** Syntheses of 2-(hetero)aryl-3-methyl-2,3-dihydroquinazolin-4(1H)-one (5b–5j) in aqueous media

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Het)Ar</th>
<th>Time [h]</th>
<th>Product</th>
<th>Yield [%]</th>
<th>Mp [°C][b] (lit.)[ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC₆H₄</td>
<td>3</td>
<td>5b</td>
<td>88</td>
<td>167–169 (150–152)³⁸</td>
</tr>
<tr>
<td>2</td>
<td>4-FC₆H₄</td>
<td>3</td>
<td>5c</td>
<td>90</td>
<td>200–201</td>
</tr>
<tr>
<td>3</td>
<td>4-ClC₆H₄</td>
<td>2</td>
<td>5d</td>
<td>93</td>
<td>202–204 (196)³⁶</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC₆H₄</td>
<td>3</td>
<td>5e</td>
<td>89</td>
<td>198–200</td>
</tr>
<tr>
<td>5</td>
<td>4-CNC₆H₄</td>
<td>3</td>
<td>5f</td>
<td>81</td>
<td>179–182</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂C₆H₄</td>
<td>2</td>
<td>5g</td>
<td>92</td>
<td>190–194 (196–198)³⁹</td>
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<tr>
<td>7</td>
<td>2-naphthyl</td>
<td>2</td>
<td>5h</td>
<td>93</td>
<td>219–221</td>
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<td>8</td>
<td>2-furyl</td>
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<td>5i</td>
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<td>156–159</td>
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<tr>
<td>9</td>
<td>3-pyridyl</td>
<td>2</td>
<td>5j</td>
<td>91</td>
<td>177–178</td>
</tr>
</tbody>
</table>

a Isolated yields; b from aqueous suspension; c 1 mol% I₂/KI; d from EtOH–H₂O (1:2);

In conclusion, we have developed an aqueous green synthesis of known and new 2-(hetero)aryl-quinazolinones. The condensations of (N-methyl)anthranilamide with (hetero)aromatic aldehydes proceeded efficiently in/on water to provide a convenient synthesis of 4a–4j or 5a–5j in excellent yields without the need for further work-up. We have also shown that Schiff bases prepared by high-energy ball milling resulted in heterocycles 4a and 5a in water at 90 °C. This method has a number of advantages over other methods: the reaction techniques are
very simple, and the syntheses occur under mild, green reaction conditions without the need for costly, highly sensitive catalysts.

**Experimental Section**

**General Procedures.** Products 4a–j, 5a, 5b, 5d and 5g are known compounds and their physical data and $^1$H NMR spectra were essentially identical with those of authentic samples. Other products, which are new, were characterized by IR, $^1$H, and $^{13}$C NMR spectroscopy and elemental analysis. $^1$H- (400 Hz), $^{13}$C- (100 MHz) and 2D NMR spectra were recorded in $d_6$-DMSO on a Bruker Avance DRX 400 spectrometer with TMS as internal reference. Analytically pure samples of 3a, 3b and new compounds (5c, 5e, 5f and 5h–j) were prepared by crystallization from MeOH/Et$_2$O/n-hexane or EtOH.

Melting points were determined on a Kofler apparatus and are uncorrected. FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser.

The ball-milling experiments were performed in a Retsch MM400 mixer mill with two stainless-steel balls 15 mm in diameter in a stainless-steel jar (25 mL) at 25 Hz at rt.

**Preparation of Schiff bases 3a and 3b**

1a or 1b (4.0 mmol), freshly distilled 2a (0.42 g, 0.40 mL, 4.0 mmol) and two stainless-steel balls 15 mm in diameter were placed in a stainless-steel jar. The vessel was vibrated at 25 Hz for 2 h. The reaction progress was monitored by TLC. 10 mL of MeOH was added to the reaction mixture in the jar. The suspension was mixed at 25 Hz for 5 min, filtered, the filtrate was evaporated to ca. 2 ml at rt. After addition of 10 mL of Et$_2$O–n-hexane (1 : 1), crystalline products 3a and 3b were filtered off, washed with diethyl ether (2 mL) and dried. Analytical and spectroscopic data on 3a and 3b are given below.

**2-(Benzyldieneamino)benzamide (3a).** Pale yellow crystals, mp 163–165 °C (MeOH–Et$_2$O–n-hexane); IR (cm$^{-1}$): 3384, 3193, 3054, 2894, 1626, 1591, 1372, 769; $^1$H NMR δ (ppm): 7.23 (d, $J = 7.8$ Hz), 1H, ArH), 7.35 (m, 1 H, ArH), 7.52–7.64 (m, 5H, ArH and NHCO), 7.90–8.00 (m, 3H, ArH), 8.21 (br s, 1H, NHCO), 8.61 (s, 1H, N=CH); $^{13}$C NMR (HMBC) δ (ppm): 119.0, 125.7, 128.9 (4×C), 129.8, 131.9, 132.1, 135.4, 149.1, 149.3, 162.2, 167.0; Anal. calcd. for C$_{14}$H$_{12}$N$_2$O (224.26) (%): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.75; H, 5.51; N, 12.21;

**2-(Benzyldieneamino)-N-methylbenzamide (3b).** Pale yellow needles, mp 124–126 °C (MeOH–Et$_2$O–n-hexane); IR (cm$^{-1}$): 3292, 3064, 3039, 2937, 1631, 1614, 1589, 1394, 750; $^1$H NMR δ (ppm): 2.82 (d, $J = 4.8$ Hz, 3H, CH$_3$) 7.25 (d, $J = 7.6$ Hz, 1H, ArH), 7.34 (m, 1H, ArH), 7.49–7.63 (m, 4H, ArH), 7.85 (dd, $J = 7.8$ Hz, $J = 1.3$ Hz, 1H, ArH), 7.95–8.00 (m, 2H, ArH), 8.61 (s, 1H, N=CH), 8.65 (br m, 1H, NHCO); $^{13}$C NMR (HMBC) δ (ppm): 25.7, 118.9, 125.5, 128.7 (4×C), 129.8, 131.9, 132.1, 135.4, 148.9, 149.0, 162.0, 166.4; Anal. calcd. for C$_{15}$H$_{14}$N$_2$O (238.28) (%): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.74; H, 5.71; N, 11.51;
Preparation of quinazolinones 4a and 5a
Schiff base 3a (0.22 g, 1 mmol) or 3b (0.24 g, 1 mmol) was heated in 5 mL of water at 90 °C for 1 h. From the cooled suspension, product 4a or 5a was precipitated, filtered off and dried.

2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (4a): white powder, mp 224–226 °C. 1H NMR spectrum was identical with that of an authentic sample.

3-Methyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (5a): white powder, mp 168–170 °C. 1H NMR spectrum was identical with that of an authentic sample.

Synthesis of 2-(hetero)aryl-2,3-dihydroquinazolin-4(1H)-ones 4b–4j and 5b–5j. To a stirred mixture of 1a or 1b (4.0 mmol), and in 10 mL of water (for 4b–e, h,j and 5b–e, h,j) or 10 mL of water and 1 mL of 1% I2/KI (for 4f and 5f) or in 10 mL of EtOH–water (1 : 2) (for 4g and 5g) 2b–2j (4 mmol) was added in portions. After vigorous stirring at rt for 10 min the aqueous suspension was heated at 90 °C for 2–4 h. After cooling to room temperature the precipitates 4b–4j and 5b–5j were collected by filtration, washed with water (3 mL) and dried. Crude 4b–4j, 5b, 5c and 5g were characterized by the melting points and 1H NMR spectra. Analytically pure samples of 5e, 5f and 5h–j were prepared by crystallization from EtOH. Analytical and spectroscopic data of new compounds are given below.

2-(4-Fluorophenyl)-3-methyl-2,3-dihydroquinazolin-4(1H)-one (5c). Colorless crystals, mp 200–201 °C (EtOH); IR (cm⁻¹): 3292, 3113, 3064, 2939, 2820, 1633, 1613, 1508, 1488, 1391, 1225, 753; 1H NMR δ (ppm): 2.84 (s, 3H, CH3), 5.85 (d, J = 2.3 Hz, CH), 6.61–6.70 (m, 2H, ArH), 7.16–7.24 (m, 3H, ArH), 7.28 (d, J = 2.2 Hz, 1H, NH), 7.33–7.41 (m, 2H, ArH), 7.65 (dd, J = 7.7 Hz, J = 1.5 Hz, 1H, ArH); 13C NMR δ (ppm): 31.8, 71.3, 114.1, 114.3, 115.3, 115.5, 117.0, 127.3, 128.3, 132.2, 133.2, 136.9 (2xC), 146.2, 160.8, 162.4, 163.3; Anal. calcd. for C13H13F3N2O (256.27) (%): C, 70.30; H, 5.11; N, 12.49. Found: C, 70.55; H, 5.21; N, 12.30;

2-(4-Bromophenyl)-3-methyl-2,3-dihydroquinazolin-4(1H)-one (5e). Colorless crystals, mp 198–200 °C (EtOH); IR (cm⁻¹): 3292, 3064, 2935, 2819, 1633, 1612, 1594, 1485, 1390, 756; 1H NMR δ (ppm): 2.86 (s, 3H, CH3), 5.84 (d, J = 2.4 Hz, CH), 6.61–6.70 (m, 2H, ArH), 7.18–7.30 (m, 3H, ArH), 7.32 (d, J = 2.3 Hz, 1H, NH), 7.54–7.59 (m, 2H, ArH), 7.65 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H, ArH); 13C NMR δ (ppm): 32.0, 71.2, 114.1, 114.3, 117.1, 121.6, 127.3, 128.2 (2xC), 131.5 (2xC), 133.2, 140.0, 146.1, 162.4; Anal. calcd. for C15H13BrN2O (317.18) (%): C, 56.80; H, 4.13; N, 8.83. Found: C, 56.58; H, 4.21; N, 8.50;

4-(1,2,3,4-Tetrahydro-3-methyl-4-oxo-2-quinazolyl)-benzonitrile (5f). Colorless crystals, mp 179–182 °C (EtOH); IR (cm⁻¹): 3330, 3056, 2930, 2229, 1634, 1612, 1506, 1487, 1392, 751; 1H NMR δ (ppm): 2.91 (s, 3H, CH3), 5.96 (d, J = 2.6 Hz, CH), 6.60–6.71 (m, 2H, ArH), 7.21 (m, 1H, ArH), 7.44 (d, J = 2.5 Hz, 1H, NH), 7.46–7.52 (m, 2H, ArH), 7.66 (dd, J = 7.8 Hz, J = 1.3 Hz, 1H, ArH), 7.80–7.88 (m, 2H, ArH); 13C NMR δ (ppm): 32.2, 71.2, 111.2, 114.2, 114.4, 117.3, 118.4, 127.0 (2xC), 127.4, 132.6 (2xC), 133.4, 145.9 (2xC), 162.3; Anal. calcd. for C16H15N3O (263.29) (%): C, 72.99; H, 4.98; N, 15.96. Found: C, 73.18; H, 5.21; N, 15.70;

3-Methyl-2-(2-naphthaleny)-2,3-dihydroquinazolin-4(1H)-one (5h). Colorless crystals, mp 219–221 °C (EtOH); IR (cm⁻¹): 3350, 3062, 2909, 1624, 1609, 1519, 1486, 1390, 821, 757, 750;
1H NMR δ (ppm): 2.91 (s, 3H, CH3), 6.01 (s, 1H, CH), 6.62–6.72 (m, 2H, ArH), 7.21 (m, 1H, ArH), 7.38 (s, 1H, NH), 7.47–7.58 (m, 3H, ArH), 7.71 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, ArH), 7.79 (m, 1H, ArH), 7.86–7.96 (m, 3H, ArH); 13C NMR δ (ppm): 31.9, 72.3, 114.0, 114.3, 117.0, 124.0, 125.1, 126.4, 126.5, 127.4, 127.5, 127.9, 128.6, 132.4, 132.9, 133.2, 137.9, 146.4, 162.6; Anal. calcd. for C10H16N2O (288.34) (%): C, 79.14; H, 5.59; N, 9.72. Found: C, 79.18; H, 5.31; N, 9.83;

2-(2-Furanyl)-3-methyl-2,3-dihydroquinazolin-4(1H)-one (5i). Pale red–brown crystals, mp 156–159 °C (EtOH); IR (cm⁻¹): 3237, 3128, 3103, 3060, 3028, 2918, 1626, 1612, 1524, 1485, 1399, 1151, 1138, 1014, 914, 882, 749; 1H NMR δ (ppm): 2.97 (s, 3H, CH3), 5.90 (d, J = 2.8 Hz, 1H, CH), 6.22 (d, J = 3.3 Hz, 1H, furyl-H), 6.36 (m, 1H, furyl-H), 6.66–6.78 (m, 2H, ArH), 7.24 (m, 1H, ArH), 7.36 (d, J = 2.5 Hz 1H, NH), 7.58 (m, 1H, furyl-H), 7.67 (m, 1H, ArH); 13C NMR δ (ppm): 32.0, 66.0, 107.4, 110.2, 114.3, 114.8, 117.3, 127.3, 133.1, 143.0, 146.4, 153.0, 162.5; Anal. calcd. for C13H12N2O2 (228.25) (%): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.58; H, 5.39; N, 12.03;

3-Methyl-2-(3-pyridinyl)-2,3-dihydroquinazolin-4(1H)-one (5j). Colorless crystals, mp 177–178 °C (EtOH); IR (cm⁻¹): 3283, 3058, 3034, 2999, 2932, 2821, 1634, 1613, 1594, 1579, 1504, 1486, 1418, 1390, 782, 767; 1H NMR δ (ppm): 2.89 (s, 3H, CH3), 5.94 (d, J = 2.6 Hz, 1H, CH), 6.62–6.73 (m, 2H, ArH), 7.22 (m, 1H, ArH), 7.35–7.41 (m, 2H, pyridyl-H and NH), 7.64–7.70 (m, 2H, pyridyl- and ArH), 8.50–8.56 (m, 2H, pyridyl-H, ArH); 13C NMR δ (ppm): 32.0, 70.0, 114.3, 114.5, 117.4, 123.7, 127.4, 133.3, 133.6, 135.9, 146.1, 147.6, 149.7, 162.5; Anal. calcd. for C14H13N3O (239.27) (%): C, 70.28; H, 5.48; N, 17.56. Found: C, 70.58; H, 5.21; N, 17.42;

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