Green and efficient synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-2,3-dihydropthalalazine-1,4-dione

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2-Hydrazinoquinazolin-3H-4-ones 1a,b were reacts with each of the anhydrides, phthalic anhydride 2a, succinic anhydride 2b and maleic anhydride 2c independently in PEG-600 at RT to yield 2-[2-(4-oxo-3,4-dihydroquinazolin-2-yl)hydrazinecarbonyl]benzoic acid 3a,b, 4-oxo-4-(2-(4-oxo-3,4-dihydroquinazolin-2-yl)hydrazinyl)butanoic acid 3c,d and 4-oxo-4-(2-(4-oxo-3,4-dihydroquinazolin-2-yl)hydrazinyl)but-2-enoic acid 3ef, respectively. 3a,b, 3c,d, 3ef have been transformed into 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-2,3-dihydropthalalazine-1,4-dione 4a.b, 1-(4-oxo-3,4-dihydroquinazolin-2-yl)piperazine-3,6-dione 4c,d and 1-(4-oxo-3,4-dihydroquinazolin-2-yl)-1,2-dihydropyridazine-3,6-dione 4ef, respectively by heating each in PEG-600 at 100 °C for 3-3.5 hr in high yields and in high purity, involving a dehydrative ring closure. The final compounds 4a-f have also been prepared alternatively by reacting 1 with 2 in PEG-600 at 100 °C for 3.5-4 hr.

Keywords: 2-Hydrazinoquinazolin-4(3H)-one, phthalic anhydride, succinic anhydride, maleic anhydride, phthalalazine, PEG-600

Quinazolinones possess a variety of useful biological properties like antihypotensive1, choleretic and antiphlogistic2, anticancer3, antifungal4, anticonvulsant5, CNS depressant6, muscle relaxant7 etc.

Saleh et al.8 synthesised 3-amino-2-methyl-3H-[1,2,4]triazolo[5,1-b]-quinazolin-9-one by condensation of 2-hydrazino-3-phenylamino-3H-quinazolin-4-one with phthalic anhydride in refluxing methanol for 6 hr. Mogilaiah et al.9 reported the synthesis of 1,8-naphthyridine-3-carbonylphthalalazine-1,4-diones by the condensation of 1,8-naphthyridine-3-carboxylic acid hydrazides with phthalic anhydride using p-toluenesul-phonic acid as a catalyst under solid state conditions. Mogilaiah et al.10 also reported the microwave irradi-ation of a mixture of 3-aryl-2-hydrazino-1,8-naphhtyridines with phthalic anhydride in the presence of a catalytic amount of dimethylformamide resulting in 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydropthalalazine-1,4-dione.

In continuation of our interest11,12 in the synthesis of novel quinazolin-4(3H)-one derivatives, using green methods, we herein describe the PEG-600 mediated synthesis of some quinazolin-4(3H)-one derivatives.

Results and Discussion

Commercially available anthranilamide was treated with carbon disulfide in isopropyl alcohol containing KOH giving the previously reported13 2-mercaptoquinazolin-4(3H)-one. The latter was heated with hydrazine hydrate in ethanol to obtain 2-hydrazinoquinazolin-4(3H)-one (1a, i.e. 1, R=H) also known in literature14, 2-Mercaptoquinazolin-3-phenyl-4(3H)-one (1b, i.e. 1, R= ph), the other starting material, was prepared by refluxing the commercially available anthranilic acid with phenylisothiocyanate in acetic acid giving the previously reported15 2-mercapto-3-phenylquinazolin-3H-4-one followed by treatment of the latter with hydrazine hydrate in refluxing ethanol. Condensation of 1a with phthalic anhydride 2b in PEG-600 at RT for 30 min resulted in the formation of 2-[N-(oxo-3,4-dihydroquinazolin-2-yl)hydrazinocarbonyl]benzoic acid 3a. Its structure has been established on the basis of its spectral data. Thus, its IR (KBr) showed absorptions at 3433 and 3245 cm⁻¹ assignable to the NH or OH stretching vibrations whereas the bonded OH and bonded NH stretching vibrations appeared as broad peak at 3061 cm⁻¹ of medium intensity. The strong, sharp absorptions at 1703 and 1671 cm⁻¹ in the IR spectrum were assigned to carbonyl groups. Its ¹H NMR in DMSO-d₆ showed signals at δ 6.8-8.1 (m, 8H, Ar-H), 10.2 (s, 2H, NH, D₂O exchangeable), 10.9 (s, 1H, OH, D₂O exchangeable). Its ¹³C NMR spectrum showed signals at δ 120.80, 123.51, 126.64, 126.71, 127.30, 128.82, 130.10, 131.57, 132.08, 133.44,
134.05, 146.92, 153.33, 161.09, 64.80 and 167.65. Its mass spectrum showed the molecular ion peak at m/z 325 corresponding to a molecular mass of 324 when recorded in the Q+1 mode.

The above reaction of phthalic anhydride with 1a was found to be a general one and extended to other anhydrides such as succinic anhydride 2b and maleic anhydride 2c and the products obtained were assigned structures 3b-f (Table I) on the basis of analogy and on the basis of their spectral data (Table I).

The above product 3a (i.e. R=H) was heated in PEG-600 at 100 °C for about 3 hr which resulted in the formation of the cyclised product, i.e. 2-(4-oxo-3-phenyl-3, 4-dihydroquinazolin-2-yl)-2, 3-dihydropthalazine-1,4-dione 4a. Its structure was assigned on the basis of its spectral data. Thus, its IR (KBr) spectrum showed the absence of any absorption in the region 3000-3500 cm⁻¹ due to NH or OH groups but showed strong absorptions at 1798, 1737, 1681 cm⁻¹ due to the three carbonyl groups. Its ¹H NMR (DMSO-d₆) showed only a multiplet in the region δ 7.1-8.0 due to aromatic protons, 10.2 (broad, 2H, NH, D₂O exchangeable). Its ¹³C NMR spectrum showed signals at δ 114.61, 115.12, 122.93, 126.43, 126.95, 130.82, 131.22, 134.21, 134.39, 135.02, 139.79, 152.7, 160.68, 161.55 and 165.79. Its mass spectrum showed the molecular ion peak at m/z 307 corresponding to a molecular mass of 306 when recorded in the Q+1 mode.

### Table I — Synthesis of 3a-f from 1a-b and 2a-c in PEG-600

<table>
<thead>
<tr>
<th>Substrate 1</th>
<th>Substrate 2</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2a</td>
<td>3a</td>
<td>22</td>
<td>95</td>
<td>&gt;260</td>
</tr>
<tr>
<td>1a</td>
<td>2b</td>
<td>3b</td>
<td>26</td>
<td>88</td>
<td>236-38</td>
</tr>
<tr>
<td>1a</td>
<td>2c</td>
<td>3c</td>
<td>26</td>
<td>81</td>
<td>230-32</td>
</tr>
<tr>
<td>1b</td>
<td>2a</td>
<td>3d</td>
<td>24</td>
<td>91</td>
<td>249-51</td>
</tr>
<tr>
<td>1b</td>
<td>2b</td>
<td>3e</td>
<td>28</td>
<td>84</td>
<td>211-13</td>
</tr>
<tr>
<td>1b</td>
<td>2c</td>
<td>3f</td>
<td>27</td>
<td>90</td>
<td>198-99</td>
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</tbody>
</table>
The above reaction has been found to be a general one and has been extended to 3b-f and the products thus obtained were assigned structures 4b-f (Table II) on the basis of spectral data (see in Table III).

In an alternative approach, 4a-f could also be prepared directly by treating 1a,b with 2a-c in PEG-600 at 100°C for 4-5 hr (1+2\rightarrow 4). 6a-c were prepared by refluxing phthalic anhydride, succinic anhydride, maleic anhydride with hydrazine hydrate independently in acetic acid for 2-3 hr by the reported procedure\textsuperscript{16-18}. 5a,b also were prepared by treatment of 2-mercaptoquinazolin-4(3\textit{H})-one with dimethylsulphate by the earlier reported procedure\textsuperscript{19,20} (Scheme I).

In another approach, 4a-f was prepared directly by heating 5a,b, independently, each with 2,3-dihydropthalazine-1,4-dione 6a, tetrahydropyridazine-3,6-dione 6b and 1,2-dihydropyridazine-3,6-dione 6c at 100 °C in PEG-600 for 6-7 hr. The products, i.e. 4a-f, obtained were found to be identical in m.p., m.m.p., and co-TLC with those of the same products obtained in the route 5 + 6 \rightarrow 4 described earlier above.

Plausible Mechanism
2-Hydrazinoquinazolinone 1 attacks the carbonyl carbon of the anhydride 2 to afford the mono acid mono amide derivative 3. Then, the quinazolinone ring containing nitrogen of 3 attacks the carbonyl carbon of the acid group followed by dehydration gives quinazolinophthalazine 4 (Scheme II).

Experimental Section
Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using iodine or UV light. IR spectra were recorded using a Perkin-Elmer 1000 instrument in KBr pellets. \textsuperscript{1}H NMR spectra were recorded in DMSO-\textit{d}$_{6}$ using TMS as internal standard operating at 400 MHz.

General procedure for the preparation of 3a-f from 1a,b and 2a-c
To a solution of the 2-hydrazinoquinazolin-4(3\textit{H})-ones 1a,b (10 mM) in PEG-600 (5 mL) at RT was added a solution of the anhydride 2a-c (10 mM) in PEG-600 (15 mL) at RT. The reaction mixture was stirred for 30-40 min and then poured into ice-cold water. The separated solid was filtered, washed with water (2×10 mL), and dried. These products were purified by recrystallization from suitable solvents to obtain pure 3a-f.

Preparation of 4a-f from 3a-f
A solution of the mono acid mono amide derivative 3a-f (10 mM) in PEG-600 (15 mL) was heated at 100°C for 3-3.5 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered, washed with water (2×10 mL), and dried. The crude product was purified by recrystallization from suitable solvent to obtain pure 4a-f.

Table II — Synthesis of 4a-f from 3a-f in PEG-600

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product (4a-f)</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Starting Material</th>
<th>Product (4a-f)</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
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<tbody>
<tr>
<td>3a</td>
<td>4a</td>
<td>3.0</td>
<td>94</td>
<td>&gt;260</td>
<td>3d</td>
<td>4d</td>
<td>3.4</td>
<td>93</td>
<td>260-62</td>
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<tr>
<td>3b</td>
<td>4b</td>
<td>3.5</td>
<td>90</td>
<td>244-46</td>
<td>3e</td>
<td>4e</td>
<td>3.4</td>
<td>83</td>
<td>215-17</td>
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<tr>
<td>3c</td>
<td>4c</td>
<td>3.1</td>
<td>85</td>
<td>&gt;260</td>
<td>3f</td>
<td>4f</td>
<td>3.4</td>
<td>88</td>
<td>253-55</td>
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<td>Entry</td>
<td>IR (cm⁻¹)</td>
<td>Spectral data</td>
<td>Mass (m/z)</td>
<td>Mol. Formula</td>
<td>Found (Calcd) %</td>
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</tr>
<tr>
<td>3a</td>
<td>See under experimental section</td>
<td>C₂₂H₁₂N₄O₄</td>
<td>56.26</td>
<td>C</td>
<td>17.28</td>
<td>19.72</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>2.49 (t, 2H, CH₂), 2.72 (t, 2H, CH₂) 7.16-8.06 (m, 4H, Ar-H), 10.55 (s, 2H, NH, D₂O, exchangeable), 10.80</td>
<td>C₂₂H₁₂N₄O₄</td>
<td>52.17</td>
<td>H</td>
<td>3.38</td>
<td>20.28</td>
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<tr>
<td>3c</td>
<td>13C: 30.53, 32.82, 126.60, 126.71, 126.86, 127.30, 133.43, 146.91, 153.32, 161.06, 173.82, 177.33, 1710, 1H, -CH₃, 6.50 (s, 2H, -CH₃), 10.35 (s, 2H, NH, D₂O, exchangeable), 11.14 (s, 1H, OH, D₂O, exchangeable).</td>
<td>C₂₂H₁₀N₄O₄</td>
<td>52.56</td>
<td>N</td>
<td>3.68</td>
<td>20.43</td>
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<tr>
<td>3d</td>
<td>7.16-8.06 (m, 13H, Ar-H), 10.23 (s, 2H, NH, D₂O, exchangeable), 10.85 (s, 1H, OH, D₂O, exchangeable)</td>
<td>C₂₂H₁₀N₄O₄</td>
<td>66.00</td>
<td>C</td>
<td>4.03</td>
<td>13.99</td>
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<tr>
<td>3e</td>
<td>2.49 (t, 2H, CH₂), 2.72 (t, 2H, CH₂), 6.80-8.06 (m, 9H, Ar-H), 10.12 (s, 2H, NH, D₂O, exchangeable), 10.90</td>
<td>C₂₂H₁₀N₄O₄</td>
<td>61.36</td>
<td>H</td>
<td>4.58</td>
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<tr>
<td>4a</td>
<td>See under experimental section</td>
<td>C₂₂H₁₀N₄O₃</td>
<td>62.74</td>
<td>C</td>
<td>3.29</td>
<td>18.29</td>
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<tr>
<td>4b</td>
<td>2.76 (s, 4H, CH₂), 7.12-8.05 (m, 4H, Ar-H), 10.21</td>
<td>C₂₂H₁₀N₄O₃</td>
<td>55.81</td>
<td>H</td>
<td>3.90</td>
<td>21.70</td>
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<tr>
<td>4c</td>
<td>6.50 (s, 1H, -CH₃), 10.90 (s, 2H, NH, D₂O, exchangeable)</td>
<td>C₂₂H₁₀N₄O₃</td>
<td>56.25</td>
<td>N</td>
<td>3.15</td>
<td>21.87</td>
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<tr>
<td>4d</td>
<td>7.16-8.06 (m, 13H, Ar-H), 10.21 (s, 1H, NH or OH, D₂O, exchangeable).</td>
<td>C₂₂H₁₀N₄O₃</td>
<td>69.10</td>
<td>C</td>
<td>3.69</td>
<td>14.65</td>
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<tr>
<td>5f</td>
<td>6.72 (s, 2H, -CH₂), 7.20-8.26 (m, 9H, Ar-H), 10.21</td>
<td>C₂₂H₁₀N₄O₃</td>
<td>65.06</td>
<td>H</td>
<td>3.64</td>
<td>16.86</td>
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</table>

Table III — Characterization data for compounds 3a-f and 4a-f
Scheme I

1a-b + 2a-c → PEG-600

RT/3G-40 min → 3a-f

PEG-600 heating at 100 °C, 3-4 hr → 4a-f

PEG-600/water bath 100 °C, 3-3.5 hr

R = H, Ph; 2a = 2b = CH₂CH₂ 2c = CH₂CH₂

Scheme II

H₂NHH₂ + 2 → 3

3 → 4

4 → 3a

R = H, Ph; 2a = 2b = CH₂CH₂ 2c = CH₂CH₂
Preparation of 4a-f from 1a,b and 2a-c
To a solution of the hydrazinoquinazolinone derivatives 1 (10 mM) in PEG-600 (15 mL) was added a solution of the anhydrides 2a-c (10 mM) in PEG-600 and the mixture heated at 100 °C for 4-5 hr. Then, the reaction mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered, washed with water (2×10 mL) and then dried. This product was purified by recrystallization from suitable solvent to obtain pure 4a-f.

Preparation of 4a-f from 5a,b and 6a-c
To a solution of the 5a,b (10 mM) in PEG-600 (10-15 mL) was added the anhydrides 6a-c (10 mM) and the mixture heated at 100°C for 6-7 hr. Then, the reaction mixture was cooled to RT. The separated solid was filtered, washed with water (2×10 mL) and dried. The product was purified by recrystallization from suitable solvent to obtain pure 4a-f. The recovered PEG-600 with water was reused for further cycles.

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References