# Water-Accelerated Synthesis of Novel Bis-2,3-dihydroquinazolin-4(1*H*)-one Derivatives

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**Abstract:** Bisdihydroquinazolinones were synthesized for the first time by a novel pseudo five-component condensation of isatoic anhydride, a primary amine, and a dialdehyde in water. Several solvents were examined for this reaction; however, in terms of reaction yield and time, water was found to be the optimum solvent.

**Key words:** multicomponent reactions, heterocycles, catalysis, bis-dihydroquinazolinones, water

The ever-increasing demand for novel medicinally active compounds and the laborious process of lead discovery and optimization have resulted in the continuous search for simple and efficient methods for the generation of libraries for biological screening.[1] Heterocycles are an important class of substrates that are found in natural products and pharmaceuticals. The rigidity of the heterocyclic core, which results from the substitution of the core, limits the conformational freedom especially when compared with the corresponding acyclic structure. 2,3-Dihydroquinazolin-4(3*H*)-ones **1** are a class of heterocycles which exhibit biological and pharmaceutical activity as anti-tumor, diuretic, and herbicidal agents, as well as plant growth regulators, and anti-cancer drugs.[2] Also these compounds can be easily oxidized to their quinazolin-4(3*H*)-one analogues,[3] which are among the most important biologically active heterocyclic compounds,[4] and can be found in some natural products.[5]

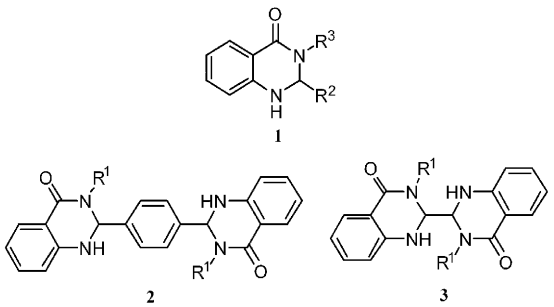

**Figure 1**

Furthermore, the study of bis-heterocyclic systems has attracted interest, owing to their potential biological activities.[6] To the best of our knowledge, there are no reports on the synthesis of bis-dihydroquinazolinone compounds **2** and **3** in the literature (Figure 1).

Very recently we reported a novel method for the synthesis of 2,3-dihydroquinazolin-4(3*H*)-ones by the condensation of isatoic anhydride, primary amines, and aromatic aldehydes in the presence of silica sulfuric acid.[7] To further improve the utility and user-friendliness of this process we have developed its practical pseudo five-component variant, which is described herein.

For the preparation of our potential target compounds **2** and **3**, isatoic anhydride was treated with primary amine and terphtaldehyde (**4**) or glyoxal (**5**) in the presence of *p*-toluenesulfonic acid (Scheme 1). Different organic solvents were examined for the reaction and we found that ethanol was the solvent of choice (Table 1).

Currently the use of non-toxic and environmentally friendly organic solvents is of much interest. Room temperature ionic liquids are novel solvents with outstanding environmental and technical features.[8] Tetra-*n*-butylammonium bromide (TBAB) and 1-butyl-3-methylimidazolium bromide ([bmim]Br) were investigated as solvents for the above reaction. Ionic liquids proved to be almost

**Table 1** Solvent Effects[a]

| Solvent | Yield (%)[b] | Time (h) |
|---|---|---|
| $CH_2Cl_2$ | – | – |
| $CH_3C_6H_5$ | 10 | 48 |
| $CH_3CN$ | 25 | 24 |
| $CH_3OH$ | 38 | 14 |
| $CH_3CH_2OH$ | 70 | 5.5 |
| TBAB | 58 | 5 |
| [bmim]Br | 60 | 5 |
| $H_2O$ | 64 | 3 |

[a] Reaction of $EtNH_2$, isatoic anhydride, and terephthaldehyde in the presence of *p*-TsOH.
[b] Isolated yield based on isatoic anhydride.

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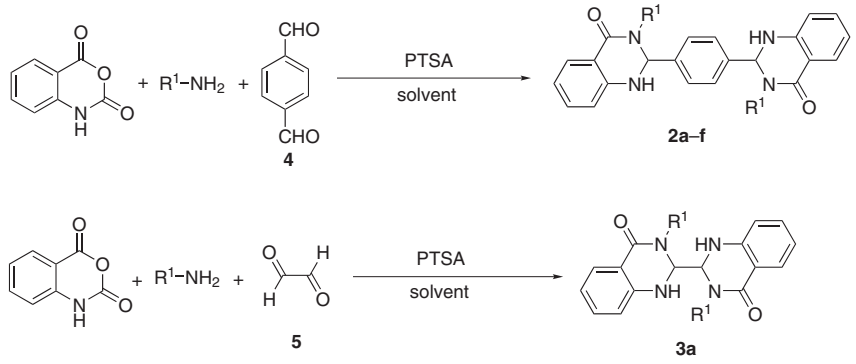



**Scheme 1**

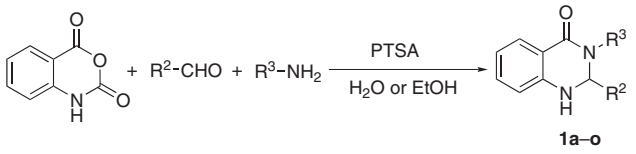
as good as ethanol, with 1-butyl-3-methylimidazolium bromide giving a slightly better yield than tetra-*n*-butylammonium bromide.

The use of water as a solvent for organic transformations offers several environmental benefits. In many reactions, significant rate enhancements are observed in water compared to organic solvents. This acceleration has been attributed to many factors, including the hydrophobic effect, enhanced hydrogen bonding in the transition state, and the cohesive energy density of water.[9]

When the reactions were conducted in water, the expected products were obtained in good yields and with better reaction times compared to organic solvents or ionic liquids (Table 2).

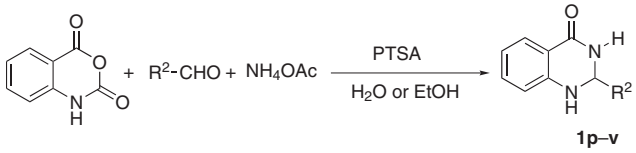
All bis-dihydroquinazolinones synthesized by this pseudo five-component reaction were reported for the first time and could be considered as potentially biologically active compounds with a quinazolinone core.

We also synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones. Water as solvent resulted in shorter reaction times than ethanol (Table 3). For the synthesis of disubstituted derivatives, isatoic anhydride, a primary amine, and an aromatic aldehyde in the presence of *p*-toluenesulfonic acid were reacted in ethanol or water under reflux conditions to afford the expected products (Scheme 2).




**Scheme 2**

Monosubstituted 2,3-dihydroquinazolin-4(1*H*)-ones were also synthesized successfully using ammonium acetate as an ammonia source (Scheme 3).




**Scheme 3**

In addition to the above-mentioned advantages are the simple work-up procedure, that makes this process environmentally friendly, and the easy purification, that re-

**Table 2** Synthesis of Bis-2,3-dihydroquinazolin-4(1*H*)-ones[a]

| Product | Aldehyde | $R^1$ | $H_2O$ | | EtOH | | [bmim]Br | |
|---|---|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%)[a] | Time (h) | Yield (%) | Time (h) | Yield (%) |
| **2a** | 5 | 4-$CH_3C_6H_4$ | 3.5 | 60 | 12 | 62 | 12 | 62 |
| **2b** | 5 | 4-$ClC_6H_4$ | 4 | 59 | 8 | 57 | 8 | 57 |
| **2c** | 5 | H | 3 | 62 | 6 | 66 | 6 | 66 |
| **2d** | 5 | $CH_3CH_2$ | 3 | 64 | 5.5 | 70 | 5.5 | 70 |
| **2e** | 5 | 2-Thiazolyl | 5 | 50 | 10 | 54 | 10 | 54 |
| **2f** | 5 | $C_6H_5CH_2$ | 3.5 | 66 | 6.5 | 71 | 6.5 | 71 |
| **3a** | 6 | H | 3 | 66 | 5 | 64 | 5 | 64 |

[a] Reaction of isatoic anhydride, dialdehyde, and a primary amine or ammonium acetate in the presence of *p*-TsOH.
[a] Isolated yields based on isatoic anhydride.

**Table 3** Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones[a]

| Product[b] | $R^2$ | $R^3$ | $H_2O$ | | EtOH | | Mp (°C) |
|---|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%)[c] | Time (h) | Yield (%) | Found[7] |
| **1a** | Ph | Me | 1.5 | 85 | 3 | 73 | 165 |
| **1b** | 4-$ClC_6H_4$ | Me | 2 | 83 | 3.5 | 74 | 190 |
| **1c** | 4-$CH_3OC_6H_4$ | Me | 1.5 | 82 | 3 | 70 | 146 |
| **1d** | Ph | Et | 1.5 | 86 | 3.5 | 75 | 136–137 |
| **1e** | 4-$ClC_6H_4$ | Et | 1 | 84 | 3.5 | 74 | 134–137 |
| **1f** | 4-$NO_2C_6H_4$ | Et | 1 | 86 | 3 | 80 | 157–160 |
| **1g** | 3-$NO_2C_6H_4$ | Et | 1 | 90 | 3 | 82 | 175–178 |
| **1h** | 4-$CH_3OC_6H_4$ | Et | 2 | 86 | 4 | 74 | 125–128 |
| **1i** | Ph | Ph | 2.5 | 79 | 6.5 | 65 | 205–206 |
| **1j** | 4-$NO_2C_6H_4$ | Ph | 2 | 80 | 7 | 68 | 196–199 |
| **1k** | 4-$ClC_6H_4$ | Ph | 2 | 78 | 6 | 70 | 216–217 |
| **1l** | 3-$NO_2C_6H_4$ | Ph | 2 | 80 | 5.5 | 73 | 187–190 |
| **1m** | Ph | 4-$ClC_6H_4$ | 1.5 | 75 | 7 | 63 | 216–218 |
| **1n** | 4-$NO_2C_6H_4$ | Pr | 1 | 86 | 4 | 77 | 120–121 |
| **1o** | 4-$HOC_6H_4$ | Et | 1.5 | 80 | 6 | 70 | 180–182 |
| **1p** | Ph | H | 1 | 84 | 4 | 75 | 218–220 |
| **1q** | 4-$ClC_6H_4$ | H | 1.5 | 85 | 5 | 85 | 198–200 |
| **1r** | 4-$CH_3OC_6H_4$ | H | 2 | 88 | 7 | 75 | 178–180 |
| **1s** | 2-$CH_3OC_6H_4$ | H | 2 | 81 | 4 | 67 | 165–167 |
| **1t** | 4-$CH_3C_6H_4$ | H | 2 | 80 | 5 | 70 | 233–234 |
| **1u** | 3,4-$(CH_3O)_2C_6H_3$ | H | 2 | 78 | 5 | 70 | 210–213 |
| **1v** | 2-Furyl | H | 2.5 | 75 | 4 | 75 | 166–167 |

[a] Reaction of isatoic anhydride, a primary amine or ammonium acetate and aromatic aldehyde in the presence of *p*-TsOH.
[b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the reported procedure.[7]
[c] Isolated yield based on isatoic anhydride.

quires only filtration of the products followed by recrystallization from ethanol.

In conclusion, a simple and environmentally friendly method for the synthesis of a novel class of quinazolinones is described. In this pseudo five-component procedure six C–N bonds are formed in a tandem one-pot process, which is comparable with other important reactions in multicomponent chemistry.[10] Also the work-up procedure is very simple, and chromatography is not required. Starting materials are inexpensive and commercially available. By the reaction of a range of amines and dialdehydes, novel libraries of bisdihydroquinazolinones could be obtained, which would make this method a suitable candidate for combinatorial and parallel synthesis in drug discovery.

Products **1a–m** and **1p–v** are known compounds and their physical data, IR and $^1H$ NMR spectra were essentially identical with those of authentic samples. Other products, which are new, were characterized by IR, $^1H$, and $^{13}C$ NMR spectroscopy, MS, and elemental analysis. MPs were obtained in open capillary tubes and were measured on an electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. Elemental analysis was performed using a Heracus CHN-O-Rapid analyzer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz, respectively.

**Bis-2,3-dihydroquinazolin-4(1*H*)-ones; General Procedure ($H_2O$ or EtOH)**
Isatoic anhydride (1 mmol, 0.163 g), terephthaldehyde or glyoxal (0.5 mmol), and primary amine or ammonium acetate (1.2 mmol) were placed in a round-bottomed flask. Solvent (5 mL) was added, followed by *p*-TsOH (0.6 mmol), and the mixture was heated to reflux. When the reaction was complete (TLC; *n*-hexane–EtOAc, 2:1) the mixture was cooled to r.t. and the precipitate was filtered.

**Bis-2,3-dihydroquinazolin-4(1*H*)-ones; General Procedure (Ionic Liquid)**
A mixture of isatoic anhydride (1 mmol, 0.163 g), dialdehyde (1 mmol), amine or ammonium acetate (1.2 mmol), and *p*-TsOH (0.6 mmol) were added to an ionic liquid (0.3 g) and stirred at 100 °C for the time indicated in Table 2. When the reaction was complete (TLC) the mixture was cooled to r.t. and EtOH (5 mL) was added. The precipitate was filtered and washed with cold EtOH.

**Mono- and Disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones; General Procedure (Water)**
To a round-bottomed flask containing $H_2O$ (5 mL) was added isatoic anhydride (1 mmol, 0.163 g), aldehyde (1 mmol), amine or ammonium acetate (1.2 mmol), and *p*-TsOH (0.5 mmol). The mixture was heated under reflux for the time indicated in Table 3. The precipitate was filtered and recrystallized (EtOH).

**Mono- and Disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones; General Procedure (Ethanol)**
*p*-TsOH (0.5 mmol) was added to a mixture of isatoic anhydride (1 mmol, 0.163 g), amine or ammonium acetate (1.2 mmol), and aldehyde (1 mmol) and heated under reflux for the time indicated in Table 3. When the reaction was complete (TLC; *n*-hexane–EtOAc, 2:1), the solvent was evaporated under reduced pressure and $H_2O$ (10 mL) was added. The precipitate was filtered and recrystallized (EtOH).

**2,3-Dihydro-2-[4(1,2,3,4-tetrahydro-4-oxo-3-*p*-tolylquinazolin-2-yl)phenyl]-3-*p*-tolylquinazolin-4(1*H*)-one (2a)**
White solid; mp 254–256 °C.

IR (KBr): 3290 (NH), 1640 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 2.24 (s, 6 H, $CH_3$), 6.15 (d, *J* = 1.8 Hz, 2 H, CH), 6.66–7.67 (m, 20 H, ArH), 7.53 (d, *J* = 1.8 Hz, 2 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 20.5 (2 C, $CH_3$), 72.5 (2 C, CH), 114.6, 115.1, 117.4, 126.4, 126.6, 127.9, 129.0, 133.6, 135.3, 138.0, 140.8, 146.5, 162.0 (2 C, C=O).

MS (EI, 70 eV): *m*/*z* (%) = 550 (50) [$M^+$], 442 (45), 237 (75), 120 (100), 91 (60), 77 (76).

Anal. Calcd for $C_{36}H_{30}N_4O_2$: C, 78.5; H, 5.5; N, 10.1. Found: C, 78.4; H, 5.5; N, 9.7.

**3-(4-Chlorophenyl)-2-{4-[3-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl]phenyl}-2,3-dihydroquinazolin-4(1*H*)-one (2b)**
White solid; mp 258 °C (dec.).

IR (KBr): 3320 (NH), 1615 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 6.17 (s, 2 H, CH), 6.65–7.64 (m, 22 H, 20 × ArH, 2 × NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 70.8 (2 C, CH), 113.3, 113.4, 116.1, 125.4, 126.5, 126.7, 128.9, 132.5, 137.9, 139.0, 145.2, 160.8 (2 C, C=O).

MS (EI, 70 eV): *m*/*z* (%) = 246 (3), 172 (21), 120 (100), 119 (47).

Anal. Calcd for $C_{34}H_{24}Cl_2N_4O_2$: C, 69.0; H, 4.0; N, 9.4. Found C, 68.5; H, 4.3; N, 8.9.

**2,3-Dihydro-2-[4-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)phenyl]quinazolin-4(1*H*)-one (2c)**
White solid; mp 243–245 °C.

IR (KBr): 3265 (NH), 3187 (NH), 1640 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 5.73 (d, *J* = 2.0 Hz, 2 H, CH), 6.62–8.19 (m, 16 H, 12 × ArH, 4 × NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 66.4 (2 C, CH), 114.9, 115.4, 117.6, 127.1, 127.8, 133.8, 142.4, 148.1, 164.0 (2 C, C=O).

MS (EI, 70 eV): *m*/*z* (%) = 366 (20) [$M^+$], 136 (10), 119 (100).

Anal. Calcd for $C_{22}H_{18}N_4O_2$: C, 71.3; H, 4.9; N, 15.1. Found: C, 71.2; H, 4.9; N, 14.9.

**3-Ethyl-2-[4-(3-ethyl-1,2,3,4-tetrahydro-4-oxoquiazolin-2-yl]phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (2d)**
White solid; mp 235 °C (dec.).

IR (KBr): 3305 (NH), 2978 (CH), 1627 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 1.02 (t, *J* = 7.0 Hz, 6 H, $CH_3$), 2.79 (dt, *J* = 13.6, 7.0 Hz, 2 H, CH), 3.80 (dt, *J* = 13.6, 7.0 Hz, 2 H, CH), 5.84 (s, 2 H, CH), 6.57–7.31 (m, 14 H, 12 × ArH, 2 × NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 13.6 (2 C, $CH_3$), 69.9 (2 C, CH), 114.6, 115.3, 117.6, 126.8, 127.8, 133.6, 142.0, 146.7, 162.3 (2 C, C=O).

MS (EI, 70 eV): *m*/*z* (%) = 426 (22) [$M^+$], 252 (70), 175 (100), 119 (30).

Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 73.2; H, 6.1; N, 13.1. Found: C, 73.0; H, 6.1; N, 13.0.

**2,3-Dihydro-2-{4-[1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl]phenyl}-3-(thiazol-2-yl)quinazolin-4(1*H*)-one (2e)**
Light brown solid; mp >260 °C (dec.).

IR (KBr): 3320 (NH), 1615 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 6.71–8.00 (m, 20 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 68.2 (2 C, CH), 114.0, 116.2, 118.8, 125.9, 126.3, 128.6, 128.7, 135.6, 137.9, 139.0, 145.2, 160.8 (2 C, C=O).

MS (EI, 70 eV): *m*/*z* (%) = 536 (0.5) [$M^+$], 263 (20), 219 (25), 120 (100), 119 (47).

Anal. Calcd for $C_{28}H_{20}N_6O_2S_2$: C, 62.7, H, 3.8; N, 15.6. Found: C, 62.7; H, 4.0; N, 15.3.

**3-Benzyl-2-[4-(3-benzyl-1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one (2f)**
White solid; mp >270 °C (dec.).

IR (KBr): 3290 (NH), 1640 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 3.79 (d, *J* = 15.4 Hz, 2 H, CH), 5.29 (d, *J* = 15.4 Hz, 2 H, CH), 5.72 (d, *J* = 2.3 Hz, 2 H, CH), 6.61–7.68 (m, 22 H, ArH), 7.39 (2 H, d, *J* = 2.3 Hz, $D_2O$ exchange, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 45.98 (2 C, $CH_2$), 68.2 (2 C, CH), 113.2, 113.4, 116.1, 125.1, 125.9, 126.2, 126.4, 127.2, 132.3, 136.3, 139.7, 145.0, 161.1 (2 C, C=O).

MS (EI, 70 eV): *m*/*z* (%) = 550 (20) [$M^+$], 237 (37), 119 (20), 91 (100).

Anal. Calcd for $C_{36}H_{30}N_4O_2$: C, 78.5; H, 5.5; N, 10.1. Found: C, 78.4; H, 5.5; N, 9.9.

**2,3-Dihydro-2-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)quinazoline-4(1*H*)-one (3a)**
White solid; mp 238 °C (dec.).

IR (KBr): 3354 (NH), 3300 (NH), 1635 (C=O) $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 4.81–4.85 (m, 2 H, CH), 6.63–7.76 (m, 10 H, 8 × ArH, 2 × NH), 8.43 (2 H, d, $J$ = 5.3 Hz, $D_2O$ exchange, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 67.2 (2 C, CH), 117, 117.5, 118.4, 126.3, 127.3, 132.4, 132.5, 144.8, 167.4 (2 C, C=O).

MS (EI, 70 eV): $m/z$ (%) = 294 (1) [M$^+$], 277 (60), 172 (50), 119 (22), 91 (100).

Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.3; H, 4.8; N, 19.0. Found: C, 65.3; H, 4.7; N, 18.8.

**2,3-Dihydro-2-(4-nitrophenyl)-3-propylquinazolin-4(1*H*)-one (1n)**

Yellow solid; mp 120–121 °C.

IR (KBr): 3420, 1680 (C=O) cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 1.64 (m, 2 H, $CH_2$), 2.77 (ddd, $J$ = 14.1, 8.6, 5.8 Hz, 1 H, CH), 4.05 (ddd, $J$ = 13.9, 8.7, 6.6 Hz, 1 H, CH), 5.82 (s, 1 H, CH), 6.50–8.20 (m, 8 H, ArH).

$^{13}$C NMR ($CDCl_3$): δ = 12.5 ($CH_3$), 22.3 ($CH_2$), 48.1 ($NCH_2$), 71.9 (CH), 116.0, 117.4, 120.9, 125.3, 128.3, 129.5, 134.9, 145.4, 148.3, 149.2, 164.1 (C=O).

MS (EI, 70eV): $m/z$ (%) = 311 (64) [M$^+$], 174 (47.6), 119 (45.2), 105 (44.3), 77 (51.6).

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.6; H, 5.5; N, 13.5. Found: C, 65.5; H, 5.5; N, 13.2.

**3-Ethyl-2,3-dihydro-2-(4-hydroxyphenyl)quinazolin-4(1*H*)-one (1o)**

White solid; mp 180–182 °C.

IR (KBr): 3440, 1680 (C=O) cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 1.00 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.83 (dq, $J$ = 13.6, 7.0 Hz, 1 H, CH), 3.71 (dq, $J$ = 13.6, 7.2 Hz, 1 H, CH), 5.73 (d, $J$ = 1.9 Hz, 1 H, CH), 6.60–6.70 (m, 4 H, ArH), 7.11–7.18 (m, 3 H, ArH), 7.20 (d, $J$ = 1.9 Hz, 1 H, NH), 7.62 (dd, $J$ = 7.6, 1.4 Hz, 1 H, ArH), 9.48 (s, 1 H, OH).

$^{13}$C NMR (DMSO-$d_6$): δ = 14.6 ($CH_3$), 71.6 (CH), 115.6, 116.3, 116.7, 118.5, 128.9, 129.3, 133.0, 134.4, 148.1, 159.2, 163.3 (C=O).

MS (EI, 70eV): $m/z$ (%) = 268 (60) [M$^+$], 174 (67.1), 105 (53.5), 77 (40.5).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.6; H, 5.9; N, 10.2.

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