One-pot five-component reaction for synthesis of some novel bis-dihydroquinoxaline derivatives

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Abstract
An efficient and expedient procedure for the synthesis of some novel 3-(2-(4-oxo-2-aryl-1,2-dihydroquinazolin-3(4H)-yl)ethyl)-2-aryl-2,3-dihydroquinazolin-4(1H)-one and 3-(4-(4-oxo-2-aryl-1,2-dihydroquinazolin-3(4H)-yl)phenyl)-2-aryl-2,3-dihydroquinazolin-4(1H)-one derivatives is described. The method involves the one-pot five-component condensation of two molecules of isatoic anhydride, two molecules aldehyde with and one molecule of diamine in the presence of a catalytic amount of KAl(SO$_4$)$_2$.12H$_2$O (alum). It affords the corresponding product in high yield with very short reaction time (50-75 min).

Keywords: Bisquinazolinone, aldehyde, isatoic anhydride, diamine, alum

Introduction

2,3-Dihydroquinazoline-4(3H)-ones are important fused heterocycles due to their potential biological and pharmaceutical activities. They have been used for the analgesic,\(^1\) antitumor,\(^2\) diuretic,\(^3\) antidefibrillary,\(^4\) antihistamine,\(^5\) vasodilating agent,\(^6\) tranquilizer\(^7\) properties. Several methods have been reported for the synthesis of 2,3-dihydroquinazolinones,\(^8-17\) using various catalysts such as stannous chloride,\(^18\) ionic liquids,\(^19\) cyanuric chloride,\(^20\) and Sc(III)-indapybox.\(^21\)

The synthesis of bis-quinazoline derivatives was reported in only a few papers.\(^22-27\) The synthesis of 3,3'-(hexane-1,6-diyl)bis(2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one) was described through a condensation catalyzed by iodine in ionic liquids in very long reaction time (6-12 h) and 3-(2-(4-oxo-2-aryl-1,2-dihydroquinazolin-3(4H)-yl)ethyl)-2-aryl-2,3-dihydroquinazolin-4(1H)-one was reported by Reddy, et. al. in 1993 via two step in AcOH.\(^29\)
Results and Discussion

We have concentrated most of our recent studies on the preparation of biological and pharmaceutical nitrogen-containing heterocycles and have already described simple and efficient procedures for the preparation of dihydropyrimidinones,\textsuperscript{30} spiro-quinazolines,\textsuperscript{31} and quinazolinones.\textsuperscript{32,33} Along these lines, we designed the five-component one-pot synthesis of bis-dihydroquinazolinone 4a-\textit{r} from two molecules of isatoic anhydride 1, two molecules of aldehyde 2a-\textit{r} with diamine 3a-\textit{c} using alum as a heterogenous catalyst in EtOH 96\%. The alum acts as a reusable Lewis acid to catalyze the reaction of isatoic anhydride, aldehydes, and ethylene diamine via the activation the carbonyl group for the synthesis of bis-dihydroquinazolinone.\textsuperscript{34-36} (Scheme1) The effect of various solvents (CH\textsubscript{3}CN, CHCl\textsubscript{3}, H\textsubscript{2}O and EtOH) and catalyst concentration (0.05, 0.10, 0.15, 0.20, 0.25, and 0.30 g) were studied. The use of ethanol as solvent and 0.15 g catalyst provide the highest yield and shortest reaction time. Furthermore, the benefits of using this catalyst are numerous since it is non-toxic, inexpensive, non-hazardous, easily available, reusable with no substantial loss in activity and allows easy work-up for its separation.

From a mixture of isatoic anhydride 1 (2 mmol), benzaldehyde 2a (2 mmole), ethylene diamine 3a (1 mmol), and alum (0.15 g), 3,3'-((ethane-1,2-diyl)bis(2-phenyl-2,3-dihydroquinazolin-4(1\textit{H})-one) 4a was isolated in 91\% yield. The reaction was carried out under reflux conditions for 70 min (until the isatoic anhydride disappeared, as shown by the TLC analysis). Encouraged by this success, we extended this reaction with a range of different aldehydes 2b-\textit{r} and diamines 3a-\textit{c} under the standardized reaction, furnishing the bisquinazolinones 4b-\textit{r} with good yields. Interestingly, all the products are insoluble in hot ethanol and precipitated during the reaction. The results have been summarized in Table 1.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Synthesis of bisquinazolinone 4a-\textit{r}.}
\end{figure}
For wide variety of aromatic aldehydes (electron withdrawing or electron donating), the desired products were obtained in very short reaction time (within 50-75 min), good to excellent yields and simple workup procedure. The solid products obtained were just filtered of the reaction mixture. Water (25 mL) was added to the resulting solid (for removal of alum), filtered and washed with hot ethanol to give purified product. All products were characterized by their IR, MS, $^1$H NMR, and $^{13}$C NMR spectral data.

Table 1. Synthesis of bisquinazolinone 4a-r using alum as catalysts

<table>
<thead>
<tr>
<th>Products</th>
<th>Diamines</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>Lit. Yield (Lit. Time)</th>
<th>Lit. Mp (°C)</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>3</td>
<td>H</td>
<td>70</td>
<td>91</td>
<td>297-9</td>
<td>88 (3h)$^{29}$</td>
<td>291</td>
</tr>
<tr>
<td>b</td>
<td>a</td>
<td>4-Cl</td>
<td>55</td>
<td>93</td>
<td>281-3</td>
<td>74 (3h)$^{29}$</td>
<td>255</td>
</tr>
<tr>
<td>c</td>
<td>a</td>
<td>4-Me</td>
<td>55</td>
<td>96</td>
<td>295-7</td>
<td>85 (3h)$^{29}$</td>
<td>270</td>
</tr>
<tr>
<td>d</td>
<td>a</td>
<td>4-NO$_2$</td>
<td>55</td>
<td>96</td>
<td>286-8 (dec)</td>
<td>61(3h)$^{29}$</td>
<td>275</td>
</tr>
<tr>
<td>e</td>
<td>a</td>
<td>2,4-diCl</td>
<td>50</td>
<td>90</td>
<td>310-13 (dec)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>f</td>
<td>a</td>
<td>3-EtO,4-OH</td>
<td>70</td>
<td>88</td>
<td>262-4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>g</td>
<td>a</td>
<td>3-Cl</td>
<td>55</td>
<td>93</td>
<td>264-6</td>
<td>64 (3h)$^{29}$</td>
<td>245</td>
</tr>
<tr>
<td>h</td>
<td>a</td>
<td>4-MeO</td>
<td>55</td>
<td>94</td>
<td>250-2</td>
<td>69 (3h)$^{29}$</td>
<td>260</td>
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<tr>
<td>i</td>
<td>a</td>
<td>4-CO$_2$H</td>
<td>70</td>
<td>90</td>
<td>308-10</td>
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<td>-</td>
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<tr>
<td>j</td>
<td>a</td>
<td>3-MeO</td>
<td>55</td>
<td>94</td>
<td>237-9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>k</td>
<td>a</td>
<td>4,2-diMeO</td>
<td>60</td>
<td>88</td>
<td>247-9</td>
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<tr>
<td>l</td>
<td>b</td>
<td>H</td>
<td>75</td>
<td>90</td>
<td>296-8</td>
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<tr>
<td>m</td>
<td>b</td>
<td>4-Cl</td>
<td>70</td>
<td>91</td>
<td>238-40 (dec)</td>
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<td>n</td>
<td>b</td>
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<td>281-3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>o</td>
<td>b</td>
<td>4-NO$_2$</td>
<td>65</td>
<td>92</td>
<td>291-3</td>
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<td>p</td>
<td>b</td>
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<td>-</td>
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<tr>
<td>q</td>
<td>c</td>
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<td>90</td>
<td>182-4</td>
<td>88 (6h)$^{28}$</td>
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<tr>
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<td>c</td>
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<td>85</td>
<td>213-5</td>
<td>79 (6h)$^{28}$</td>
<td>212-4</td>
</tr>
</tbody>
</table>

$^a$Isolated yields for purified compounds.
Conclusions

In conclusion, the present method indicates an operationally simple and efficient one-pot five-component reaction for the preparation of bis quinazolin-4(3H)-one using the inexpensive, non-toxic, and easily available KAl(SO\(_4\))\(_2\).12H\(_2\)O (alum) catalyst. In addition, low cost, excellent yields of products, easy experimental work-up procedure, and short reaction time make this methodology a valid contribution to the existing processes for the synthesis of bisquinazolin-4(3H)-one.

Experimental Section

General. Melting points were obtained in open capillary tubes and were measured on an electrothermal 9200 apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. \(^1\)H and \(^{13}\)C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75MHz. Elemental analysis for C, H and N were performed using a Heraus CHN rapid analyzer. All the reactions are monitored by thin layer chromatography (TLC) with UV light as detecting agent.

General Procedure for the synthesis of bis(1,2-dihydro quinazolinon-4(1H)-one) derivatives (4 a-r). A mixture of isatoic anhydride 1 (2 mmol), aldehyde 2 (2 mmol), diamine 3 (1 mmol), 0.15 g (0.3 mmol) alum, and 10 mL EtOH 96% in a 50 mL flask was stirred at reflux for the time period as indicated in table 1. After completion of the reaction (monitored by TLC, ethyl acetate / n-hexane, 4:1), the solid products obtained were just filtered off the reaction mixture. Water (25 mL) was added to the resulting solid (for separation of alum), and the resulting solid was separated by filtration. The crude product was washed with hot ethanol to afford the purified product.

3,3'-(Ethane-1,2-diyl)bis(2-(2,4-dichlorophenyl)-2,3-dihydroquinazolin-4(1H)-one) (4e). Colourless solid; Yield: 88%; mp 310-13 °C (dec); IR (KBr): \(v_{\text{max}}\) 3248 (NH), 3030, 1629 (C=O), 3.96-4.00 (m, 1H, Ar-H), 7.18-7.27 (m, 7H, 2NH, 5Ar-H), 7.35-7.37 (m, 1H, Ar-H), 7.63-7.65 (m, 4H, Ar-H) ppm; \(^{13}\)C NMR (DMSO-d\(_6\)) \(\delta\) 43.09, 68.3, 68.5, 114.9, 115.4, 118.3, 125.3, 128.3, 128.6, 129.2, 130.3, 134.4, 134.9, 143.9, 146.4, 163.1 ppm; MS: \(m/z\) (%) 614; Anal. Calcd for C\(_{30}\)H\(_{22}\)Cl\(_4\)N\(_4\)O\(_2\): C, 58.84; H, 3.62; N, 9.15; Found: C, 58.76; H, 3.53; N, 9.07%.

3,3'-(Ethane-1,2-diyl)bis(2-(3-ethoxy-4-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one) (4f). Colourless solid; Yield: 81%; mp 262-4 °C; IR (KBr): \(v_{\text{max}}\) 3397 (OH), 3281 (NH), 2976, 2929, 1634 (C=O), 1514 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) 1.26 (t, 6H, J 7.0Hz, CH\(_3\)), 2.85-2.89 (m, 2H, CH\(_2\)), 3.91 (q, 4H, J 7.0Hz, CH\(_2\)), 4.02-4.04 (m, 2H, CH\(_2\)), 5.69 (s, 2H, CH), 6.61-6.71 (m, 4H, Ar-H) ppm; \(^{13}\)C NMR (DMSO-d\(_6\)) \(\delta\) 49.9, 68.2, 71.9, 114.9, 115.8, 118.3, 125.5, 128.3, 129.2, 130.3, 134.4, 134.9, 143.9, 146.4, 163.1 ppm; MS: \(m/z\) (%) 592; Anal. Calcd for C\(_{30}\)H\(_{22}\)O\(_3\)N\(_4\)O\(_2\): C, 58.84; H, 3.62; N, 9.15; Found: C, 58.76; H, 3.53; N, 9.07%.
8H, Ar-H), 6.90 (s, 2H, Ar-H), 7.17-7.19 (m, 4H, 2NH, 2Ar-H), 7.61 (d, 2H, J 8.0Hz, Ar-H), 8.99 (s, 2H, OH) ppm; $^{13}$C NMR (DMSO-d$_6$) $\delta$ 15.5, 42.8, 64.6, 71.4, 112.8, 115.0, 115.5, 116.0, 117.8, 119.6, 128.2, 132.2, 134.0, 147.4, 147.5, 147.9, 163.3 ppm; MS: m/z (%) 594; Anal. Calcd for C$_{34}$H$_{34}$N$_4$O$_6$: C, 68.67; H, 5.76; N, 9.42; Found: C, 68.61; H, 5.66; N, 9.35%.

4,4′-(3,3′-(Ethane-1,2-diyl)bis(4-oxo-1,2,3,4-tetrahydroquinazoline-3,2-diyl))dibenzonic acid (4i). Colourless solid; Yield: 80%; mp 308-10 °C; IR (KBr): $v_{\text{max}}$ 3414 (OH), 3325 (NH), 2894, 1709 (C=O), 1693 (C=O), 1621 (C=O), 1568 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$) $\delta$ 2.9-3.00 (m, 2H, CH$_2$), 4.05-4.18 (m, 2H, CH$_2$), 5.95(d, 2H, J 2.1Hz, CH), 6.61 (d, 2H, J 8.0Hz, Ar-H), 6.66 (t, 2H, J 7.6Hz, Ar-H), 7.19 (t, 2H, J 7.0Hz, Ar-H), 7.39 (d, 4H, J 8.3Hz, Ar-H), 7.43 (d, 2H, J 2.1Hz, NH), 7.62 (d, 2H, J 6.8Hz, Ar-H), 7.86 (d, 4H, J 8.2Hz, Ar-H), 12.94 (broad, 2H, CO$_2$H) ppm; $^{13}$C NMR (DMSO-d$_6$) $\delta$ 43.4, 70.6, 115.2, 115.5, 118.2, 127.2, 128.3, 130.4, 131.7, 134.2, 146.3, 147.0, 163.3, 167.6 ppm; MS: m/z (%) 562; Anal. Calcd for C$_{32}$H$_{26}$N$_4$O$_6$: C, 68.32; H, 4.66; N, 9.96; Found: C, 68.23; H, 4.68; N, 9.88%.

3,3′-(Ethane-1,2-diyl)bis(2-(3-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one) (4j). Colourless solid; Yield: 94%; mp 237-9 °C; IR (KBr): $v_{\text{max}}$ 3240 (NH), 3002, 2936, 2828, 1631 (C=O), 1609 (C=O), 1514 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$) $\delta$ 2.89-2.94 (m, 1H, CH$_2$), 2.97-3.03 (m, 1H, CH$_2$), 3.68 (s, 6H, 2CH$_3$), 3.99-4.06 (m, 1H, CH$_2$), 4.10-4.18 (m, 1H, CH$_2$), 5.84 (d, 1H, J 1.5Hz, CH), 5.89 (d, 1H, J 1.7Hz, CH), 6.44 (t, 2H, J 8.3Hz, Ar-H), 6.69 (s, 2H, Ar-H), 6.85-6.89 (m, 6H, Ar-H), 7.18-7.27 (m, 4H, Ar-H), 7.36 (s, 1H, NH), 7.37 (s, 1H, NH), 7.63-7.65 (m, 2H, Ar-H) ppm; $^{13}$C NMR (DMSO-d$_6$) $\delta$ 43.2, 43.4, 55.8, 71.2, 71.5, 113.13, 113.18, 114.3, 114.4, 115.1, 115.4, 115.5, 118.0, 119.0, 128.2, 130.5, 130.6, 134.1, 143.3, 147.3 160.2, 163.3, 163.4 ppm; MS: m/z (%) 534; Anal. Calcd for C$_{32}$H$_{30}$N$_4$O$_4$: C, 71.89; H, 5.66; N, 10.48; Found: C, 71.81; H, 5.59; N, 10.42%.

3,3′-(Ethane-1,2-diyl)bis(2-(2,4-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one) (4k). Colourless solid; Yield: 90%; mp 247-9 °C; IR (KBr): $v_{\text{max}}$ 3384 (NH), 3067, 2936, 2837, 1649 (C=O), 1610, 1497 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$) $\delta$ 2.78-2.82 (m, 2H, CH$_2$), 3.68 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 3.96-4.00 (m, 2H, CH$_2$), 6.02 (d, 2H, J 1.9Hz, CH), 6.35 (d, d, 2H, J 2.3Hz, J 8.5Hz, Ar-H), 6.57 (d, 2H, J 2.3Hz, Ar-H), 6.62 (t, 2H, J 7.1Hz, Ar-H), 6.65 (d, 2H, J 8.0Hz, Ar-H), 6.81 (d, 2H, J 1.2Hz, 2NH), 6.92 (d, 2H, J 8.4Hz, Ar-H), 7.16 (t, 2H, J 8.3Hz, Ar-H), 7.61 (d, 2H, J 7.7Hz, Ar-H) ppm; $^{13}$C NMR (DMSO-d$_6$) $\delta$ 42.9, 56.0, 56.5, 66.3, 99.6, 105.2, 115.2, 117.6, 120.9, 121.2, 127.7, 128.1, 133.9, 141.6, 158.5, 161.5, 163.7 ppm; MS: m/z (%) 594; Anal. Calcd for C$_{34}$H$_{34}$N$_4$O$_6$: C, 68.67; H, 5.76; N, 9.42; Found: C, 68.58; H, 5.68; N, 9.34%.

3,3′-(1,4-Phenylene)bis(2-phenyl-2,3-dihydroquinazolin-4(1H)-one) (4l). Cream solid; Yield: 82%; mp 296-8 °C; IR (KBr): $v_{\text{max}}$ 3305 (NH), 1638 (C=O), 1612, 1512 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$) $\delta$ 6.26 (s, 2H, CH), 6.70-6.75 (m, 4H, Ar-H), 7.24 (s, 4H, Ar-H), 7.29-7.33 (m, 12H, Ar-H), 7.66-7.70 (m, 4H, 2NH, 2Ar-H) ppm; MS: m/z (%) 522; Anal. Calcd for C$_{34}$H$_{32}$N$_4$O$_2$: C, 78.14; H, 5.01; N, 10.72; Found: C, 78.07; H, 4.92; N, 10.64%. $^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$: very low soluble in DMSO.
3,3′-(1,4-Phenylene)bis(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one) (4m).
Colourless solid; Yield: 87%; mp 238-40 °C (dec); IR (KBr): vmax 3305 (NH), 1641 (C=O), 1512 cm⁻¹; ¹H NMR (DMSO-d₆) δ 6.29 (d, 2H, J 2.3Hz, CH), 6.72 (t, 2H, J 7.3Hz, Ar-H), 6.74 (d, 2H, J 8.1Hz, Ar-H), 7.22 (s, 4H, Ar-H), 7.27-7.29 (m, 2H, Ar-H), 7.34-7.73 (m, 8H, Ar-H), 7.67 (d, 2H, J 2.3Hz, NH), 7.07 (d, 2H, J 7.0Hz, Ar-H) ppm; ¹³C NMR (DMSO-d₆) δ δ 72.5, 115.7, 116.1, 118.6, 127.0, 128.8, 129.2, 129.3, 133.7, 134.8, 139.0, 140.5, 147.1, 162.9 ppm; MS: m/z (%): 590; Anal. Calcd for C₃₄H₂₄Cl₂N₄O₂: C, 69.04; H, 4.09; N, 9.47; Found: C, 68.95; H, 3.99; N, 9.39%.

3,3′-(1,4-phenylene)bis(2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one) (4n). Colourless solid; Yield: 92%; mp 281-3 °C; IR (KBr): vmax 3308 (NH), 3022, 2926, 1642 (C=O), 1611, 1512 cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.22 (s, 6H, 2CH₃), 6.20 (s, 2H, CH), 6.70-6.72 (m, 4H, Ar-H), 7.09-7.23 (m, 10H, Ar-H), 7.54-7.77 (m, 8H, 2NH, 6Ar-H) ppm; MS: m/z (%) 550; Anal. Calcd for C₃₆H₃₀Cl₂N₂O₂: C, 78.52; H, 5.49; N, 10.17; Found: C, 78.44; H, 5.40; N, 10.10%.

¹³C NMR (125 MHz, DMSO-d₆) δ: very low soluble in DMSO.

3,3′-(1,4-Phenylene)bis(2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one) (4o). Yellow solid; Yield: 90%; mp 291-3 °C; IR (KBr): vmax 3401 (NH), 3102, 3071, 1662 (C=O), 1614, 1513 cm⁻¹; ¹H NMR (DMSO-d₆) δ 6.48 (d, 2H, J 2.1Hz, CH), 6.73 (t, 2H, J 7.4Hz, Ar-H), 6.76 (d, 2H, J 8.1Hz, Ar-H), 7.28 (t, 2H, J 7.2Hz, Ar-H), 7.33 (s, 4H, Ar-H), 7.62 (d, 4H, J 8.6Hz, Ar-H), 7.73 (d, 2H, J 7.6Hz, Ar-H), 7.82 (d, 2H, J 2.1Hz, 2NH), 8.15 (d, 4H, J 8.6Hz, Ar-H) ppm; ¹³C NMR (DMSO-d₆) δ 72.3, 115.9, 116.0, 118.9, 124.5, 127.0, 128.6, 128.9, 134.9, 139.0, 146.8, 148.2, 148.8, 162.8 ppm; MS: m/z (%) 612; Anal. Calcd for C₃₄H₂₄N₄O₆: C, 66.66; H, 3.95; N, 13.72; Found: C, 66.56; H, 3.87; N, 13.63%.

3,3′-(1,4-Phenylene)bis(2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one) (4p). Colourless solid; Yield: 88%; mp 251-3 °C; IR (KBr): vmax 3307 (NH), 2948, 2925, 2833, 1638, 1613, 1512 cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.68 (s, 6H, CH₃), 6.19 (d, 2H, J 2.5Hz, CH), 6.68 (t, 2H, J 7.1Hz, Ar-H), 6.74 (d, 2H, J 8Hz, Ar-H), 6.85 (d, 4H, J 8.7, Ar-H), 7.21 (s, 4H, Ar-H), 7.23-7.27 (m, 6H, Ar-H), 7.58 (d, 2H, J 2.4Hz, 2NH), 7.71 (d, 2H, J 7.0Hz, Ar-H) ppm; ¹³C NMR (DMSO-d₆) δ 55.9, 72.9, 114.5, 115.6, 116.1, 118.3, 126.9, 128.5, 128.8, 133.5, 134.6, 139.2, 147.4, 159.9, 163.1 ppm; MS: m/z (%) 582; Anal. Calcd for C₃₆H₃₀N₄O₄: C, 74.21; H, 5.19; N, 9.62; Found: C, 74.14; H, 5.10; N, 9.54%.

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Supplementary Information

General experimental procedures, IR, $^1$H and $^{13}$C NMR, and MS data for compounds 4 a-r are available as supplementary information.

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