A new concise synthesis of 2,3-dihydroquinazolin-4(1H)-ones derivatives

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Supplementary Material

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I. General Information

All the reagents were commercially available and were used without further purification. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates (E. Merck) and visualized with UV light. Flash column chromatography was performed on a Biotage SP4 apparatus.

$^1$H NMR spectra were recorded at 400 MHz and $^{13}$C NMR spectra at 100 MHz. The chemical shifts for $^1$H and $^{13}$C NMR are referenced via residual solvent signal ($^1$H, DMSO-d$_6$ at 2.51 ppm; $^{13}$C, DMSO-d$_6$ at 39.51 ppm).

Analytical LC/MS data were performed on an Agilent MSD mass spectrometer connected to an Agilent 1100 system with:

**System A:** Column ACE 3 C8 (50 x 3.0 mm); H$_2$O (+ 0.1% TFA) and MeCN were used as mobile phases at a flow rate of 1 mL/min, with a gradient time of 3.0 min; or

**System B:** Column Xterra MSC18 (50 x 3.0 mm); H$_2$O (containing 10 mM NH$_4$HCO$_3$; pH = 10) and MeCN were used as mobile phases at a flow rate of 1 mL/min, with a gradient time of 3.0 min.

Percent conversion in Table 1 was estimated by comparing the peak area of 3a to the combined peak area of 1a and/or 2a. All starting materials and reagents are commercially available and were used as received.

Compounds 3a, 3b, 3c, 3d, 3g, 3h, 3i, 3j, 3k, 3n, 3o, 3p and 3q are all known compounds, spectral data were in agreement with the proposed structures and matched those reported in the literature.

Melting points were obtained using a Stuart Scientific SMP3 apparatus and are uncorrected.
II. Experimental section

General experimental procedure for compounds 3a-3c and 3f-3o

T3P® (50% in EtOAc) (1 equiv, 0.5 mmol) was added to a solution of 2-aminobenzamide (1a, 0.5 mmol) and aldehyde (0.5 mmol) in acetonitrile (1 mL) in a sealed tube. After completion of the reaction (indicated by TLC, eluent CH₂Cl₂/MeOH 95/5, Table 2), the precipitate formed was filtered, washed with cold acetonitrile (2 × 1 mL) and dried to afford the expected compound in sufficient purity.

![Structure of 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (3a)]

**2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (3a)**

**Yield:** 103 mg (92% yield, white solid).

**^1H NMR** (400 MHz, DMSO-d₆) δ (ppm): 8.29 (br s, 1H), 7.63 (d, 1H, J = 7.8 Hz), 7.51 (d, 2H, J = 7.1 Hz), 7.41-7.35 (m, 3H), 7.26 (t, 1H, J = 7.8 Hz), 7.11 (br s, 1H), 6.76 (d, 1H, J = 7.8 Hz), 6.69 (t, 1H, J = 7.8 Hz), 5.76 (s, 1H).

**^13C NMR** (100 MHz, DMSO-d₆) δ (ppm): 163.6, 147.8, 141.6, 133.3, 128.4, 128.3 (2 C), 127.3, 126.8 (2C), 117.1, 114.9, 114.4, 66.5.

**LCMS** [M+H]^+ m/z 225.

![Structure of 2-(p-Tolyl)-2,3-dihydroquinazolin-4(1H)-one (3b)]

**2-(p-Tolyl)-2,3-dihydroquinazolin-4(1H)-one (3b)**

**Yield:** 107 mg (90% yield, white solid).

**^1H NMR** (400 MHz, DMSO-d₆) δ (ppm): 8.22 (br s, 1H), 7.62 (dd, 1H, J = 8.0 Hz, J = 1.3 Hz) 7.38 (d, 2H, J = 7.8 Hz), 7.25-7.21 (m, 1H), 7.20 (d, 2H, J = 7.8 Hz), 7.04 (br s, 1H), 6.74 (d, 1H, J = 8.0 Hz), 6.68-6.64 (m, 1H), 5.71 (s, 1H), 2.29 (s, 3H).

**^13C NMR** (100 MHz, DMSO-d₆) δ (ppm): 163.6, 147.8, 138.6, 137.6, 133.2, 128.7, 127.3, 126.7, 117.0, 114.9, 114.3, 66.3, 20.7.

**LCMS** [M+H]^+ m/z 239.

![Structure of 2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3c)]

**2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3c)**
Yield: 113 mg (89% yield, white solid).

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.17 (br s, 1H), 7.62 (m, 1H, $J = 6.8$ Hz), 7.42 (d, 2H, $J = 7.3$ Hz), 7.30-7.18 (m, 1H), 7.00-6.94 (m, 3H), 6.74-6.65 (m, 2H), 5.70 (s, 1H), 3.75 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 113.9 mg (89% yield, white solid).

LCMS [M+H]$^+$ m/z 255.

2-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzonitrile (3f)

Yield: 116 mg (93% yield, white solid), m.p. (EtOH) 178-180°C.

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.30 (br s, 1H), 7.92 (d, 1H, $J = 7.6$ Hz), 7.80-7.75 (m, 2H), 7.68 (dd, 1H, $J = 7.6$ Hz, 1.3 Hz), 7.63-7.59 (m, 1H), 7.31 (t, 1H, $J = 7.6$ Hz), 7.11 (br s, 1H), 6.77-6.72 (m, 2H), 6.07 (s, 1H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.6, 159.4, 147.9, 133.4, 133.2, 128.1, 127.3, 117.0, 114.9, 114.3, 113.6, 66.2, 55.1.

LCMS [M+H]$^+$ m/z 250.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (3h)

Yield: 129 mg (88% yield, white solid).

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.44 (s, 1H), 7.78 (d, 2H, $J = 8.3$ Hz), 7.71 (d, 2H, $J = 8.3$ Hz), 7.62 (dd, 1H, $J = 8.0$ Hz, $J = 1.3$ Hz), 7.27-7.23 (m, 2H), 6.76 (d, 1H, $J = 8.0$ Hz), 6.70-6.66 (m, 1H), 5.86 (s, 1H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.4, 147.4, 146.4 (q, $J = 1.5$ Hz), 133.4, 129.0, 128.7, 127.6, 127.3, 125.5, 125.3 (q, $J = 3.6$ Hz), 122.8, 117.3, 114.9, 114.4, 65.7.

LCMS [M+H]$^+$ m/z 293.
Yield: 124 mg (92% yield, yellow powder).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 8.52 (br s, 1H), 8.27 (d, 2H, \(J = 8.7\) Hz), 7.75 (d, 2H, \(J = 8.7\) Hz), 7.62 (dd, 1H, \(J = 7.9\) Hz, \(J = 1.6\) Hz), 7.33 (br s, 1H), 7.28-7.24 (m, 1H), 6.78 (d, 1H, \(J = 7.9\) Hz), 6.71-6.67 (m, 1H), 5.91 (s, 1H).

\(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 163.4, 147.6, 140.6, 133.3, 132.9, 128.7, 128.2, 127.3, 123.5, 117.4, 114.8, 114.5, 65.2.

LCMS [M+H]\(^+\) \(m/z\) 270.

![Image of 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3i)]

Yield: 115 mg (89% yield, white powder).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 8.33 (br s, 1H), 7.62 (dd, 1H, \(J = 8.0\) Hz, \(J = 1.1\) Hz), 7.52 (d, 2H, \(J = 8.6\) Hz), 7.47 (d, 2H, \(J = 8.6\) Hz), 7.27-7.23 (m, 1H), 7.14 (br s, 1H), 6.76 (dd, 1H, \(J = 8.0\) Hz, \(J = 1.1\) Hz), 6.70-6.66 (m, 1H), 5.77 (s, 1H).

\(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 163.4, 147.6, 140.6, 133.3, 132.9, 128.7, 128.2, 127.3, 117.2, 114.9, 114.4, 65.7.

LCMS [M+H]\(^+\) \(m/z\) 259, 261.

![Image of 2-(3-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3j)]

Yield: 116 mg (90% yield, white powder).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 8.40 (br s, 1H), 7.62 (d, 1H, \(J = 7.6\) Hz), 7.53 (s, 1H), 7.44-7.41 (m, 3H), 7.27 (t, 1H, \(J = 7.6\) Hz), 7.21 (br s, 1H), 6.77 (d, 1H, \(J = 7.6\) Hz), 6.70 (t, 1H, \(J = 7.6\) Hz), 5.78 (s, 1H).

\(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 163.4, 147.4, 144.3, 133.4, 132.9, 130.9, 128.2, 127.3, 126.7, 125.4, 117.3, 114.9, 114.4, 65.5.

LCMS [M+H]\(^+\) \(m/z\) 259, 261.

![Image of 2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3k)]

Yield: 116 mg (90% yield, white powder).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 8.21 (br s, 1H), 7.72-7.62 (m, 2H), 7.50-7.48 (m, 1H), 7.41-7.39 (m, 2H), 7.28 (t, 1H, \(J = 7.6\) Hz), 7.01 (br s, 1H), 6.77 (d, 1H, \(J = 7.6\) Hz), 6.73 (t, 1H, \(J = 7.6\) Hz), 6.14 (s, 1H).
$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.6, 147.6, 137.8, 133.4, 131.8, 130.2, 129.5, 128.7, 127.4, 127.3, 117.4, 114.6, 114.5, 63.6.

**LCMS** [M+H]$^+$ m/z 259, 261.

2-(Thiophen-3-yl)-2,3-dihydroquinazolin-4(1H)-one (3l)

**Yield:** 107 mg (93% yield, white powder), m.p. (EtOH) 191-193°C.

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.33 (br s, 1H), 7.61 (d, 1H, $J = 7.5$ Hz), 7.52-7.50 (m, 1H), 7.46 (s, 1H), 7.26 (t, 1H, $J = 7.5$ Hz), 7.20 (d, 1H, $J = 4.5$ Hz), 7.12 (br s, 1H), 6.77 (d, 1H, $J = 7.5$ Hz), 6.69 (t, 1H, $J = 7.5$ Hz), 5.79 (s, 1H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 172.6, 162.6, 146.4, 142.4, 133.5, 127.3, 1 20.8, 117.7, 114.9, 114.8, 63.7.

**LCMS** [M+H]$^+$ m/z 231.

2-(Thiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (3m)

**Yield:** 109 mg (94% yield, white powder), m.p. (EtOH) 206-207°C.

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.74 (br s, 1H), 7.77 (d, 1H, $J = 2.8$ Hz), 7.64-7.61 (m, 2H), 7.56 (br s, 1H), 7.28 (t, 1H, $J = 7.3$ Hz), 6.78 (d, 1H, $J = 7.3$ Hz), 6.72 (t, 1H, $J = 7.3$ Hz), 5.98 (s, 1H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 172.6, 162.6, 146.4, 142.4, 133.5, 127.3, 120.8, 117.7, 114.9, 114.8, 63.7.

**LCMS** [M+H]$^+$ m/z 232.

2-(Naphthalen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (3n)

**Yield:** 119 mg (87% yield, white powder).

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.38 (br s, 1H), 7.96-7.91 (m, 4H), 7.72-7.64 (m, 2H), 7.55-7.52 (m, 2H), 7.28 (t, 1H, $J = 7.5$ Hz), 7.20 (br s, 1H), 6.78 (d, 1H, $J = 7.5$ Hz), 6.71 (t, 1H, $J = 7.5$ Hz), 5.95 (s, 1H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.5, 147.8, 138.8, 133.3, 132.9, 132.4, 128.1, 127.9, 127.5, 127.3, 126.4, 126.3, 125.8, 124.8, 117.1, 114.9, 114.4, 66.8.

**LCMS** [M+H]$^+$ m/z 275.
2-Cyclohexyl-2,3-dihydroquinazolin-4(1H)-one (3o)

**Yield:** 103 mg (89% yield, white powder).

**$^1$H NMR** (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 7.87 (br s, 1H), 7.56 (dd, 1H, $J$ = 7.6 Hz, 1.4 Hz), 7.22-7.17 (m, 1H), 6.75 (d, 1H, $J$ = 7.6 Hz), 6.62 (t, 1H, $J$ = 7.6 Hz), 6.55 (br s, 1H), 4.45 (dd, 1H, $J$ = 4.1 Hz, 2.0 Hz), 1.76-1.46 (m, 6H), 1.21-1.03 (m, 5H).

**$^{13}$C NMR** (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.6, 148.3, 133.0, 127.2, 116.3, 114.7, 114.0, 68.5, 42.8, 26.9, 26.6, 25.9, 25.6, 25.5.

**LCMS** [M+H]$^+$ m/z 231.

**General experimental procedure for compounds 3d, 3e, 3p, 3q.**

T3P® (50% in EtOAc) (1 equiv, 0.5 mmol) was added to a solution of 2-aminobenzamide (0.5 mmol) and aldehyde (0.5 mmol) in acetonitrile (1 mL) in a sealed tube. After completion of the reaction (indicated by TLC, eluent CH$_2$Cl$_2$/MeOH 95/5, Table 2), the reaction mixture was purified by column chromatography on silica gel on a Biotage SP4 apparatus, gradient CH$_2$Cl$_2$/MeOH 1 to 10%.

2-(3-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3d)

**Yield:** 108 mg (85% yield, white powder).

**$^1$H NMR** (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 8.29 (br s, 1H), 7.61 (dd, 1H, $J$ = 8.0 Hz, $J$ = 1.1 Hz), 7.31-7.27 (m, 1H), 7.26-7.22 (m, 1H), 7.12 (s, 1H), 7.06-7.04 (m, 2H), 6.92 (ddd, 1H, $J$ = 8.0 Hz, $J$ = 2.5 Hz and $J$ = 1.0 Hz), 6.76 (dd, 1H, $J$ = 8.0 Hz, $J$ = 1.1 Hz), 6.69 (td, 1H, $J$ = 8.0 Hz, $J$ = 1.1 Hz), 5.72-5.71 (m, 1H), 3.74 (s, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.5, 159.2, 147.7, 143.3, 133.3, 129.4, 127.3, 118.9, 117.0, 114.9, 114.3, 113.6, 112.5, 66.2, 55.0.

**LCMS** [M+H]$^+$ m/z 255.
2-(2-Methylphenyl)-2,3-dihydroquinazolin-4(1H)-one (3e)

Yield: 108 mg (91% yield, white powder), m.p. (EtOH) 188-189°C.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 8.05 (br s, 1H), 7.66 (d, 1H, \(J = 7.6\) Hz), 7.57 (d, 1H, \(J = 7.6\) Hz), 7.30-7.21 (m, 4H), 6.86 (br s, 1H), 6.76 (d, 1H, \(J = 7.6\) Hz), 6.72-6.68 (m, 1H), 6.00 (s, 1H), 2.43 (s, 3H).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 164.0, 148.5, 138.0, 136.0, 133.1, 130.6, 128.4, 127.4, 125.9, 117.1, 114.8, 114.4, 64.6, 48.5, 18.7.

LCMS [M+H\(^+\)] \(m/\ell\) 239.

\[
\begin{align*}
\text{O} & \\
\text{N} & \\
\text{Sp} & \\
\end{align*}
\]

2-Isopropyl-2,3-dihydroquinazolin-4(1H)-one (3p)

Yield: 81 mg (85% yield, light yellow powder).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 7.87 (br s, 1H), 7.58 (dd, 1H, \(J = 7.9\) Hz, \(J = 1.6\) Hz), 7.23-7.18 (m, 1H), 6.79 (d, 1H, \(J = 7.6\) Hz), 6.59-6.55 (m, 1H), 6.52 (br s, 1H), 4.52-4.50 (m, 1H), 1.90 (q, 1H, \(J = 7.0\) Hz), 0.95 (d, 3H, \(J = 7.0\) Hz), 0.93 (d, 3H, \(J = 7.0\) Hz).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 163.9, 148.5, 138.0, 136.0, 133.1, 130.6, 128.4, 127.2, 116.5, 114.7, 114.1, 69.1, 32.7, 16.8, 16.5.

LCMS [M+H\(^+\)] \(m/\ell\) 191.

\[
\begin{align*}
\text{O} & \\
\text{N} & \\
\text{Sp} & \\
\end{align*}
\]

2-(Tert-butyl)-2,3-dihydroquinazolin-4(1H)-one (3q)

Yield: 88 mg (86% yield, light brown powder).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 7.78 (br s, 1H), 7.54 (dd, 1H, \(J = 7.6\) Hz, \(J = 1.6\) Hz), 7.20-7.16 (m, 1H), 6.79 (d, 1H, \(J = 7.6\) Hz), 6.59-6.55 (m, 1H), 6.52 (br s, 1H), 4.34 (t, 1H, \(J = 2.3\) Hz), 0.88 (s, 9H).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 163.5, 148.3, 133.0, 127.0, 115.9, 114.1, 113.6, 72.1, 37.4, 24.4.

LCMS [M+H\(^+\)] \(m/\ell\) 205.
III. $^1$H and $^{13}$C NMR spectra

DMSO

DMSO + D$_2$O
Chemical Shift (ppm)

Normalized Intensity

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1305CC264.010.esp

Chemical Shift (ppm)

Normalized Intensity

1307CC116.010.esp

Chemical Shift (ppm)
Chemical Shift (ppm)

Normalized Intensity

DMSO

Water

8.29
7.61
7.59
7.31
7.29
7.27
7.12
7.06
6.76
6.74
6.67
6.67
5.72
5.71
5.71
3.74
IV. References


