A Novel and Efficient Synthesis of 1-Hydroxyquinazolin-4-ones via Tin(II) Chloride Induced Cyclization of 2-Nitrobenzamides and Ketones

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Abstract: A mild, efficient and novel synthesis of 2,3-dihydro-1hydroxyquinazolin-4(1H)-ones via cyclization of 2-nitrobenzamides and ketones induced by tin(II) chloride dihydrate is described. This new method has the advantages of accessible starting materials, convenient manipulation, short reaction times, and high yields.

Key words: tin(II) chloride dihydrate, 1-hydroxyquinazolin-4-one, 2-nitrobenzamide, ketone

Quinazolinone derivatives are interesting because of their diverse range of biological activity as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive agents.¹ Recently, these compounds have also been reported as an Na⁺/Ca²⁺ exchanger inhibitor.² The main synthetic approaches to such compounds consist of the condensation of imidates with anthranilic acid,³ the reaction of anthranilamides with aldehydes,⁴ palladium-catalyzed cyclization reaction of N-aryl-N'-benzylureas,⁵ and the aza-Wittig reactions of α -azido-substituted aromatic imides.⁶ We have previously reported the synthesis of quinazolin-4(3*H*)-ones⁷ and imidazo[1,2-*c*]quinazolines⁸ with the aid of a low-valent titanium reagent. However, none of the compounds prepared by these methods contained 1-hydroxyquinazolin-4-ones. Yamaguchi⁹ has reported the synthesis of this kind of compound in the presence of sodium amide, but with 1-hydroxyquinazolin-4-ones as byproducts in low yields. The Raney nickel catalyzed hydrogenation of 2,3-dihydro-3-(2-nitrobenzoyl)benzoxazole to 1-hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4(1H,3H)-dione, however, inaccessible starting materials and low yield restrict this reaction.¹⁰ Therefore, a simple and efficient procedure is still strongly desired for the synthesis of this important heterocyclic compound.

Here we wish to describe a method induced by tin(II) chloride dihydrate for the preparation of 1-hydroxyquinazolin-4-ones **3** using 2-nitrobenzamides **1** and ketones **2** as the starting materials (Scheme 1).

We began our study of the reaction showed in Scheme 1 by optimizing the reaction conditions for the preparation of **3**. A summary of the optimization experiments is provided in Table 1. The results showed that at 60 °C the reaction proceeded smoothly in high yield. To find the optimum ratio of substrate to reductive agent, the reaction was carried out in ethanol using a 1:1 to 1:5 ratio of substrate to reductive agent (Table 1, entries 5, 3, 6, 7, 8), leading to **3a** in 61%, 92%, 88%, 52%, and 45% yields, respectively. We concluded the best ratio of substrate to reductive agent was 1:2. Moreover, different organic solvents were further investigated as shown in Table 1; we concluded that ethanol was the best solvent for this reaction.

In order to demonstrate the efficiency and the applicability of the present method, we performed the reaction of a variety of 2-nitrobenzamides **1** and ketones **2** with tin(II) chloride at 60 °C in ethanol. The results are summarized in Table 2.

As shown in Table 2, when N-substituted 2-nitrobenzamides 1 and ketones 2 were treated with tin(II) chloride under the same reaction conditions, only acetone gave the corresponding products 3 in high yields (entries 1–8 vs entries 9 and 10). However, when N-unsubstituted 2-nitrobenzamides 1 and ketones 2 were treated with tin(II) chloride under same reaction conditions, other aliphatic ketones (such as butan-2-one and pentan-3-one) can also give the desired products 3 in high yields (entries 12 and 13). So we infer from these results that steric hindrance plays a critical role in this reaction. However, when N-un-



Scheme 1

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Table 1Optimization of Reductive Solvent, Temperature, andSubstrate/Reductive Reagent Ratio in the Synthesis of 3a

Entry	Solvent	Temp (°C)	Ratio (substrate/SnCl ₂)	Yield (%)	
1	EtOH	r.t.	1:2	60	
2	EtOH	40	1:2	80	
3	EtOH	60	1:2	92	
4	EtOH	80	1:2	80	
5	EtOH	60	1:1	61	
6	EtOH	60	1:3	88	
7	EtOH	60	1:4	52	
8	EtOH	60	1:5	45	
9	MeOH	60	1:2	64	
10	DMF	60	1:2	35	
11	THF	60	1:2	31	
12	MeCN	60	1:2	79	
13	DCE	60	1:2	14	

Table 2Synthesis of Compounds 3

Entry	Product	Х	R ¹	R ²	R ³	Yield (%)
1	3a	Н	4-ClC ₆ H ₄	Me	Me	92
2	3b	Cl	Ph	Me	Me	91
3	3c	Cl	4-Tol	Me	Me	92
4	3d	Cl	4-MeOC ₆ H ₄	Me	Me	95
5	3e	Cl	$4-ClC_6H_4$	Me	Me	74
6	3f	Cl	3-Cl-4-MeC ₆ H ₃	Me	Me	89
7	3g	Cl	3-ClC ₆ H ₄	Me	Me	89
8	3h	Cl	Bn	Me	Me	95
9	3i	Н	4-Tol	Et	Et	0
10	3ј	Н	4-Tol	Me	$4-ClC_6H_4$	0
11	3k	Cl	Н	Me	Et	97
12	31	Cl	Н	Me	Pr	92
13	3m	Cl	Н	Ph	Bn	0

substituted 2-nitrobenzamides 1 were treated with substituted acetophenones 4, the desired products 3 were not detected and quinazolinones 5 were obtained without exception (Table 3).

Moreover, the reaction of N-unsubstituted 2-nitrobenzamides 1 and cyclic ketones 6 with tin(II) chloride dihy
 Table 3
 Reductive Cyclization of N-Unsubstituted 2-Nitrobenzamides and Substituted Acetophenones



drate at room temperature afforded products 7 and the results are summarized in Table 4.

Furthermore, treatment of bis(2-nitrobenzamides) **8a–c** and acetone with tin(II) chloride dihydrate in ethanol at 60 °C gave the desired products **9a–c** in good yields (Table 5).

All the products were characterized by ¹H and ¹³C NMR, IR, and HRMS spectra. The structures of **3a**, **5b**, **7e**, and **9a** were further confirmed by X-ray diffraction analysis.¹¹ The molecular structures of the products **3a**, **5b**, **7e**, and **9a** are shown in Figures 1–4.

A plausible mechanistic pathway to products **3**, **5**, **7**, and **9** from 2-nitrobenzamides and ketones is illustrated in Scheme 2, although the details are still unclear. In the initial step, 2-nitrobenzamides are reduced by tin(II) chloride to **A**. The hydroxylamine compounds **A** then reacted with

Table 4Reductive Cyclization of N-Unsubstituted 2-Nitrobenz-amides and Cyclic Ketones



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 Table 5
 Reductive Cyclization of Bis(2-nitrobenzamides) and Acetone





Figure 1 Molecular structure of 3a



Figure 2 Molecular structure of 5b



Figure 3 Molecular structure of 7e



Figure 4 Molecular structure of 9a

aliphatic ketones or cyclic ketones to give the expected products **3**, **7**, and **9**. However, in the case of acetophenone, the lower reactivity than acetone allows the reduction of hydroxylamine **A** to amine **B**, then quinazolines **5** would be formed from the resulting amine and the amide group.

In summary, a series of 1-hydroxyquinazolin-4-ones were synthesized via cyclization of 2-nitrobenzamides and ketones induced by tin(II) chloride. The advantages of this new method are the easily accessible starting materials, convenient manipulation, short reaction time, and high yields.

Reactions were carried via a SnCl₂-mediated cyclization of 2-nitrobenzamides and ketones. Commercial solvents and reagents were used as received. IR spectra were obtained on a Tensor 27 spectrophotometer. NMR spectra were recorded for ¹H NMR and ¹³C NMR using Bruker DPX-400 MHz instrument, at 293 K unless otherwise noted, with residue peaks of the solvents DMSO- d_6 (δ = 2.50 for ¹H and δ = 40.00 for ¹³C) used for reference. HRMS were obtained on a TOF-MS instrument using EI ionization. X-ray crystallographic analysis was performed with a Siemens Smart-1000 CCD diffractometer.

Quinazolinones 3, 5, 7, and 9; General Procedure

A soln of 2-nitrobenzamide (3 mmol), ketone (3 mmol), and $SnCl_2 \cdot 2 H_2O$ (6 mmol) in EtOH (20 mL) was stirred at 60 °C or r.t. for 2 h. The mixture was quenched with 3% HCl (100 mL) and filtered and the crude product was purified by recrystallization (EtOH) to give the pure products **3**, **5**, **7**, or **9**.

3-(4-Chlorophenyl)-2,3-dihydro-1-hydroxy-2,2-dimethylquinazolin-4(1*H***)-one (3a) Solid; mp 203–205 °C.**

IR (KBr): 3238, 3053, 2989, 2938, 1632, 1578, 1494, 1470, 1426, 1391, 1312, 1274, 1232, 1175, 1104, 1085, 1047, 1014, 980, 950, 870, 822, 761, 719, 698 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 9.58$ (s, 1 H, OH), 7.72 (d, J = 7.2 Hz, 1 H, ArH), 7.57–7.52 (m, 3 H, ArH), 7.30–7.23 (m, 3 H, ArH), 7.03–6.99 (m, 1 H, ArH), 1.33 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.13, 151.39, 138.82, 138.50, 130.12, 129.62, 129.29, 129.06, 128.22, 120.52, 115.24, 113.98, 80.53, 23.28.

HRMS: m/z [M]⁺ calcd for C₁₆H₁₅³⁵ClN₂O₂: 302.0822; found: 302.0834.

Crystal data11

CCDC-682915; $C_{16}H_{15}CIN_2O_2$; M = 302.75, colorless block crystals, $0.35 \times 0.29 \times 0.24$ mm, monoclinic, space group $P2_1/c$, a = 7.211(9) Å, b = 17.13(2) Å, c = 12.062(15) Å, $\beta = 94.591(19)^\circ$,



Scheme 2

V = 1485(3) Å³, Z = 4, $D_c = 1.354$ g·cm⁻¹, F(000) = 632, μ (MoK α) = 0.263 mm⁻¹. Intensity data were collected on a diffractometer with graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å) using ω scan mode with 2.07° < θ < 25.01°. 2585 unique reflections were measured and 1170 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R1 = 0.0896 and wR2 = 0.1913.

7-Chloro-2,3-dihydro-1-hydroxy-2,2-dimethyl-3-phenylquinazolin-4(1H)-one (3b) Solid; mp 214–216 °C.

IR (KBr): 3231, 2996, 2943, 1627, 1600, 1492, 1437, 1389, 1373, 1311, 1281, 1224, 1191, 1179, 1114, 1083, 1016, 1000, 894, 860, 823, 772, 762, 702, 665 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 9.81$ (s, 1 H, OH), 7.72 (d, J = 8.0 Hz, 1 H, ArH), 7.50–7.40 (m, 3 H, ArH), 7.25 (d, J = 7.2 Hz, 2 H, ArH), 7.21 (d, J = 2.0 Hz, 1 H, ArH), 7.04 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, 1 H, ArH), 1.34 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 162.01, 150.27, 137.70, 134.15, 132.68, 132.12, 129.28, 127.51, 120.73, 116.43, 114.92, 80.18, 23.22.

HRMS: m/z [M]⁺ calcd for C₁₆H₁₅³⁵ClN₂O₂: 302.0822; found: 302.0824.

7-Chloro-2,3-dihydro-1-hydroxy-2,2-dimethyl-3-(4-methylphenyl)quinazolin-4(1*H***)-one (3c) Solid; mp 208–210 °C.**

IR (KBr): 3205, 2982, 2896, 1629, 1595, 1509, 1438, 1385, 1364, 1311, 1282, 1259, 1222, 1193, 1108, 1083, 1035, 1017, 1003, 897, 873, 859, 813, 772, 721, 692 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 9.80$ (s, 1 H, OH), 7.71 (d, J = 8.4 Hz, 1 H, ArH), 7.27 (d, J = 8.0 Hz, 2 H, ArH), 7.19 (d, J = 1.6 Hz, 1 H, ArH), 7.11 (d, J = 8.0 Hz, 2 H, ArH), 7.03 (dd,

*J*₁ = 1.6 Hz, *J*₂ = 8.4 Hz, 1 H, ArH), 2.36 (s, 3 H, CH₃), 1.33 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.49, 151.68, 139.06, 137.85, 136.17, 130.10, 129.91, 120.78, 115.60, 114.24, 80.83, 23.58, 21.15.

HRMS: m/z [M]⁺ calcd for C₁₇H₁₇³⁵ClN₂O₂: 316.0979; found: 316.0990.

7-Chloro-2,3-dihydro-1-hydroxy-3-(4-methoxyphenyl)-2,2dimethylquinazolin-4(1*H***)-one (3d) Solid; mp 143–144 °C.**

IR (KBr): 3198, 2983, 2965, 2897, 1637, 1597, 1508, 1468, 1456, 1434, 1388, 1369, 1300, 1250, 1218, 1194, 1168, 1152, 1116, 1079, 1029, 899, 858, 827, 771, 689 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.79 (s, 1 H, OH), 7.71 (d, *J* = 8.0 Hz, 1 H, ArH), 7.19 (d, *J* = 2.0 Hz, 1 H, ArH), 7.15 (d, *J* = 8.8 Hz, 2 H, ArH), 7.03 (dd, *J*₁ = 2.0 Hz, *J*₂ = 8.4 Hz, 1 H, ArH), 7.00 (d, *J* = 8.8 Hz, 2 H, ArH), 3.80 (s, 3 H, CH₃O), 1.33 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.67, 159.11, 151.69, 139.06, 131.37, 129.92, 120.75, 115.59, 114.70, 114.23, 80.92, 55.77, 23.54.

HRMS: m/z [M]⁺ calcd for C₁₇H₁₇³⁵ClN₂O₃: 332.0928; found: 332.0942.

7-Chloro-3-(4-chlorophenyl)-2,3-dihydro-1-hydroxy-2,2-dimethylquinazolin-4(1*H***)-one (3e) Solid; mp 202–204 °C.**

IR (KBr): 3315, 2997, 2986, 2900, 1649, 1591, 1490, 1436, 1389, 1366, 1310, 1288, 1266, 1213, 1191, 1115, 1090, 1033, 1015, 1004, 941, 924, 896, 858, 816, 767, 723, 688 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.84 (s, 1 H, OH), 7.72 (d, *J* = 8.4 Hz, 1 H, ArH), 7.53 (d, *J* = 8.8 Hz, 2 H, ArH), 7.30 (d, *J* = 8.4 Hz, 2 H, ArH), 7.21 (d, *J* = 1.6 Hz, 1 H, ArH), 7.04 (dd, *J*₁ = 1.6 Hz, *J*₂ = 8.0 Hz, 1 H, ArH), 1.34 (s, 6 H, 2 CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.53, 151.68, 139.31, 137.66, 133.17, 132.37, 129.96, 129.64, 120.89, 115.31, 114.37, 80.93, 23.52.

HRMS: m/z [M]⁺ calcd for C₁₆H₁₄³⁵Cl₂N₂O₂: 336.0432; found: 336.0434.

7-Chloro-3-(3-chloro-4-methylphenyl)-2,3-dihydro-1-hydroxy-2,2-dimethylquinazolin-4(1*H***)-one (3f) Solid; mp 220–221 °C.**

IR (KBr): 3232, 2947, 2921, 2862, 1636, 1602, 1534, 1492, 1437, 1388, 1373, 1311, 1283, 1232, 1190, 1175, 1083, 1052, 1019, 1003, 912, 861, 825, 810, 773, 706, 691, 668 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 9.83$ (s, 1 H, OH), 7.72 (d, J = 8.0 Hz, 1 H, ArH), 7.45 (d, J = 8.4 Hz, 1 H, ArH), 7.34 (d, J = 1.2 Hz, 1 H, ArH), 7.20 (d, J = 1.6 Hz, 1 H, ArH), 7.16 (dd, $J_1 = 1.2$ Hz, $J_2 = 8.0$ Hz, 1 H, ArH), 7.04 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.4$ Hz, 1 H, ArH), 2.38 (s, 3 H, CH₃), 1.35 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.54, 151.68, 139.29, 137.67, 136.04, 133.74, 131.96, 130.66, 129.97, 129.29, 120.87, 115.30, 114.35, 80.96, 23.45, 19.75.

HRMS: m/z [M]⁺ calcd for C₁₇H₁₆³⁵Cl₂N₂O₂: 350.0589; found: 350.0589.

7-Chloro-3-(3-chlorophenyl)-2,3-dihydro-1-hydroxy-2,2-dimethylquinazolin-4(1*H*)-one (3g)

Solid; mp 192–193 °C.

IR (KBr): 3198, 2981, 2939, 2871, 1633, 1599, 1475, 1435, 1388, 1372, 1309, 1281, 1261, 1225, 1189, 1172, 1156, 1082, 1020, 1003, 909, 881, 869, 828, 806, 784, 772, 705 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 9.85$ (s, 1 H, OH), 7.72 (d, J = 8.4 Hz, 1 H, ArH), 7.54–7.51 (m, 2 H, ArH), 7.39 (s, 1 H, ArH), 7.29–7.25 (m, 1 H, ArH), 7.21 (d, J = 2.0 Hz, 1 H, ArH), 7.05 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, 1 H, ArH), 1.36 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO- d_6): δ = 161.49, 151.69, 140.16, 139.36, 133.73, 131.14, 130.53, 129.97, 129.45, 128.79, 120.92, 115.25, 114.39, 80.98, 23.64, 23.44.

HRMS: m/z [M]⁺ calcd for C₁₆H₁₄³⁵Cl₂N₂O₂: 336.0432; found: 336.0446.

3-Benzyl-7-chloro-2,3-dihydro-1-hydroxy-2,2-dimethylquinazolin-4(1*H*)-one (3h)

Solid; mp 196-198 °C.

IR (KBr): 3221, 3032, 3001, 2975, 2870, 1630, 1597, 1496, 1455, 1440, 1394, 1368, 1352, 1312, 1277, 1252, 1186, 1115, 1085, 1023, 1008, 975, 872, 857, 808, 774, 739, 698 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 9.68$ (s, 1 H, OH), 7.77 (d, J = 8.4 Hz, 1 H, ArH), 7.36–7.22 (m, 5 H, ArH), 7.15 (d, J = 1.6 Hz, 1 H, ArH), 7.03 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.4$ Hz, 1 H, ArH), 4.83 (s, 2 H, CH₂), 1.36 (s, 6 H, 2 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.89, 151.46, 139.92, 138.94, 129.86, 128.82, 127.27, 127.18, 120.71, 115.13, 114.08, 80.68, 44.98, 22.28.

HRMS: m/z [M]⁺ calcd for C₁₇H₁₇³⁵ClN₂O₂: M, 316.0979; found: 316.0965.

7-Chloro-2-ethyl-2,3-dihydro-1-hydroxy-2-methylquinazolin-4(1*H*)-one (3k)

Solid; mp 184–186 °C.

IR (KBr): 3226, 2970, 2881, 1655, 1601, 1439, 1383, 1296, 1252, 1208, 1188, 1158, 1082, 1040, 1022, 872, 857, 821, 778, 697, 666, 624 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.41 (s, 1 H, OH), 8.40 (s, 1 H, NH), 7.62 (d, J = 8.0 Hz, 1 H, ArH), 7.07 (s, 1 H, ArH), 6.92 (d, J = 8.4 Hz, 1 H, ArH), 1.85–1.58 (m, 2 H, CH₂), 1.31 (s, 3 H, CH₃), 0.90 (t, J = 7.2 Hz, 3 H, CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.54, 151.89, 138.42, 128.93, 119.42, 114.89, 113.23, 77.19, 29.30, 22.65, 8.20.

HRMS: m/z [M]⁺ calcd for C₁₁H₁₃³⁵ClN₂O₂: 240.0666; found: 240.0658.

7-Chloro-2,3-dihydro-1-hydroxy-2-methyl-2-propylquinazolin-4(1*H*)-one (3l)

Solid; mp 177-179 °C.

IR (KBr): 3384, 3100, 2965, 2872, 1659, 1600, 1466, 1450, 1415, 1369, 1306, 1291, 1276, 1198, 1186, 1159, 1145, 1085, 1024, 991, 922, 868, 837, 805, 776, 737, 687, 627 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.41 (s, 1 H, OH), 8.44 (s, 1 H, NH), 7.62 (d, J = 8.0 Hz, 1 H, ArH), 7.06 (s, 1 H, ArH), 6.92 (d, J = 8.0 Hz, 1 H, ArH), 1.78–1.30 (m, 7 H, CH₃ and CH₂CH₂), 0.86 (t, J = 7.2 Hz, 3 H, CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.41, 151.83, 138.41, 128.93, 119.42, 114.94, 113.18, 76.86, 23.04, 16.59, 14.27.

HRMS: m/z [M]⁺ calcd for C₁₂H₁₅³⁵ClN₂O₂: 254.0822; found: 254.0831.

2-(4-Chlorophenyl)-2,3-dihydro-2-methylquinazolin-4(1*H*)-one (5a)

Solid; mp 213-214 °C.

IR (KBr): 3242, 3174, 3031, 2943, 1636, 1615, 1522, 1491, 1454, 1432, 1388, 1327, 1270, 1221, 1202, 1150, 1097, 1011, 989, 826, 792, 743, 717, 695 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 8.83 (s, 1 H, NH), 7.69 (s, 1 H, NH), 7.49 (t, J = 8.4 Hz, 3 H, ArH), 7.37 (d, J = 8.4 Hz, 2 H, ArH), 7.22 (t, J = 7.6 Hz, 1 H, ArH), 6.76 (d, J = 8.0 Hz, 1 H, ArH), 6.60 (t, J = 7.6 Hz, 1 H, ArH), 1.63 (s, 3 H, CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 164.20, 147.41, 147.20, 133.90, 132.26, 128.45, 127.74, 127.62, 117.54, 115.44, 114.80, 70.35, 30.91.

HRMS: m/z [M]⁺ calcd for C₁₅H₁₃³⁵ClN₂O: 272.0716; found: 272.0737.

7-Chloro-2,3-dihydro-2-methyl-2-(4-methylphenyl)quinazolin-4(1*H*)-one (5b)

Solid; mp 244-246 °C.

IR (KBr): 3243, 3175, 3020, 2926, 1638, 1607, 1524, 1511, 1479, 1451, 1422, 1379, 1363, 1317, 1274, 1238, 1222, 1192, 1157, 1101, 1074, 1019, 989, 960, 899, 848, 831, 815, 779, 717, 688 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.86 (s, 1 H, NH), 7.87 (s, 1 H, NH), 7.47 (d, *J* = 8.0 Hz, 1 H, ArH), 7.34 (d, *J* = 8.0 Hz, 2 H, ArH), 7.11 (d, *J* = 8.0 Hz, 2 H, ArH), 6.78 (s, 1 H, ArH), 6.60 (d, *J* = 8.4 Hz, 1 H, ArH), 2.22 (s, 3 H, CH₃), 1.64 (s, 3 H, CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.51, 148.67, 144.73, 138.17, 136.89, 129.70, 129.12, 125.46, 117.32, 114.32, 113.83, 70.75, 31.01, 20.95.

Crystal data¹¹

CCDC-682916; C₁₆H₁₅ClN₂O; M = 286.75, colorless block crystals, $0.38 \times 0.26 \times 0.20$ mm, monoclinic, space group $P2_1/c$, a = 12.2843(8) Å, b = 9.3487(6) Å, c = 12.3510(7) Å, $\beta = 101.7300(10)^\circ$, V = 1388.79(15) Å³, Z = 4, $D_c = 1.371$ g·cm⁻¹, F(000) = 600, μ (MoK α) = 0.272 mm⁻¹. Intensity data were collected on a diffractometer with graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å) using ω scan mode with 1.69° < $\theta < 25.01^\circ$.

1344 unique reflections were measured and 1116 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R1 = 0.0451 and wR2 = 0.1098.

7-Chloro-2-(4-chlorophenyl)-2,3-dihydro-2-methylquinazolin
-4(1H)-one (5c)

Solid; mp 271-272 °C.

IR (KBr): 3230, 3174, 3020, 1639, 1606, 1524, 1479, 1453, 1422, 1361, 1322, 1270, 1240, 1200, 1157, 1097, 1081, 1011, 990, 962, 900, 859, 834, 787, 720, 689 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 8.95 (s, 1 H, NH), 7.96 (s, 1 H, NH), 7.50–7.46 (m, 3 H, ArH), 7.40 (d, J = 8.4 Hz, 2 H, ArH), 6.79 (d, J = 1.6 Hz, 1 H, ArH), 6.63 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1 H, ArH), 1.64 (s, 3 H, CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 164.20, 147.41, 147.20, 133.89, 132.26, 128.46, 127.74, 127.62, 117.54, 115.44, 114.80, 70.35, 30.91.

1'-Hydroxyspiro[cyclohexane-1,2'(1'H)-quinazolin]-4'(3'H)-one (7a)

Solid; mp 195–197 °C.

IR (KBr): 3267, 3170, 3081, 2929, 2862, 1656, 1608, 1558, 1540, 1507, 1469, 1429, 1387, 1342, 1313, 1288, 1276, 1255, 1151, 1110, 910, 819, 789, 759, 701 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.22 (s, 1 H, OH), 8.30 (s, 1 H, NH), 7.63 (d, J = 7.6 Hz, 1 H, ArH), 7.46–7.41 (m, 1 H, ArH), 7.14 (d, J = 8.4 Hz, 1 H, ArH), 6.94–6.89 (m, 1 H, ArH), 1.85–1.79 (m, 2 H, 2 CH), 1.70–1.52 (m, 7 H, 7 CH), 1.08–1.04 (m, 1 H, CH).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 162.17, 150.47, 133.60, 126.86, 120.13, 117.16, 114.85, 75.52, 31.29, 24.88, 21.03.

HRMS: m/z [M]⁺ calcd for $C_{13}H_{16}N_2O_2$: 232.1212; found: 232.1222.

1'-Hydroxyspiro[cycloheptane-1,2'(1H')-quinazolin]-4'(3'H)one (7b)

Solid; mp 200–201 °C.

IR (KBr): 3209, 3075, 2924, 1656, 1607, 1507, 1469, 1389, 1199, 1152, 1069, 857, 759 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.22 (s, 1 H, OH), 8.42 (s, 1 H, NH), 7.59 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1 H, ArH), 7.41–7.38 (m, 1 H, ArH), 7.06 (d, J = 7.6 Hz, 1 H, ArH), 6.88–6.84 (m, 1 H, ArH), 2.11 (dd, J_1 = 8.4 Hz, J_2 = 14.4 Hz, 2 H, CH₂), 1.81 (dd, J_1 = 9.2 Hz, J_2 = 14.4 Hz, 2 H, CH₂), 1.59–1.48 (m, 8 H, 4 × CH₂).

HRMS: m/z [M]⁺ calcd for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1380.

1'-Hydroxy-4-methylspiro[cyclohexane-1,2'(1'H)-quinazolin]-4'(3'H)-one (7c)

Solid; mp 202–204 °C.

IR (KBr): 3263, 3085, 2909, 2871, 1664, 1606, 1517, 1468, 1431, 1388, 1348, 1311, 1265, 1152, 1112, 1020, 1000, 902, 875, 801, 762, 703 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.22 (s, 1 H, OH), 8.28 (s, 1 H, NH), 7.62 (d, J = 7.2 Hz, 1 H, ArH), 7.43 (t, J = 8.0 Hz, 1 H, ArH), 7.13 (d, J = 8.4 Hz, 1 H, ArH), 6.90 (t, J = 7.6 Hz, 1 H, ArH), 1.91–0.88 (m, 9 H, 4 CH₂, CH), 0.87 (s, 3 H, CH₃).

HRMS: m/z [M]⁺ calcd for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1360.

7'-Chloro-1'-hydroxyspiro[cyclopentane-1,2'(1'H)-quinazolin]-4'(3'H)-one (7d)

Solid; mp 208–210 °C.

IR (KBr): 3320, 3165, 3072, 3030, 2943, 1656, 1606, 1572, 1466, 1376, 1330, 1291, 1255, 1182, 1159, 1137, 1094, 1007, 954, 905, 818, 791, 709, 667 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.52 (s, 1 H, OH), 8.78 (s, 1 H, NH), 7.55 (d, J = 2.4 Hz, 1 H, ArH), 7.48 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1 H, ArH), 7.16 (d, J = 8.4 Hz, 1 H, ArH), 2.16–2.09 (m, 2 H, 2 CH), 1.71–1.60 (m, 6 H, 6 CH).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.66, 152.68, 138.33, 129.08, 120.05, 115.82, 113.84, 85.27, 34.81, 24.21.

HRMS: m/z [M]⁺ calcd for C₁₂H₁₃³⁵ClN₂O₂: 252.0666; found: 252.0663.

7'-Chloro-1'-hydroxyspiro[cyclohexane-1,2'(1'H)-quinazolin]-4'(3'H)-one (7e)

Solid; mp 206-208 °C.

IR (KBr): 3263, 3161, 2929, 2862, 1662, 1601, 1507, 1439, 1374, 1306, 1281, 1259, 1218, 1157, 1111, 1082, 1012, 984, 912, 888, 874, 840, 779, 707, 669 $\rm cm^{-1}.$

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.49 (s, 1 H, OH), 8.46 (s, 1 H, NH), 7.62 (d, J = 8.0 Hz, 1 H, ArH), 7.10 (d, J = 2.0 Hz, 1 H, ArH), 6.96 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, 1 H, ArH), 1.87–1.80 (m, 2 H, 2 × CH), 1.72–1.58 (m, 7 H, 7 × CH), 1.08–1.05 (m, 1 H, CH).

¹³C NMR (100 MHz, DMSO- d_6): δ = 161.35, 151.64, 138.46, 128.95, 119.85, 115.68, 113.87, 76.07, 31.26, 24.74, 20.96.

HRMS: m/z [M]⁺ calcd for $C_{13}H_{15}^{35}ClN_2O_2$: 266.0822; found: 266.0827.

Crystal data¹¹

CCDC-682917; $C_{13}H_{15}ClN_2O_2$; M = 265.71, colorless block crystals, $0.48 \times 0.35 \times 0.33$ mm, triclinic, space group $P\overline{1}$, a = 12.484(5) Å, b = 12.873(5) Å, c = 17.065(6) Å, $a = 91.005(5)^{\circ}$, $\beta = 106.187(4)^{\circ}$, $\gamma = 101.340(4)^{\circ}$, V = 2574.6(16) Å³, Z = 8, $D_c = 1.371$ g·cm⁻¹, F(000) = 1112, μ (MoK α) = 0.292 mm⁻¹. Intensity data were collected on a diffractometer with graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å) using ω scan mode with $1.62^{\circ} < \theta < 25.01^{\circ}$. 8950 unique reflections were measured and 4418 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R1 = 0.0515 and wR2 = 0.1139.

7'-Chloro-1'-hydroxyspiro[cycloheptane-1,2'(1'H)-quinazolin]-4'(3'H)-one (7f)

Solid; mp 223-225 °C.

IR (KBr): 3296, 3109, 3090, 2928, 2904, 1651, 1603, 1600, 1440, 1370, 1306, 1281, 1225, 1199, 1153, 1072, 1020, 963, 935, 867, 830, 782, 700 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.50 (s, 1 H, OH), 8.57 (s, 1 H, NH), 7.59 (d, J = 8.0 Hz, 1 H, ArH), 7.03 (d, J = 2.0 Hz, 1 H, ArH), 6.99 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1 H, ArH), 2.10 (dd, J_1 = 8.4 Hz, J_2 = 14.0 Hz, 2 H, CH₂), 1.81 (dd, J_1 = 8.4 Hz, J_2 = 14.4 Hz, 2 H, CH₂), 1.59–1.48 (m, 8 H, 4 CH₂).

HRMS: m/z [M]⁺ calcd for $C_{14}H_{17}^{35}ClN_2O_2$: 280.0979; found: 280.0989.

2,3-Dihydro-3-{2-[1,4-dihydro-1-hydroxy-2,2-dimethyl-4-oxoquinazolin-3(2*H*)-yl]ethyl}-1-hydroxy-2,2-dimethylquinazolin-4(1*H*)-one (9a)

Solid; mp 223-225 °C.

IR (KBr): 3464, 3254, 2997, 2969, 2905, 1638, 1616, 1571, 1473, 1405, 1363, 1318, 1301, 1265, 1193, 1181, 1015, 985, 940, 868, 758, 698, 671 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.50 (s, 2 H, 2 OH), 7.72 (d, *J* = 7.6 Hz, 2 H, ArH), 7.47 (t, *J* = 7.6 Hz, 2 H, ArH), 7.17 (d, *J* = 8.4 Hz, 2 H, ArH), 6.96 (t, *J* = 7.6 Hz, 2 H, ArH), 3.64–3.55 (m, 4 H, 2 CH₂), 1.54 (s, 12 H, 4 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 162.56, 150.22, 134.12, 127.44, 120.72, 116.19, 114.73, 80.06, 41.63, 22.52.

HRMS: m/z [M]⁺ calcd for $C_{22}H_{26}N_4O_4$: 410.1954; found: 410.1877.

Crystal data11

CCDC-682918; $C_{22}H_{28}N_4O_5$; M = 428.48, colorless block crystals, $0.42 \times 0.23 \times 0.19$ mm, monoclinic, space group $P2_1/c$, a = 8.627(3) Å, b = 10.972(4) Å, c = 23.345 (8) Å, $\beta = 99.898(5)^\circ$, V = 2176.8(13) Å³, Z = 4, $D_c = 1.307$ g·cm⁻¹, F(000) = 1062, μ (MoK α) = 0.0936 mm⁻¹. Intensity data were collected on a diffractometer with graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å) using ω scan mode with 2.566° < θ < 20.623°. 3819 unique reflections were measured and 1775 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R1 = 0.0620 and wR2 = 0.1520.

7-Chloro-3-{2-[7-chloro-1,4-dihydro-1-hydroxy-2,2-dimethyl-4-oxoquinazolin-3(2*H*)-yl]ethyl}-2,3-dihydro-1-hydroxy-2,2-dimethylquinazolin-4(1*H*)-one (9b)

Solid; mp 254–256 °C.

IR (KBr): 3273, 2980, 2944, 2867, 1626, 1597, 1558, 1538, 1437, 1389, 1362, 1296, 1251, 1183, 1148, 1111, 1080, 1019, 1004, 944, 899, 868, 859, 838, 803, 774, 744, 695, 682, 666 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.75 (s, 2 H, 2 OH), 7.73–7.68 (m, 2 H, ArH), 7.13 (s, 2 H, ArH), 7.00 (d, J = 8.4 Hz, 2 H, ArH), 3.63 (s, 4 H, 2 CH₂), 1.54 (s, 12 H, 4 CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 161.73, 151.26, 138.95, 129.56, 120.61, 114.82, 113.98, 80.50, 41.62, 22.55.

7-Chloro-3-{3-[7-chloro-1,4-dihydro-1-hydroxy-2,2-dimethyl-4-oxoquinazolin-3(2*H*)-yl]propyl}-2,3-dihydro-1-hydroxy-2,2dimethylquinazolin-4(1*H*)-one (9c) Solid; mp 230–232 °C.

IR (KBr): 3271, 3143, 2996, 2864, 1621, 1599, 1567, 1442, 1372, 1334, 1312, 1275, 1252, 1203, 1178, 1156, 1135, 1084, 1059, 1044, 1022, 1006, 939, 864, 805, 770, 690, 668, 614 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.71 (s, 2 H, 2 OH), 7.68 (d, *J* = 8.0 Hz, 2 H, ArH), 7.11 (s, 2 H, ArH), 6.98 (d, *J* = 7.2 Hz, 2 H, ArH), 3.55 (t, *J* = 7.2 Hz, 4 H, 2 CH₂), 1.87–1.82 (m, 2 H, CH₂), 1.47 (s, 12 H, 4 CH₃).

¹³C NMR (100 MHz, DMSO- d_6): δ = 161.37, 151.22, 138.68, 129.58, 120.57, 115.19, 113.94, 80.36, 40.26, 22.40.

HRMS: m/z [M]⁺ calcd for $C_{23}H_{26}^{35}Cl_2N_4O_4$: 492.1331; found: 492.1334.

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- (11) Crystallographic data for the structures of 3a (CCDC-682915), 5b (CCDC-682916), 7e (CCDC-682917), and 9a (CCDC-682918) have been deposited at the Cambridge Crystallographic Data Centre. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033; email: deposit@ccdc.cam.ac.uk].