# Efficient and Convenient Synthesis of Pyrrolo[1,2-*a*]quinazoline Derivatives with the Aid of Tin(II) Chloride

Manman Wang, Guolan Dou, and Daqing Shi*

*Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, Jiangsu 215123, P. R. China*

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An efficient, convenient, one-pot synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one and 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione was accomplished in good yields via the novel reductive cyclization of 2-nitrobenzamides with haloketones or keto acids mediated by $SnCl_2 \cdot 2H_2O$ system. A variety of substrates can participate in the process with good yields, making this methodology suitable for library synthesis in drug discovery efforts.

## Introduction

The quinazolinone skeleton is a building block for the preparation of natural purine base,[1] alkaloids, many biologically active compounds and intermediates in organic synthesis.[2] Quinazolinone derivatives are interesting because of their diverse range of biological activities, such as antiinflammatory,[2] antihypertensive,[3] anticancer,[4] antitumor,[5] anticonvulsant,[6] and antibacterial activity.[7] Hence, the synthesis of quinazoline derivatives is currently of great interest in organic synthesis. For example, our group has synthesized a series of quinazoline derivatives using 2-nitrobenzamide and aldehyde or ketone as reactants induced by low-valence titanium.[8] As an important quinazolinone derivative, the pyrrolo[1,2-*a*]quinazolinone moiety, in particular, is a very novel tricyclic compound. And some of them have antiedema activity.[9]

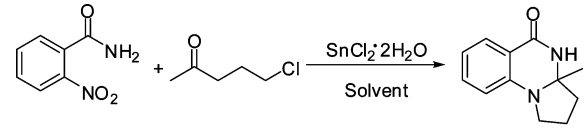
The synthsis of pyrrolo[1,2-*a*]quinazolinone derivatives have hitherto been reported by only few workers. For example, Aeberli et al.[10] synthesized 3-a-methyl- and 3-a-phenyl-l,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazoline-l,5-dione by reaction of anthranilamide with 4-oxopentanoic acid and 4-oxo-4-phenylbutanoic acid. Bell et al.[11] prepared pyrrolo[1,2-*a*]quinazolines from the reaction of anthranilamides with either $\gamma$-cyanopropionaldehyde or succinicanhydride. Kurihara et al.[12] also reported the reaction of ethyl 3-ethoxymethylene-2,4-dioxovalerate with 2-aminobenzamide derivatives to give pyrrolo[1,2-$\alpha$]quinazoline-1,5-dione derivatives. However, these synthetic methods are considerably limited because of unsatisfactory yields, long-reaction time, complex manipulation, and inaccessible starting materials. Recently, Iminov et al.,[13,14] reported the synthesis of pyrroloquinazoline carboxylic acids and 7a,8,9,10-tetrahydrocyclopenta[2,3]pyrrolo[1,2-*a*]quinazoline-6,12(7*H*,11*H*)-diones from the reaction of 2-aminobenzamides with 2-oxoglutaric acid and 2-oxocyclopentaneheptaneacetic acids esters, respectively. But, the reaction still needs 7−8 h. Therefor, the development of more efficient methods for the preparation of this kind of compounds is still an active research area.

In recent years, our interest has been focused on the usage of $SnCl_2$ reagent. We have previously reported the synthesis of 2-aryl-2*H*-indazoles,[15] 1-hydroxyquinazolinones,[16] quinoxaline derivatives,[17] imidazo[1,2-*c*]quinazoline-5(6*H*)-thione,[18] and imidazo[1,2-*c*]quinazolin-5(6*H*)-one[18] mediated by the $SnCl_2$ reagent. In this paper, we wish to describe a new route to synthesize 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one and 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione via the novel reductive cyclization of 2-nitrobenzamides with haloketones or keto acids mediated by $SnCl_2 \cdot 2H_2O$ system.

## Results and Discussion

In a preliminary study, we selected *o*-nitrobenzamide **1a** and the 5-chloropentan-2-one **2a** as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction. The results are summarized in Table 1.

**Table 1.** Optimization of Temperature, Ratio, and Solvents in the Synthesis of **3a**




**1a** **2a** **3a**

| entry | solvent | temperature/°C | ratio[a] | yield/% |
|---|---|---|---|---|
| 1 | THF | reflux | 1:4 | 67 |
| 2 | $CH_3CN$ | reflux | 1:4 | 52 |
| 3 | $CHCl_3$ | reflux | 1:4 | 45 |
| 4 | EtOH | reflux | 1:4 | 85 |
| 5 | EtOH | rt | 1:4 | 39 |
| 6 | EtOH | 40 | 1:4 | 55 |
| 7 | EtOH | 60 | 1:4 | 70 |
| 8 | EtOH | reflux | 1:2 | 54 |
| 9 | EtOH | reflux | 1:3 | 68 |
| 10 | EtOH | reflux | 1:5 | 83 |

[a] Ratio of **1** and $SnCl_2 \cdot 2H_2O$ system.

* To whom correspondence should be addressed. E-mail: dqshi@suda.edu.cn.

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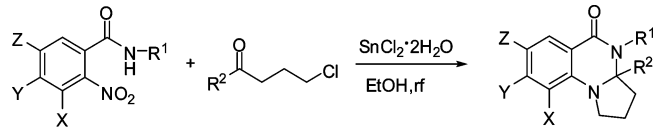
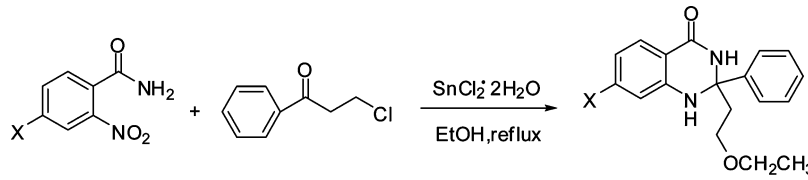
**Table 2.** Synthesis of Compounds **3** from *o*-Nitrobenzamides **1** and Haloketones **2**




**1** **2** **3**

| entry | X | Y | Z | $R^1$ | $R^2$ | compound | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | $CH_3$ | **3a** | 85 |
| 2 | H | H | $CH_3$ | H | $CH_3$ | **3b** | 80 |
| 3 | $CH_3$ | H | H | H | $CH_3$ | **3c** | 78 |
| 4 | H | $OCH_3$ | $OCH_3$ | H | $CH_3$ | **3d** | 86 |
| 5 | H | Cl | H | H | $CH_3$ | **3e** | 82 |
| 6 | H | H | Cl | H | $CH_3$ | **3f** | 79 |
| 7 | H | H | H | 4-$CH_3C_6H_4$ | $CH_3$ | **3g** | 65 |
| 8 | H | H | H | 4-$OCH_3C_6H_4$ | $CH_3$ | **3h** | 69 |
| 9 | H | H | H | 4-$ClC_6H_4$ | $CH_3$ | **3i** | 73 |
| 10 | H | H | H | 4-$FC_6H_4$ | $CH_3$ | **3j** | 67 |
| 11 | H | Cl | H | 4-$FC_6H_4$ | $CH_3$ | **3k** | 75 |
| 12 | H | H | H | 2-$ClC_6H_4$ | $CH_3$ | **3l** | 70 |
| 13 | H | H | H | 4-$FC_6H_4CH_2$ | $CH_3$ | **3m** | 76 |
| 14 | H | H | H | $C_6H_5CH_2$ | $CH_3$ | **3n** | 73 |
| 15 | H | Cl | H | H | 4-$BrC_6H_4$ | **3o** | 75 |
| 16 | H | H | H | H | 4-$BrC_6H_4$ | **3p** | 76 |
| 17 | $CH_3$ | H | H | H | 4-$BrC_6H_4$ | **3q** | 72 |
| 18 | H | Cl | H | $CH_3$ | 4-$BrC_6H_4$ | **3r** | 68 |

**Scheme 1.** Synthesis of Compounds **3s** and **3t**




**3s: X=Cl**
**3t: X=H**

As shown in Table 1, we first examined the effect of different organic solvents (entries 1−4) and concluded that ethanol was the best solvent for this reaction. Then, we also briefly examined the effect of different temperatures and ratio of **1a**/$SnCl_2 \cdot 2H_2O$. The results showed that at refluxing temperature the reaction preceded smoothly in high yield. To further evaluate the influence of the ratio of **1a**/$SnCl_2 \cdot 2H_2O$, the reaction was carried out in ethanol using a 1:2 to 1:5 ratio of **1a**/$SnCl_2 \cdot 2H_2O$ (Table 1, entries 8, 9, 4, 10), leading to **3a** in 54%, 68%, 85%, and 83% yields, respectively. We concluded the best ratio of **1a**/$SnCl_2 \cdot 2H_2O$ was 1:4.

With the optimized conditions in hand, we then performed the reaction of a variety of *o*-nitrobenzamides **1** and haloketones **2** via $SnCl_2 \cdot 2H_2O$ system. The results are summarized in Table 2.

As shown in Table 2, we were pleased to find that the method was applicable to a broad substrate scope on both substituted *o*-nitrobenzamides and haloketones. It can be seen that this protocol can be applied not only to the *o*-nitrobenzamides (entries 1−6, 15−17) with electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups) but also to N-substituted *o*-nitrobenzamides (entries 7−14, 18) under the same conditions, which highlighted the wide scope of this reaction. The yields of *o*-nitrobenzamides were superior to those of *N*-substituted ones. Meanwhile, the effects of different haloketones were also investigated. 5-Chloropentan-2-one (entries 1−14) and 1-(4-bromophenyl)-4-chlorobutan-1-one (entries 15−18) can also give moderate to good yields. However, the reaction was impeded by severe steric hindrance. For example, no desired product was obtained when 1-(4-bromophenyl)-4-chlorobutan-1-one reacted with *N*-aryl-*o*-nitrobenzamides.

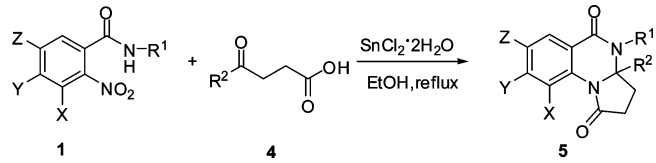
However, no desired products 2a-phenyl-2a,3-dihydro-1*H*-azeto[1,2-*a*]quinazolin-4(2*H*)-one and 7-chloro-2a-phenyl-2a,3-dihydro-1*H*-azeto[1,2-*a*]quinazolin-4(2*H*)-one were obtained when we treated 3-chloro-1-phenylpropan-1-one with *o*-nitrobenzamide or 4-chloro-2-nitrobenzamide under the same conditions. To our surprise, compounds **3s** and **3t** were obtained as our final products (Scheme 1).

Encouraged by these results, we next focused our attention on the reaction of 2-nitrobenzamides with keto acids to synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione.

To demonstrate the efficiency and the applicability of the present method, we performed the reaction of a variety of *o*-nitrobenzamides **1** and keto acids **4** under the optimized conditions. Table 3 summarizes our results on the reductive cyclization of **1** and **4**.

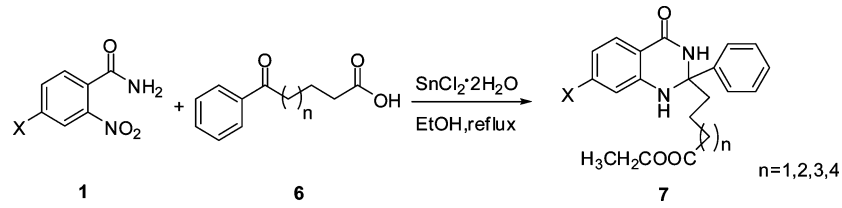
Similarly, it can be seen that either *o*-nitrobenzamides (entries 1−3, 9, 10) or N-substituted ones (entries 4−8, 11) were well tolerated. *o*-Nitrobenzamides containing electron-donating and electron-withdrawing substituents were reacted under the optimized conditions, and the corresponding products were obtained in good yields. No remarkable

**Table 3.** Synthesis of Compounds **5** from *o*-Nitrobenzamides **1** and Keto Acids **4**



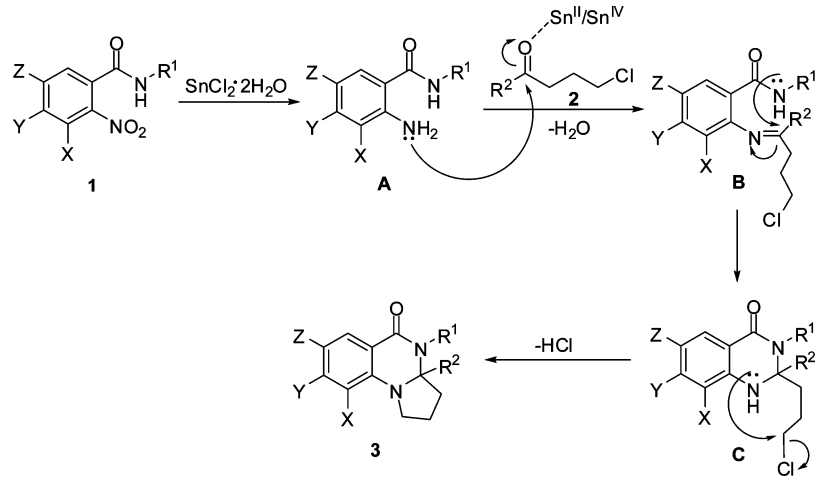

| entry | X | Y | Z | $R^1$ | $R^2$ | compound | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | $CH_3$ | **5a** | 83 |
| 2 | H | Cl | H | H | $CH_3$ | **5b** | 86 |
| 3 | H | H | Cl | H | $CH_3$ | **5c** | 80 |
| 4 | H | H | H | 4-$BrC_6H_4$ | $CH_3$ | **5d** | 76 |
| 5 | H | H | Cl | 4-$CH_3C_6H_4$ | $CH_3$ | **5e** | 68 |
| 6 | H | H | H | 4-$OCH_3C_6H_4$ | $CH_3$ | **5f** | 72 |
| 7 | H | Cl | H | 4-$FC_6H_4$ | $CH_3$ | **5g** | 75 |
| 8 | H | Cl | H | $C_6H_5CH_2$ | $CH_3$ | **5h** | 70 |
| **9** | H | H | H | H | $C_6H_5$ | **5i** | 82 |
| **10** | H | H | $CH_3$ | H | $C_6H_5$ | **5j** | 78 |
| **11** | H | H | H | $CH_3$ | $C_6H_5$ | **5k** | 73 |

**Table 4.** Synthesis of Compounds **7**




| entry | X | *n* | compound | yield (%) |
|---|---|---|---|---|
| 1 | Cl | 1 | **7a** | 85 |
| 2 | H | 1 | **7b** | 86 |
| 3 | Cl | 2 | **7c** | 83 |
| 4 | Cl | 3 | **7d** | 82 |
| 5 | Cl | 4 | **7e** | 85 |

**Scheme 2.** Supposed Reaction Mechanism




electronic effects on the reaction was observed. The effects of different keto acids were also investigated. 4-Oxopentanoic acid (entries 1−8) and 4-oxo-4-phenylbutanoic acid (entries 9−11) all reacted well to give moderate to good yields. However, no desired product was obtained when 4-oxo-4-phenylbutanoic acid reacted with *N*-aryl-*o*-nitrobenzamides because of severe steric hindrance.

However, when we study the reaction of *o*-nitrobenzamides **1** and keto acids **6** under the same reaction, to our surprise, compounds **7** were obtained as our final products. The results are summarized in Table 4.

A plausible mechanistic pathway to products **3** from *o*-nitrobenzamides and haloketones is illustrated in Scheme 2, although the details are still unclear. In the initial step, *o*-nitrobenzamides **1** are reduced by tin(II) chloride to intermediate **A**, and Sn(II) was oxidated to Sn(IV). The amine compounds **A** then reacted with haloketones **2** with the aid of Sn(IV) or excess Sn(II) to give the intermediate **B**. Intermediate **C** was formed by attack of the amino group onto the central carbon atom of the imine. Finally, products **3** were obtained by eliminating of a hydrogen chloride molecule.

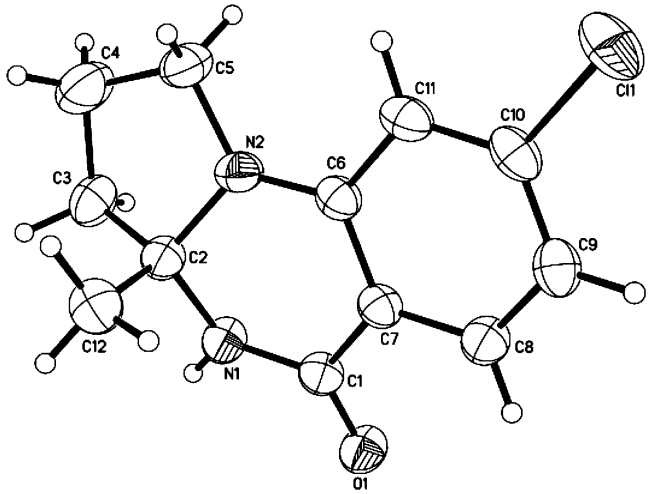



**Figure 1.** Molecular structure of **3e**.

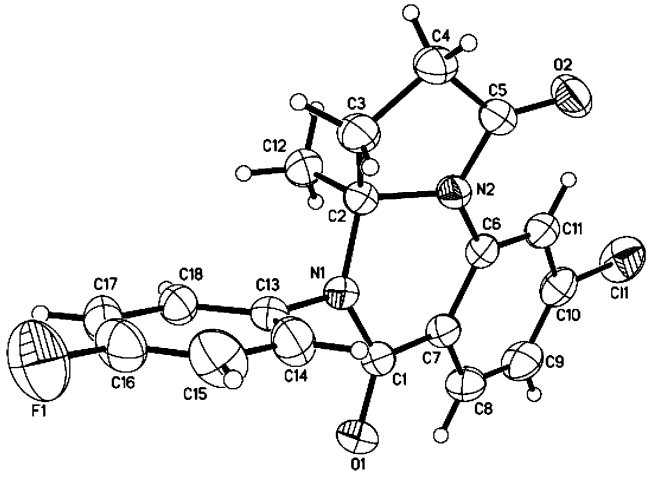



**Figure 2.** Molecular structure of **5g**.

All the products were characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS spectra. The structures of **3e** and **5g** were further confirmed by X-ray diffraction analysis.[19] The molecular structures of the products **3e** and **5g** are shown in Figures 1 and 2, respectively.

In conclusion, a series of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one and 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione compounds were synthesized by the reaction of 2-nitrobenzamides with haloketones or keto acids mediated by $SnCl_2 \cdot 2H_2O$ system. A variety of substrates can participate in the process with moderate to good yields. Our protocol is characterized by (i) faster reaction times, (ii) accessible materials and handy manipulation (only one pot), and (iii) isolation of products via simple recrystallization to give higher purities.

## Experimental Section

**General Information.** Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm$^{-1}$. $^1$H NMR was determined on Varian-300 MHz or Varian-400 MHz spectrometer in DMSO-$d_6$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. MS data were obtained using microma GCT-TOF instrument (EI$^+$) or LC/MS 1200/6200 (ESI$^+$). X-ray crystallographic analysis was performed with a Rigaku Mercury CCD/AFC diffractometer.

**General Procedure for the Synthesis of Compounds 3, 5, and 7.** A solution of *o*-nitrobenzamides **1** (1 mmol), haloketones, or keto acids **2**, **4**, **6**(1 mmol) and $SnCl_2 \cdot 2H_2O$ (4 mmol) in EtOH (5 mL) was stirred at reflux for 2−4 h. After this period, the TLC analysis of the mixture showed the reaction to be completed. The mixture was quenched with 3% HCl (10 mL) and filtered to yield a crude product, which was purified by recrystallization from 95% ethanol and DMF.

**3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (3a):** mp 166−167 °C; IR (KBr) *ν* 3170, 3042, 2972, 2893, 2850, 1661, 1652, 1505, 1384, 1366, 1308, 1187, 1145, 800, 749, 627 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) *δ* 1.22 (3H, s, $CH_3$), 1.91−2.07 (4H, m, $2CH_2$), 3.39−3.45 (2H, m, $CH_2$), 6.58 (1H, d, $J$ = 8.1 Hz, ArH), 6.68 (1H, t, $J$ = 7.5 Hz, ArH), 7.32 (1H, t, $J$ = 7.2 Hz, ArH), 7.65 (1H, dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, ArH), 8.25 (1H, s, NH); HRMS [found *m*/*z* 202.1089 (M$^+$), calcd for $C_{12}H_{14}N_2O$ M, 202.1106].

**3a-(4-Bromophenyl)-8-chloro-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (3o):** mp 148−150 °C; IR (KBr) *ν* 3161, 3030, 2975, 2899, 1661, 1602, 1482, 1302, 1196, 1082, 989, 822, 645 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) (*δ*, ppm) 1.63−1.73 (1H, m, CH), 2.03−2.07 (1H, m, CH), 2.16−2.21 (1H, m, CH), 2.33−2.41 (1H, m, CH), 3.47−3.56 (1H, m, CH), 3.84−3.91 (1H, m, CH), 6.67 (1H, dd, $J_1$ = 8.1 Hz, $J_2$ = 1.8 Hz, ArH), 6.91 (1H, d, $J$ = 1.5 Hz, ArH), 7.21 (2H, d, $J$ = 8.7 Hz, ArH), 7.49 (3H, dd, $J_1$ = 8.4 Hz, $J_2$ = 5.4 Hz, ArH), 9.24 (1H, s, NH); HRMS [Found *m*/*z* 375.9978 (M$^+$), calcd for $C_{17}H_{14}N_2O^{35}Cl^{79}Br$ M, 375.9978].

**7-Chloro-2-(2-ethoxyethyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3s):** mp 216−218 °C; IR (KBr) *ν* 3355, 3306, 3065, 2971, 2890, 1644, 1605, 1482, 1402, 1266, 1119, 930, 765, 702 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) (*δ*, ppm) 1.08(3H, t, $J$ = 7.2 Hz, $CH_3$), 2.05−2.11 (2H, m, $CH_2$), 3.37−3.41 (2H, m, $CH_2$), 3.53 (2H, t, $J$ = 7.2 Hz, $CH_2$), 6.58 (1H, d, $J$ = 8.4 Hz, ArH), 6.82 (1H, s, ArH), 7.19 (1H, t, $J$ = 6.9 Hz, ArH), 7.30 (2H, t, $J$ = 7.5 Hz, ArH), 7.44 (3H, d, $J$ = 8.4 Hz, ArH), 7.84 (1H, s, NH), 8.74 (1H, s, NH); HRMS [Found *m*/*z* 331.1207(M$^+$ + H), calcd for $C_{18}H_{20}N_2O_2{}^{35}Cl$ M + H, 331.1213].

**3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (5a):** mp 163−165 °C; IR (KBr) *ν* 3177, 3056, 2925, 1718, 1683, 1603, 1490, 1465, 1387, 1352, 1278, 1246, 1211, 1153, 1004, 791, 758 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) *δ* 1.57 (3H, s, $CH_3$), 2.39 (2H, t, $J$ = 7.8 Hz, $CH_2$), 2.68−2.73 (2H, m, $CH_2$), 7.29 (1H, t, $J$ = 7.8 Hz, ArH), 7.60 (1H, t, $J$ = 7.8 Hz, ArH), 7.99 (1H, s, NH), 8.06 (1H, d, $J$ = 7.8 Hz, ArH), 8.16 (1H, d, $J$ = 8.1 Hz, ArH); HRMS [found *m*/*z* 216.0894 (M$^+$), calcd for $C_{12}H_{12}N_2O_2$ M, 216.0899].

**7-Methyl-3a-phenyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]-quinazoline-1,5-dione (5j):** mp 296−297 °C; IR (KBr) *ν* 3186, 3085, 2888, 1712, 1671, 1496, 1451, 1357, 1204, 1089, 863, 824, 756, 696 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) (*δ*, ppm) 2.32 (3H, s, $CH_3$), 2.46−2.56 (1H, s, CH), 2.74 (3H, s, $CH_2$ + CH), 7.23−7.29 (3H, m, ArH), 7.34−7.40 (3H, m, ArH), 7.77 (1H, s, ArH), 8.11 (1H, d, $J$ = 8.4 Hz, ArH),

9.76 (1H, s, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 16.40, 25.26, 30.89, 35.28, 115.72, 116.31, 120.28, 123.81, 124.02, 124.42, 129.74, 130.24, 130.61, 138.69, 160.31, 168.61; HRMS [Found *m*/*z* 292.1214 ($M^+$), calcd for $C_{18}H_{16}N_2O_2$ M, 292.1212].

**Ethyl 4-(7-chloro-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)butanoate (7a):** mp 226−228 °C; IR (KBr) $\nu$ 3324, 3066, 2970, 1716, 1646, 1476, 1417, 1287, 1197, 1077, 916, 864, 771, 702 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) ($\delta$, ppm) 1.16 (3H, t, $J$ = 6.9 Hz, $CH_3$), 1.70−1.82 (4H, m, $2CH_2$), 2.27−2.31 (2H, m, $CH_2$), 4.03 (2H, dd, $J_1$ = 14.4 Hz, $J_2$ = 7.2 Hz, $OCH_2$), 6.58 (1H, dd, $J_1$ = 8.1 Hz, $J_2$ = 1.8 Hz, ArH), 6.87 (1H, d, $J$ = 1.8 Hz, ArH), 7.20 (1H, t, $J$ = 7.2 Hz, ArH), 7.31(2H, t, $J$ = 7.5 Hz, ArH), 7.42−7.47 (3H, m, ArH), 7.80 (1H, s, NH), 8.83 (1H, s, NH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 14.80, 20.33, 34.09, 41.99, 60.46, 73.71, 114.16, 114.21, 117.46, 125.89, 127.95, 128.80, 129.85, 138.43, 147.70, 149.05, 163.85, 173.34; HRMS [Found *m*/*z* 373.1334 ($M^+$ + H), calcd for $C_{20}H_{22}N_2O_3{}^{35}Cl$ M + H, 373.1319].

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**Supporting Information Available.** Detailed descriptions of experimental procedures and spectroscopic and analytical data are available for compounds **3**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

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(19) Crystallographic data for the structures of **3e** and **5g** have been deposited at the Cambridge Crystallographic Data Centre, deposit numbers are CCDC-777790 and CCDC-777791, respectively. Copies of available material can be obtained free of change on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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