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One-pot Synthesis of 2-Amino-4(3*H*)-Quinazolinones *via* Ring-opening of Isatoic anhydride and Palladium-catalyzed Oxidative Isocyanide-insertion

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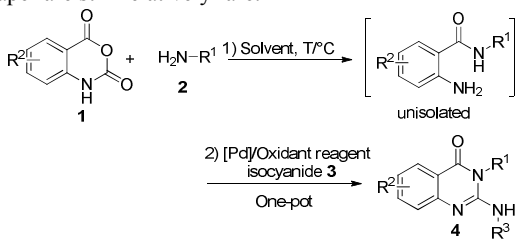
An efficient and practical two-step process has been developed for the synthesis of 2-amino-4(3*H*)-quinazolinones *via* ring-opening of isatoic anhydride and palladium-catalyzed oxidative isocyanide-insertion in one-pot. This regioselective procedure could construct a wide range of 2-amino-4(3*H*)-quinazolinones in moderate to excellent yields. Furthermore, the methodology also had distinct advantages of easily accessible starting materials and operational simplicity.

Introduction

The quinazolin-4(*3H*)-one skeleton is an unique unit that exists widely in the medically important products.[1] For example, 2-amino-4(*3H*)-quinazolinone derivatives have shown high activities as thymidylate synthase inhibitors,[2a] cognition enhancement agents,[2b] tumor necrosis factor α inhibitors,[2c] dopamine agonists,[2d] histamine H4 receptor inverse agonists,[2e] anti-inflammatory agents,[2f] anti-hypertentive agents,[2g] anti-convulsant agents,[2h] anti-hyperglycemic agents,[2i] and anti-bacterial agents.[2j]

A great number of synthetic methods for the generation of 2-amino-4(*3H*)-quinazolinone derivatives have been developed. In general, the synthetic methods can be classified into the following categories: 1) amidation of 2-aminobenzoic acid[3a] and its derivatives: 2-aminobenzonitrile,[3b] 2-aminobenzoate,[3c] isatoic anhydride[3d-3e] and so on; 2) the tandem aza-wittig reaction of iminophosphorane;[3f-3h] 3) the tandem palladium-catalyzed cyclocarbonylation;[3i-3j] 4) reactions of nucleophiles: guanidines, with ortho-fluorobenzoyl.[3k] However, these procedures often suffer from a variety of drawbacks, such as multi-step process, harsh reaction conditions, low yields, hardly accessible starting materials, the utilization of toxic CO, and low molecular diversity, which limit their usages in practical application. Therefore, the development of an efficient and step-economic procedure for the synthesis of 2-amino-4(*3H*)-quinazolinones is highly desired.

Isocyanides, a kind of unsaturated molecules similar to carbon monoxide, have emerged as versatile building blocks in the construction of medicinally important molecules and natural products.[4] Transition-metal catalyzed isocyanide-insertion reactions to assemble biological N-heterocycles have been previously undervalued and have drawn great attention only in very recent years.[5] This methodology offers several distinct advantages such as simple handling, mild condition and wide substrate scope (variable group at nitrogen) over carbon monoxide.[5] In 2012, R. V. A. Orru and co-workers reported a palladium-catalyzed oxidative isocyanide-insertion reaction involving bis-nucleophiles to synthesize 2-amino-4(3H)-quinazolinones.[6a] Nevertheless, this protocol was unfortunately not only highly inefficient for the variation at the 3-N position of 2-amino-4(*3H*)-quinazolinones, but also required multi-step process to synthesize the poor commercial available starting materials. Based on our previous work on the commercial available isatoic anhydrides[7, 8a] and isocyanides,[8] we have developed a novel and efficient one-pot process for the synthesis of a wide range of 2-amino-4(*3H*)-quinazolinones via ring-opening of isatoic anhydrides and palladium-catalyzed oxidative isocyanide-insertion reaction in a more rapid and flexible manner than the above mentioned conventional methods (Scheme 1). To the best of our knowledge, the previously reported transition-metal catalyzed isocyanide-insertion reactions are mainly confined to inserting isocyanides to C-H or C-halogen bonds, and this direct insertion of isocyanides into the active N-H bonds in this paper are still relatively rare.[6]



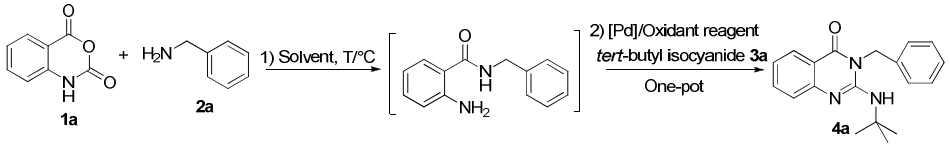
Scheme 1 Approaches towards 2-amino-4(*3H*)-quinazolinone derivatives

Results and Discussion

To explore this approach, we selected isatoic anhydride **(1a)**, benzyl amine **(2a)** and *tert*-butyl isocyanide **(3a)** as the model

substrates to optimize the reaction conditions including solvents, oxidant reagents, and palladium catalysts. Initially, we performed this one-pot process according to the optimized reaction conditions of the pioneering work by R. V. A. Orru.[6a] Disappointingly, the desired substituted 2-amino-4(*3H*)-quinazolinone was obtained only in a moderate yield (Table 1, entry 1). To our delight, switching the reaction solvent to toluene could improve the yields obviously (Table 1, entries 2-4). Subsequently, other oxidant reagents such as copper (II) salts, silver (I) salts, TBHP and $K_2S_2O_8$ were screened to obtain the better yield (Table 1, entries 5-10). Notably, Ag_2CO_3 was examined to be a more effective oxidant reagent and the yield of **4a** could be improved to 78% yield. Additionally, some commercial palladium catalysts were also screened, but no obvious improvement in yields was observed (Table 1, entries 11 and 12).

Table 1 Optimization of the reaction conditions[a]

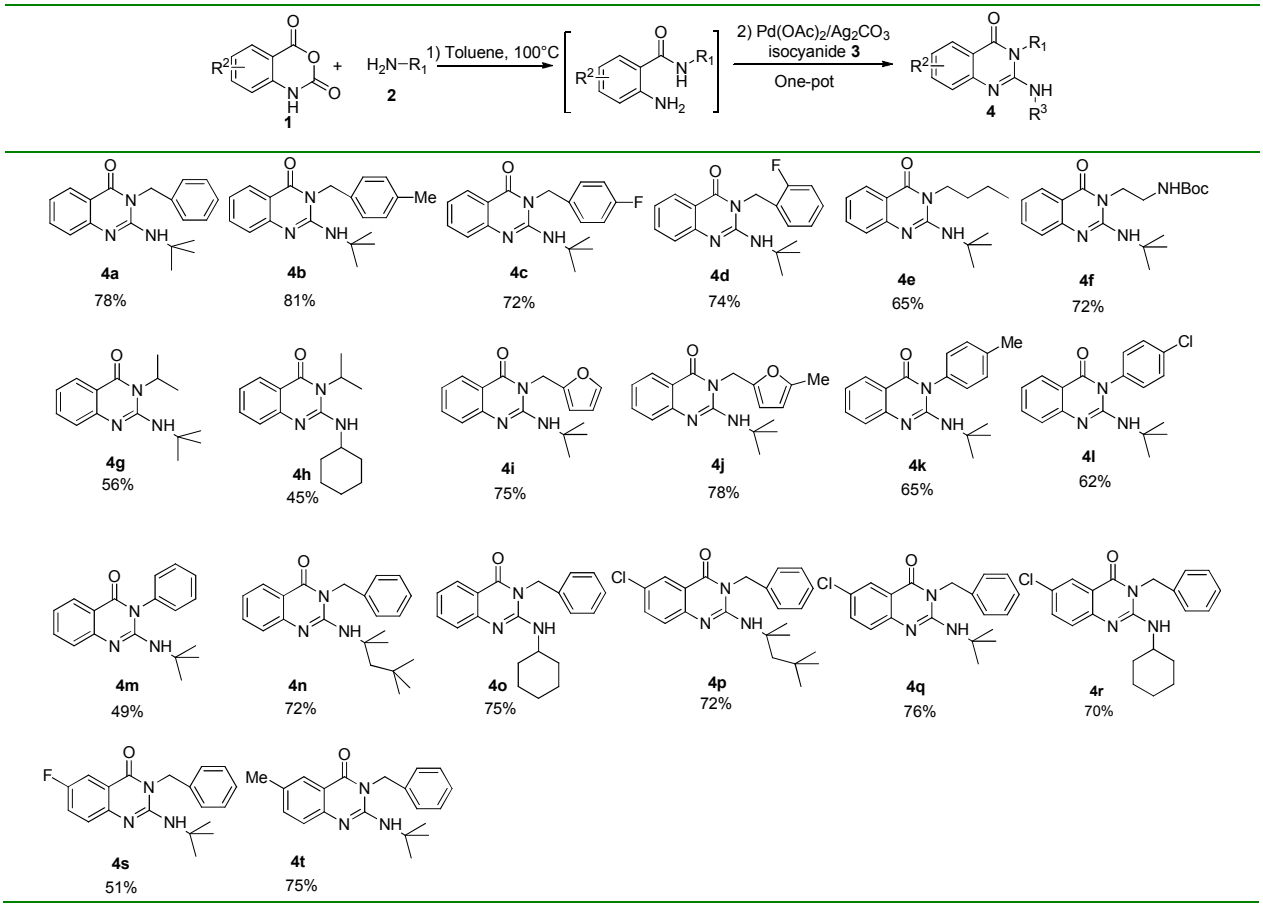


Entry	Pd catalyst	Oxidant reagent	Solvent	T/°C	Yield[c] (%)
1	$Pd(OAc)_2$	O_2[b]	MeTHF	75	42
2	$Pd(OAc)_2$	O_2[b]	toluene	100	68
3	$Pd(OAc)_2$	O_2[b]	DMF	110	37
4	$Pd(OAc)_2$	O_2[b]	MeCN	81	42
5	$Pd(OAc)_2$	$K_2S_2O_8$	toluene	100	23
6	$Pd(OAc)_2$	$Cu(TFA)_2{\cdot}XH_2O$	toluene	100	72
7	$Pd(OAc)_2$	TBHP	toluene	100	25
8	$Pd(OAc)_2$	Ag_2CO_3	toluene	100	78
9	$Pd(OAc)_2$	AgOAc	toluene	100	67
10	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	100	37
11	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	toluene	100	70
12	$Pd(amphos)Cl_2$	Ag_2CO_3	toluene	100	52

[a] *Reaction conditions:* 1) The reaction was carried out using **1a** (0.50 mmol) and **2a** (0.50 mmol) in solvent (4 ml) at T/°C for 4 h; 2) **3a** (0.75 mmol) was added subsequently in the presence of Pd catalyst (2 mol%) and Oxidant reagent (1.00 mmol) at T/°C for 24 h in one-pot. [b] In O_2 atmosphere (1 atm, balloon). [c] Isolated yields based on **1a**.

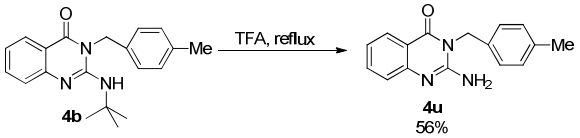
Under the optimized reaction conditions, the scope of this reaction was extended to a variety of amines, isocyanides and isatoic anhydrides. The results were summarised in Table 2. Generally, various amines, including aryl amines and alkyl amines were well tolerated. Benzyl amines bearing both electron-rich and electron-deficient aromatic ring furnished the desired products in high yields (Table 2, **4a-4c**). *Ortho*-substituted benzyl amine would not decrease the reaction rate obviously (Table 2, **4d**). In addition, primary alkyl amines and secondary alkyl amines also generated the products in moderate to high yields (Table 2, **4e-4g**). It's worth noticing that the N-boc-amino group of the product **4f** could be further modified to explore the diversification of substituted 2-amino-4(*3H*)-quinazolinones. With regard to amines bearing heterocycles, we could also isolate the corresponding products in high yields (Table 2, **4i and 4j**). Meanwhile, the reaction was also tolerant of different substituted aryl amines giving the corresponding product, albeit in moderate yields, due to relatively lower activity of aryl amines (Table 2, **4k-4m**). Unfortunately, the complex product was formed when 4-nitro-aniline was employed in this transformation. This successful utilization of a broad range of amines further efficiently increased the diversification at 3-N position of 2-amino-4(*3H*)-quinazolinones. Next, different isocyanides were also applied to probe the scope of the reaction. When cylcohexyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide were employed instead of *tert*-butyl isocyanide, the reaction worked as expected giving corresponding products in high yields (Table 2, **4n and 4o**). Finally, we examined the use of different isatoic anhydrides. Noticeably, isatoic anhydrides containing electron-donating (R^2= 6-Me) and halogen group (R^2= 6-F, 6-Cl) reacted efficiently, affording **4** in moderate to high yields (Table 2, **4q, 4s and 4t**). However, the electron-withdrawing group on the aromatic ring of isatoic anhydrides (R^2=6-NO_2, 6-COOMe) had a negative effect on this reaction, and could not obtain the desired product.

Table 2 Synthesis of 2-amino-4(*3H*)-quinazolinone derivatives[a, b]



[a] *Reaction conditions:* 1) The reaction was carried out using **1** (0.50 mmol) and **2** (0.50 mmol) in toluene (4 mL) at 100 °C, and the reaction time was determined by TLC (3-8 h); 2) **3** (0.75 mmol) was added subsequently in the presence of Pd catalyst (2 mol%) and Ag_2CO_3 (1.00 mmol) at 100 °C for 24 h in one-pot. [b] Isolated yields on **1.**

To further expand the scope of 2-amino-4(*3H*)-quinazolinone, we also tried to access the unsubstituted 2-amino-4(*3H*)-quinazolinone by the acid-promoted dealkylation sequence (Scheme 2). Addition of TFA to 2-(*tert*-butylamino)-quinazolin-4(*3H*)-one and subsequent heating under reflux finally furnished unsubstituted 2-amino-4(*3H*)-quinazolinone in a moderate yield. This process provided a valuable alternative to the use of highly toxic cyanogens bromide,[6a] especially since *tert*-butyl isocyanide was an easily accessible and convertible isocyanide.



Scheme 2 Synthesis of unsubstituted 2-amino-4(*3H*)-quinazolinone

The structures of 2-amino-4(*3H*)-quinazolinones **4a-4u** were fully characterized by Mass spectrometry, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. Moreover, the structure of **4j** was also confirmed by single-crystal X-ray analysis (Figure 1). Based on the well-established chemistry of isocyanide,[6] the proposed mechanism was depicted in Scheme 3. Initially, the ring-opening reaction of isatoic anhydride **1** with amine **2**

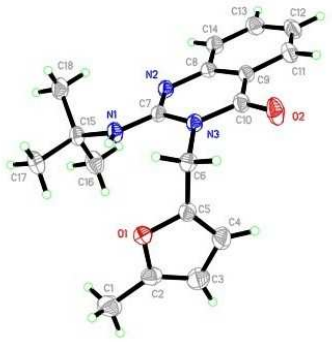
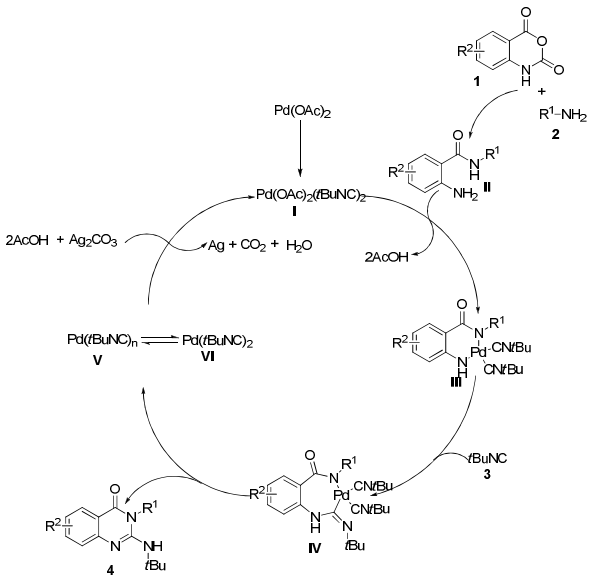


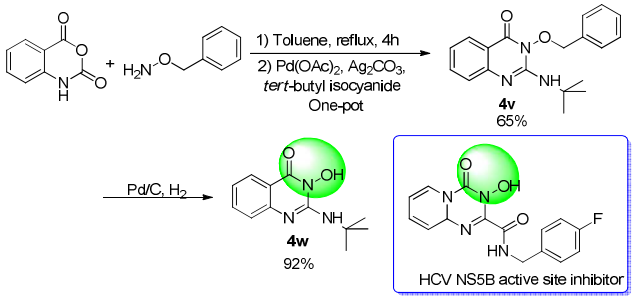
Figure 1 single-crystal X-ray analysis of **4j**

generates the bis-nucleophile **II**. Catalysis **I** reacts with the bis-nucleophile II to form the intermediate **III**. Then, isocaynide-insertion reaction occurs, resulting in the species **IV**. Species **IV** subsequently undergoes reductive elimination to afford the product **4**. Pd(0) species **VI** is stabilized by coordination of multiple isocyanides and then oxidized by silver carbonate to regenerate the catalyst. The occurrence of silver and carbon dioxide in the experiment also further confirmed this mechanism.



Scheme 3 Possible mechanism of this two-step reaction

Considering the fact that the discovery of new molecular scaffolds is essential to meet the temporary demands for improved materials and pharmaceuticals, we used this method to synthesize 2-amino-3-hydroxyquinazolin-4(*3H*)-ones (Scheme 4). Its analogous bicyclic-pyrimidinones have been proved to be effective HCV NS5B active site inhibitors.[9] The ring-opening reaction of isatoic anhydride with O-benzyl hydroxylamine and subsequent palladium-catalyzed oxdative isocyanide-insertion reaction in one-pot proceeded smoothly in the presence of $Pd(OAc)_2$ and Ag_2CO_3 to afford 3-(benzyloxy)-2-amino-quinazolin-4(*3H*)-one **4v** in 65% yield. The following hydrogenating debenzylation is well-known to furnish 2-amino-3-hydroxyquinazolin-4(*3H*)-ones **4w** in a high yield to further increase the variation at the 3-N position of 2-amino-4(*3H*)-quinazolinones.



Scheme 4 Synthesis of 2-amino-3-hydroxyquinazolin-4(*3H*)-ones

Conclusions

In counclusion, we have developed an efficient and practical one-pot process for the synthesis of 2-amino-4(*3H*)-quinazolinones *via* ring-opening of isatoic anhydride and palladium-catalyzed oxidative isocyanide-insertion. This regioselective methodology was successful with a range of amines, isatoic anhydrides and isocyanides, and could afford the desired heterocycles in moderate and high yields. This process also had distinct advantages of easily accessible starting materials, operational simplicity and molecular diversity compared to previous reported methods. It's believable that this method may be instrumental to the rapid and flexible construction of important 2-amino-quinazolin-4(*3H*)-one derivatives with promising biological and pharmaceutical activities.

Experimental section

Unless otherwise stated, all commercial reagents were used as received. All melting points were uncorrected. Mass spectra were recorded on Shimadzu LCMS-2020. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz in $CDCl_3$, and chemical shifts were reported in ppm from internal TMS (δ). Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

General procedure for the synthesis of 2-substituted-amino-4(*3H*)-quinazolinones 4a-4t: To a solution of isatoic anhydride **1** (0.50 mmol) in toluene (4 mL) was added amine **2** (0.50 mmol). The mixture was stirred at 100 °C in a sealed tube for 3-8 h (according to the determination of TLC). Upon the completion of the reaction, isocyanide **3** (0.75 mmol), $Pd(OAc)_2$ (2 mol%) and Ag_2CO_3 (1.00 mmol) was successively added. The mixture was then kept stirring at 100 °C for another 24 h. After that, the product was then concentrated under vacuum and the resulting residue was purified by column chromatography.

3-benzyl-2-(*tert*-butylamino)quinazolin-4(*3H*)-one 4a: white solid, 138-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 4.35 (s, 1H), 5.33 (s, 2H), 7.22 (t, *J*=7.0 Hz, 1H), 7.28-7.30 (m, 2H), 7.34-7.36 (m, 1H), 7.37-7.41 (m, 3H), 7.59-7.61 (m, 1H), 8.21 (d, *J*=1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.83, 43.89, 51.59, 115.97, 121.44, 124.28, 125.71, 126.27, 127.25, 128.33, 133.19, 134.49, 147.45, 148.07, 162.29; Ms (ESI) *m/z*: 308 [M+H]; Anal. Calcd for $C_{19}H_{21}N_3O$: C,74.24; H, 6.89; N, 13.67; found C, 74.39; H, 6.98; N, 13.61.

2-(*tert*-butylamino)-3-(4-methylbenzyl)quinazolin-4(*3H*)-one 4b: white solid, 141-143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36 (s, 9H), 2.37 (s, 3H), 4.41 (s, 1H), 5.28 (s, 2H), 7.17-7.19 (m, 5H), 7.40 (d, *J*=8.0 Hz, 1H), 7.59-7.60 (m, 1H), 8.20-8.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.16, 27.85, 43.76, 51.56, 115.99, 121.39, 124.25, 125.70, 126.25, 128.98, 131.34, 133.16, 137.05, 147.57, 148.07, 162.34; Ms (ESI) *m/z*: 322 [M+H]; Anal. Calcd for $C_{20}H_{23}N_3O$: C,74.74; H, 7.21; N, 13.07; found C, 74.62; H, 7.12; N, 13.12.

2-(*tert*-butylamino)-3-(4-fluorobenzyl)quinazolin-4(*3H*)-one 4c: white solid, 158-160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36 (s, 9H), 4.26 (s, 1H), 5.28 (s, 2H), 7.08 (t, *J*=8.5 Hz, 2H), 7.20 (t, *J*=7.0 Hz, 1H), 7.25-7.28 (m, 2H), 7.39 (d, *J*=8.0 Hz, 1H), 7.59-7.60 (m, 1H), 8.18-8.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.87, 43.25, 51.66, 115.23, 115.40, 115.91, 121.57, 124. 32, 126.23, 127.43, 127.49, 130.26, 133.31, 147.22, 147.99, 160.55, 162.25, 162.52; Ms (ESI) *m/z*: 326 [M+H]; Anal. Calcd for $C_{19}H_{20}FN_3O$: C,70.13; H, 6.20; N, 12.91; found C, 70.27; H, 6.27; N, 12.82.

2-(*tert*-butylamino)-3-(2-fluorobenzyl)quinazolin-4(*3H*)-one 4d: white solid, 148-150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 4.61 (s, 1H), 5.34 (s, 2H), 7.11-7.20 (m, 3H), 7.29-7.31 (m, 1H), 7.37-7.39 (m, 2H), 7.58-7.59 (m, 1H), 8.17-8.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.86, 36.33, 51.72, 114.23,

114.40, 115.87, 121.40, 121.55, 124.23, 126.19, 128.95, 133.26, 146.77, 148.02, 158.28, 160.22, 162.41; Ms (ESI) *m/z*: 326 [M+H]; Anal. Calcd for $C_{19}H_{20}FN_3O$: C,70.13; H, 6.20; N, 12.91; found C, 70.02; H, 6.14; N, 12.99.

3-butyl-2-(*tert*-butylamino)quinazolin-4(*3H*)-one 4e: white solid, 145-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00 (t, *J*=7.4 Hz, 3H), 1.44-1.48 (m, 2H), 1.55 (s, 9H), 1.66-1.72 (m, 2H), 4.00 (t, *J*=7.8 Hz, 2H), 4.37 (s, 1H), 7.13 (t, *J*= 8.0 Hz, 1H), 7.36 (d, *J*=8.2 Hz, 1H), 7.53-7.57 (m, 1H), 8.09-8.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.75, 19.28, 28.21, 28.77, 39.94, 51.57, 116.11, 121.28, 124.11, 125.93, 132.94, 146.93, 147.80, 161.85; Ms (ESI) *m/z*: 274 [M+H]; Anal. Calcd for $C_{16}H_{23}N_3O$: C,70.30; H, 8.48; N, 15.37; found C, 70.17; H, 8.41; N, 15.45.

***tert*-butyl-2-(2-(*tert*-butylamino)-4-oxoquinazolin-3(*4H*)-yl) ethylcarbamate 4f:** white solid, 204 -206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 1.59 (s, 9H), 3.28-3.32 (m, 2H), 4.07-4.10 (m, 2H), 5.23 (s, 1H), 6.28 (s, 1H), 7.10 (t, *J*=7.5 Hz, 1H), 7.37-7.38 (m, 1H), 7.52-7.55 (m, 1H), 8.04-8.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.34, 28.09, 37.54, 39.27, 52.02, 79.40, 115.50, 121.00, 124.09, 125.67, 133.12, 147.51, 148.18, 156.01, 162.22; Ms (ESI) *m/z*: 361 [M+H]; Anal. Calcd for $C_{19}H_{28}N_4O_3$: C, 63.31; H, 7.83; N, 15.54; found C, 63.23; H, 7.75; N, 15.61.

2-(*tert*-butylamino)-3-isopropylquinazolin-4(*3H*)-one 4g: white solid, 118-120°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.52 (s, 3H), 1.53 (s, 3H), 1.54 (s, 9H), 4.47 (s, 1H), 5.59 (s, 1H), 7.08-7.12 (m, 1H), 7.31 (d, *J*=8.2 Hz, 1H), 7.50-7.54 (m, 1H), 8.06-8.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.40, 28.32, 42.47, 51.68, 116.50, 121.18, 123.80, 126.07, 132.91, 147.11, 147.68, 162.35; Ms (ESI) *m/z*: 260 [M+H]; Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20; found C, 69.34; H, 8.21; N, 16.27.

2-(cyclohexylamino)-3-isopropylquinazolin-4(*3H*)-one 4h: white solid, 129-131°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26-1.32 (m, 3H), 1.45-1.51 (m, 2H), 1.54 (s, 3H), 1.56 (s, 3H), 1.65-1.68 (m, 1H), 1.73-1.75 (m, 2H), 2.12-2.13 (m, 2H), 4.17 (s, 1H), 4.53 (s, 1H), 5.54 (s, 1H), 7.12 (d, *J*=7.5 Hz, 1H), 7.38 (s, 1H), 7.54 (t, *J*=7.5 Hz, 1H), 8.07 (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.32, 23.70, 24.74, 32.11, 42.93, 49.28, 116.36, 121.40, 123.24, 126.17, 133.18, 147.90, 162.03; Ms (ESI) *m/z*: 286 [M+H]; Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72; found C, 71.42; H, 8.17; N, 14.81.

2-(*tert*-butylamino)-3-(furan-2-ylmethyl)quinazolin-4(*3H*)-one 4i: white solid, 148-150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 5.01 (s, 1H), 5.14 (s, 2H), 6.27-6.28 (m, 1H), 6.37 (d, *J*=3.2 Hz, 1H), 7.02-7.05 (m, 1H), 7.27-7.28 (m, 2H), 7.44-7.45 (m, 1H), 8.00-8.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.05, 36.89, 51.77, 108.78, 110.18, 116.00, 121.48, 124.19, 126.04, 133.21, 141.41, 147.35, 147.73, 148.41, 161.70; Ms (ESI) *m/z*: 298 [M+H]; Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13; found C, 68.55; H, 6.51; N, 14.18.

2-(*tert*-butylamino)-3-((5-methylfuran-2-yl)methyl)quinazolin -4(*3H*)-one 4j: white solid, 130-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.55 (s, 9H), 2.29 (s, 3H), 5.18 (s, 2H), 5.30 (s, 1H), 5.96 (t, *J*=2.2 Hz, 1H), 6.35 (d, *J*=3.1 Hz, 1H), 7.16 (t, *J*=7.1 Hz, 1H), 7.38-7.40 (m, 1H), 7.54-7.58 (m, 1H), 8.11-8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.49, 28.09, 36.92, 51.78, 105.98, 109.75, 116.08, 121.39, 124.13, 126.04, 133.11, 146.57, 147.56, 147.72, 151.18, 161.65; Ms (ESI) *m/z*: 312 [M+H]; Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49; found C, 69.34; H, 6.72; N, 13.56.

2-(*tert*-butylamino)-3-p-tolylquinazolin-4(*3H*)-one 4k: white solid, 148-150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (s, 9H), 2.44 (s, 3H), 3.99 (s, 1H), 7.12-7.16 (m, 3H), 7.37 (d, *J*=8.0 Hz, 2H), 7.42 (d, *J*=8.0 Hz, 1H), 7.57-7.59 (m, 1H), 8.10-8.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.35, 28.04, 51.48, 116.58, 121.33, 124.15, 126.13, 127.51, 130.21, 131.41, 133.34, 138.84, 147.30, 148.22, 161.87; Ms (ESI) *m/z*: 308 [M+H]; Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67; found C, 74.12; H, 6.80; N, 13.76.

2-(*tert*-butylamino)-3-(4-chlorophenyl)quinazolin-4(*3H*)-one 4l: white solid, 170-172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 3.84 (s, 1H), 7.16 (t, *J*=1.0 Hz, 1H), 7.23-7.25 (m, 2H), 7.33 (d, *J*=8.0 Hz, 1H), 7.55-7.56 (m, 2H), 7.56- 7.60 (m, 1H), 8.09-8.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.03, 51.71, 116.38, 121.60, 124.30, 126.10, 129.36, 129.85, 132.69, 133.61, 134.85, 146.61, 148.17, 161.72; Ms (ESI) *m/z*: 328 [M+H]; Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82; found C, 65.82; H, 5.59; N, 12.75.

2-(*tert*-butylamino)-3-phenylquinazolin-4(*3H*)-one 4m: white solid, 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (s, 9H), 3.91 (s, 1H), 7.15 (t, *J*=1.0 Hz, 1H), 7.28-7.30 (m, 2H), 7.44 (d, *J*=8.0 Hz, 1H), 7.53-7.54 (m, 1H), 7.57-7.60 (m, 3H), 8.10-8.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.00, 51.51, 116.56, 121.41, 124.22, 126.12, 127.87, 128.75, 129.56, 133.44, 134.22, 147.08, 148.27, 161.81; Ms (ESI) *m/z*: 294 [M+H]; Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32; found C, 73.76; H, 6.59; N, 14.21.

3-benzyl-2-(2,4,4-trimethylpentan-2-ylamino)-quinazolin-4(*3H*)-one 4n: white solid, 124-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67 (s, 9H), 1.28 (s, 6H), 1.73 (s, 2H), 4.26 (s, 1H), 5.20 (s, 2H), 7.08 (t, *J*=7.0 Hz, 1H), 7.16-7.18 (m, 2H), 7.22 (d, *J*=7.0 Hz, 1H), 7.25-7.31 (m, 3H), 7.47-7.49 (m, 1H), 8.08-8.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.62, 30.29, 30.43, 44.05, 49.61, 55.43, 115.84, 121.39, 124.24, 125.88, 126.24, 127.36, 128.37, 133.23, 134.39, 147.26, 147.93, 162.33; Ms (ESI) *m/z*: 364 [M+H]; Anal. Calcd for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04; N, 11.56; found C, 76.19; H, 8.11; N, 11.49.

3-benzyl-2-(cyclohexylamino)quinazolin-4(*3H*)-one 4o: white solid, 144-146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00-1.06 (m, 2H), 1.13-1.18 (m, 1H), 1.32-1.39 (m, 2H), 1.48-1.54 (m, 3H), 1.83-1.86 (m, 2H), 3.96-3.98 (m, 1H), 4.35 (s, 1H), 5.34 (s, 2H), 7.20 (m, 1H), 7.27-7.39 (m, 6H), 7.58-7.60 (m, 1H), 8.19-8.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.20, 24.58, 31.52, 43.61, 48.74, 115.92, 121.43, 123.97, 125.62, 126.36, 127.26, 128.38, 133.35, 134.34, 148.45, 162.17; Ms (ESI) *m/z*: 334 [M+H]; Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; found C, 75.52; H, 6.87; N, 12.69.

3-benzyl-6-chloro-2-(2,4,4-trimethylpentan-2-ylamino) quinazolin-4(*3H*)-one 4p: white solid, 130-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.75 (s, 9H), 1.37 (s, 6H), 1.80 (s, 2H), 4.40 (s, 1H), 5.27 (s, 2H), 7.25-7.26 (m, 2H), 7.32-7.38 (m, 4H), 7.48-7.50 (m, 1H), 8.13-8.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.58, 30.26, 30.41, 44.20, 49.59, 55.56, 116.68, 125.40, 125.86, 126.55, 127.49, 128.43, 133.53, 134.04, 146.51, 147.41, 161.36; Ms (ESI) *m/z*: 398 [M+H]; Anal. Calcd for $C_{23}H_{28}ClN_3O$: C, 69.42; H, 7.09; N, 10.56; found C, 69.30; H, 7.18; N, 10.51.

3-benzyl-2-(*tert*-butylamino)-6-chloroquinazolin-4(*3H*)-one 4q: white solid, 152-154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (s, 9H), 4.38 (s. 1H), 5.28 (s, 2H), 7.24-7.25 (m, 2H), 7.30-7.38 (m, 4H), 7.48-7.50 (m, 1H), 8.13 (d, *J*=2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.78, 44.04, 51.75, 116.76, 125.41, 125.68, 125.94, 126.59, 127.41, 128.42, 133.52, 134.10, 146.64, 147.57, 161.34; Ms (ESI) *m/z*: 342 [M+H]; Anal. Calcd for $C_{19}H_{20}ClN_3O$: C, 66.76; H, 5.90; N, 12.29; found C, 66.88; H, 5.81; N, 12.23.

3-benzyl-6-chloro-2-(cyclohexylamino)quinazolin-4(*3H*)-one 4r: white solid, 174-176 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00-1.06 (m, 2H), 1.14-1.18 (m, 1H), 1.31-1.38 (m, 2H), 1.47-1.55 (m, 3H), 1.81-1.84 (m, 2H), 3.93-3.94 (m, 1H), 4.39 (s, 1H), 5.31 (s, 2H), 7.26-7.27 (m, 2H), 7.30-7.39 (m, 4H), 7.50-7.52 (m, 1H), 8.14 (d, *J*=2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.17, 24.52, 31.48, 43.78, 48.89, 116.72, 125.59, 126.63, 127.42, 128.46, 133.67, 133.96, 147.02, 148.25, 161.17; Ms (ESI) *m/z*: 368 [M+H]; Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42; found C, 68.68; H, 6.09; N, 11.31.

3-benzyl-2-(*tert*-butylamino)-6-fluoroquinazolin-4(*3H*)-one 4s: white solid, 130-132°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (s, 9H), 4.32 (s, 1H), 5.30 (s, 2H), 7.26 -7.27(m, 1H), 7.32-7.39 (m, 6H), 7.81-7.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.79, 44.06, 51.61, 110.56, 110.75, 116.41, 121.66, 121.85, 125.69, 126.21, 126.27, 127.35, 128.38, 134.22, 144.70, 146.97, 156.36, 158.29, 161.65; Ms (ESI) *m/z*: 326 [M+H]; Anal. Calcd for $C_{19}H_{20}FN_3O$: C, 70.13; H, 6.20; N, 12.91; found C, 70.23; H, 6.15; N, 12.84.

3-benzyl-2-(*tert*-butylamino)-6-methylquinazolin-4(*3H*)-one 4t: white solid, 152-154°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (s, 9H), 2.42 (s, 3H), 4.26 (s, 1H), 5.30 (s, 2H), 7.25-7.27 (m, 2H), 7.29-7.43 (m, 5H), 7.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.95, 28.79, 44.83, 52.46, 116.55, 125.08, 126.50, 126.65, 128.16, 129.25, 132.07, 135.53, 135.69, 146.88, 147.93, 163.25; Ms (ESI) *m/z*: 322 [M+H]; Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07; found C, 74.63; H, 7.15; N, 13.14.

General procedure for the synthesis of 2-unsubstituted-amino-4(*3H*)-quinazolinones 4u: The solution of 2-(*tert*-butylamino)-3-(4-methylbenzyl)quinazolin-4(*3H*)-one **4b** (0.30 mmol) in TFA (4 mL) was stirred under reflux in a sealed tube overnight. Subsequently, the mixture was basified with aq. NaOH (3 M). The product was extracted with EtOAc and dried (Na_2SO_4), which was then purified by column chromatography to give 2-unsubstituted-amino-4(*3H*)-quinazolinones **4u**.

2-amino-3-(4-methylbenzyl)quinazolin-4(*3H*)-one 4u: white solid, 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 5.33 (s, 2H), 7.16-7.20 (m, 4H), 7.26-7.29 (m, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.64 (t, *J*=7.0 Hz, 1H), 8.21 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.08, 44.26, 116.32, 122.42, 123.11, 125.64, 126.56, 129.12, 130.79, 133.71, 137.27, 147.30, 150.45, 161.61; Ms (ESI) *m/z*: 266 [M+H]; Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84; found C, 72.56; H, 5.62; N, 15.71.

General procedure for the synthesis of 2-amino-3-hydroxyquinazolin-4(*3H*)-ones 4w: To a solution of isatoic anhydride (0.50 mmol) in toluene (4 mL) was added *O*-phenylhydroxylamine (0.50 mmol). The mixture was stirred at 100 °C in a sealed tube for 4 h. Upon the completion of the reaction, *tert*-butylisocyanide (0.75 mmol), $Pd(OAc)_2$ (2 mol%) and Ag_2CO_3 (1.00 mmol) was successively added and the mixture was stirred at 100 °C for another 24 h. The product was then concentrated under vacuum and the resulting residue was purified by column chromatography to give 3-(benzyloxy)-2-(*tert*-butylamino)quinazolin-4(*3H*)-one **4v**. Secondly, Pd/C 10% was added to the solution of **4v** in ethanol (4 mL) and the mixture was hydrogenated at the room temperature at 40 psi for 6 h. After that, the reaction mixture was passed through Celite, followed by evaporation to afford the crude product, which was purified by column chromatography to yield 2-(*tert*-butylamino)-3-hydroxyquinazolin-4(*3H*)-one **4w**.

3-(benzyloxy)-2-(*tert*-butylamino)quinazolin-4(*3H*)-one 4v: white solid, 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (s, 9H), 5.19 (s, 1H), 5.26 (s, 2H), 7.16 (t, *J*=7.0 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.41-7.44 (m, 5H), 7.55 (t, *J*=7.0 Hz, 1H), 8.12-8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.65, 50.82, 77.45, 117.63, 121.18, 124.33, 125.63, 128.12, 128.79, 129.29, 132.81, 133.16, 145.50, 147.04, 157.58; Ms (ESI) *m/z*: 324 [M+H]; Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99; found C, 70.63; H, 6.67; N, 12.91.

2-(*tert*-butylamino)-3-hydroxyquinazolin-4(*3H*)-one 4w: white solid, 174-176 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 9H), 5.80 (s, 1H), 7.11-7.14 (m, 1H), 7.39 (d, *J*=8.2 Hz, 1H), 7.55-7.58 (m, 1H), 8.03-8.05 (m, 1H), 11.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.12, 50.96, 115.61, 121.27, 123.68, 125.15, 133.68, 148.21, 164.44; Ms (ESI) *m/z*: 234 [M+H]; Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01; found C, 61.86; H, 6.39; N, 18.07.

Crystallographic data for the product **4j** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 966928. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk /data_request/cif.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra (**4a-4u**). Crystallographic data for **4j:** CCDC 966928. See DOI: 10.1039/b000000x/

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