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Copper(I)-catalyzed synthesis of 1-arylpyrazolo[5,1-*b*]quinazolin-9(1*H*)-one via intramolecular alkyne hydroamination

Dong-Sheng Chen, Mei-Mei Zhang, Yu-Ling Li, Yun Liu, Xiang-Shan Wang *

School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthesis for Functional Materials, Jiangsu Normal University, Xuzhou, Jiangsu 221116, PR China

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ABSTRACT

The 1-arylpyrazolo[5,1-*b*]quinazolin-9(1*H*)-one derivatives were obtained via intramolecular alkyne hydroamination reaction of 2-amino-*N*′-arylbenzohydrazide and alkynal diethyl acetal in the presence of CuBr and Cs_2CO_3. This new procedure provides an efficient method to construct fused tricyclic heterocycle containing both pyrazole and quinazoline analogues.

1. Introduction

Pyrazoloquinazolines are important tricyclic heterocycles containing both pyrazole and quinazoline moieties and widely occurred in biologically active molecules. They are well known structures to be used to inhibit nerve growth factors[1] or serve as kinase inhibitors, such as selective MPS1 kinase inhibitors,[2] phosphodiesterase 10A inhibitors,[3] selective polo-like kinase 1 inhibitors,[4] and multi-cyclin-dependent kinase inhibitors.[5] In addition, they are also used as novel excitatory amino acid antagonists[6] and adenosine receptor antagonists recently.[7] As a consequence, great effort has been devoted to access pyrazoloquinazoline and its derivatives.[8] However, simple, mild, versatile one-pot preparation of this class compounds is still highly desirable.

Cu(I) was an efficient and inexpensive catalyst for the coupling reactions of C–N bond.[9] We previously reported that CuBr could catalyze Ullmann-type reaction of 2-amino-*N*′-arylbenzohydrazide and *o*-halogenated benzaldehyde to construct 5-arylindazolo[3,2-*b*]quinazolin-7(5*H*)-ones in high yields.[10] In addition, Cu(I) could also promote the alkyne hydroamination reaction between amine and alkyne to form C_{sp^2}–N bond under mild conditions.[11] Therefore, we tested the reaction of 2-amino-*N*′-arylbenzohydrazide and alkynal diethyl acetal and found that the designed reaction proceeded in the presence of CuBr and Cs_2CO_3 to give 1-arylpyrazolo[5,1-*b*]quinazolin-9(1*H*)-one derivatives in high yields. Herein, we report the synthesis of 1-arylpyrazolo[5,1-*b*]quinazolin-9(1*H*)-ones via CuBr/Cs_2CO_3 catalyzed intramolecular alkyne hydroamination reaction.

2. Results and discussion

The reaction of 2-amino-*N*′-phenylbenzohydrazide **1a** with 3-phenylpropynal diethyl acetal **2a** was used as a model reaction to optimize reaction conditions (Scheme 1), and the results are summarized in Table 1. Initially, the reaction in toluene in the presence of CuCl (5 mol %), K_2CO_3 (2 equiv) could afford the desired product **3a** in 72% yield. Further investigation of various catalysts, CuBr was found to be more effective than other Cu(I) species, and the reaction yield increased to 82% when CuBr was employed (entries 1–3). Several bases such as Na_2CO_3, $NaHCO_3$, Et_3N, and Cs_2CO_3 were examined, and Cs_2CO_3 was found to give the best result (entries 4–7). Subsequently, different solvents including THF, CH_3CN, DMF, benzene, and dioxane were also evaluated and an 89% yield was obtained when dioxane was used as solvent (entry 11). In addition, lower yields were observed if the loading of catalyst reduced to 1 mol % (entries 13 and 14).

With these optimized conditions in hand, we surveyed the substrate scope of 2-amino-*N*′-phenylbenzohydrazides and alkynal diethyl acetals (Table 2, Scheme 2). Initially, 3-phenylpropynal diethyl acetal **2a** and different 2-amino-*N*′-phenylbenzohydrazides were investigated under standard conditions, and both electron-rich and electron-poor 2-amino-*N*′-phenylbenzohydrazides could afford the corresponding products in high

* Corresponding author. Fax: +86 516 83500065; e-mail address: xswang1974@yahoo.com (X.-S. Wang).

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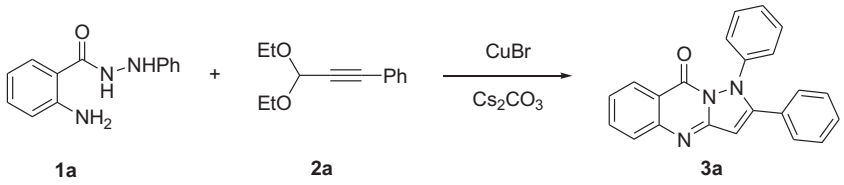


1a 2a 3a

Scheme 1. The model reaction.

Table 1
Synthesis of **3a** under different reaction conditions[a]

Entry	Cat. (mol %)	Solvent	Base	Yields[b]/%
1	CuCl (5)	Toluene[c]	K_2CO_3	72
2	CuBr (5)	Toluene[c]	K_2CO_3	82
3	CuI (5)	Toluene[c]	K_2CO_3	78
4	CuBr (5)	Toluene[c]	Na_2CO_3	75
5	CuBr (5)	Toluene[c]	$NaHCO_3$[d]	68
6	CuBr (5)	Toluene[c]	Et_3N	70
7	CuBr (5)	Toluene[c]	Cs_2CO_3	84
8	CuBr (5)	CH_3CN	Cs_2CO_3	58
9	CuBr (5)	THF	Cs_2CO_3	68
10	CuBr (5)	DMF[c]	Cs_2CO_3	85
11	CuBr (5)	Dioxane	Cs_2CO_3	89
12	CuBr (5)	Benzene	Cs_2CO_3	62
13	CuBr (1)	Dioxane	Cs_2CO_3	75
14	CuBr (10)	Dioxane	Cs_2CO_3	89

[a] Reagents and conditions: **1a** (0.227 g, 1.0 mmol), **2a** (0.205 g, 1.0 mmol), solvent (10 mL), base (2.0 mmol), reflux.
[b] Isolated yields.
[c] 100 °C.
[d] $NaHCO_3$: 4 mmol.

Table 2
The synthetic results for the products **3**[a]

Entry	Ar	R	R′	Products	Time/h	Yields[b]/%
1	Ph	Ph	H	**3a**	6	89
2	4-ClC_6H_4	Ph	H	**3b**	6	92
3	4-$CH_3C_6H_4$	Ph	H	**3c**	8	86
4	Ph	Ph	7-CH_3	**3d**	5	90
5	4-$CH_3C_6H_4$	Ph	7-CH_3	**3e**	6	85
6	Ph	Ph	7-Br	**3f**	8	86
7	4-ClC_6H_4	Ph	7-Br	**3g**	6	90
8	4-$CH_3C_6H_4$	Ph	7-Br	**3h**	6	89
9	Ph	Ph	7-Cl	**3i**	8	84
10	Ph	Ph	6-Cl	**3j**	6	90
11	4-$CH_3C_6H_4$	Ph	6-Cl	**3k**	6	91
12	4-ClC_6H_4	Ph	6-Cl	**3l**	5	88
13	Ph	Ph	5,6-$(CH_3)_2$	**3m**	8	85
14	Ph	CH_3	7-Cl	**3n**	10	86
15	4-ClC_6H_4	CH_3	7-Br	**3o**	8	89
16	Ph	CH_3	6-Cl	**3p**	8	84
17	4-ClC_6H_4	CH_3	6-Cl	**3q**	8	90
18	4-ClC_6H_4	H	7-Br	**3r**	6	82

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.0 mmol), CuBr (7 mg, 0.05 mmol), Cs_2CO_3 (652 mg, 2 mmol), dioxane (10 mL), reflux.
[b] Isolated yields.

yields (Table 2, entries 1–13). Subsequently, 2-butynal diethyl acetal and propargylaldehyde diethyl acetal were tested and were able to give pyrazolo[5,1-*b*]quinazolin-9(1*H*)-one under the standard conditions. All the products of **3** were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS, and the data were in good agreement with the preconceived structures. Among these structures, the structure of **3d** was confirmed by X-ray diffraction analysis as shown in Fig. 1.

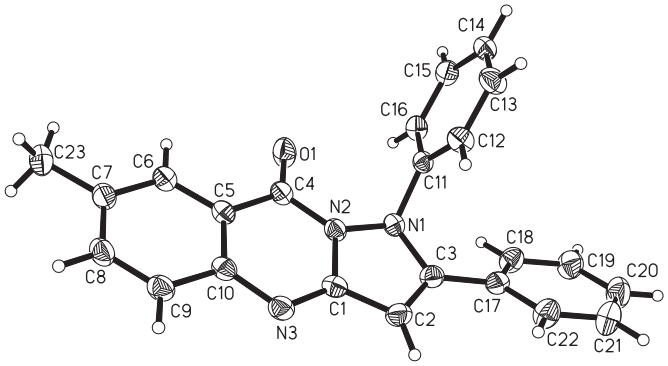


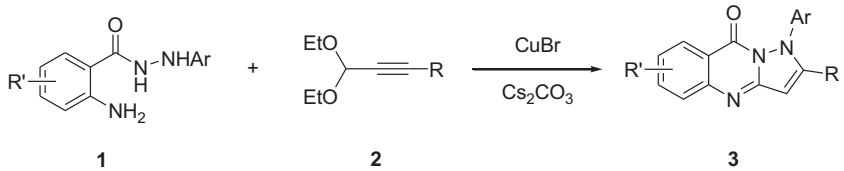
Fig. 1. The crystal structure of **3d**.

We propose that three subsequent steps are involved in the formation of **3**, namely cyclization to dihydroquinazolinone **4** catalyzed CuBr, aromatization to quinazolinone by air, and alkyne hydroamination reaction in the presence of CuBr and Cs_2CO_3. The key step is the alkyne hydroamination, which has been reported in several references.[11] The plausible reaction mechanism is outlined in Scheme 3.

In order to get more insight to the mechanism, the model reaction of **1a** and **2a** was treated with CuBr in the absence of Cs_2CO_3 and the reaction was end up to form the compound of **4** in 90% at room temperature, which also supported the proposed three step mechanism (Scheme 4).

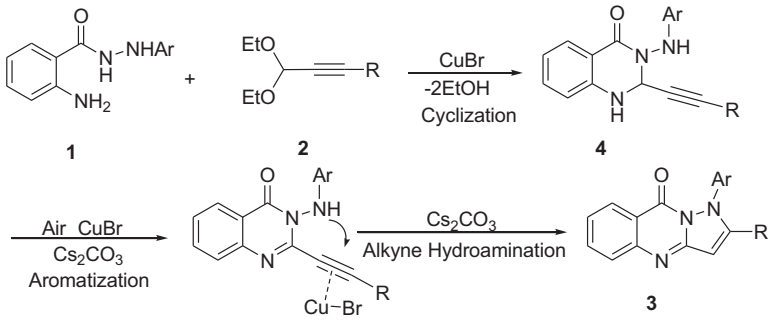
3. Conclusion

In conclusion, we report a novel and efficient method for the synthesis of 1-arylpyrazolo[5,1-*b*]quinazolin-9(1*H*)-one derivatives using 5 mol % CuBr as catalyst. The method employs readily available reactant, inexpensive catalyst and affords the tricyclic heterocycles in high yields.

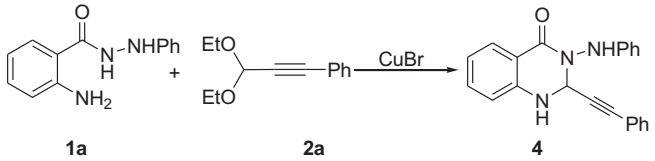


1 2 3

Scheme 2. The reaction of **1** and **2**.



Scheme 3. The plausible reaction mechanism.



Scheme 4. The model reaction in the absence of Cs_2CO_3.

4. Experimental section

4.1. General

The 2-amino-*N*′-arylbenzohydrazides were prepared according to Ref. 12.

4.2. General procedure for the syntheses of 1-aryl pyrazolo [5,1-*b*]quinazolin-9(1*H*)-one derivatives 3

2-Amino-*N*′-arylbenzohydrazide (1.0 mmol), alkynal diethyl acetal (1.0 mmol), CuBr (7 mg, 0.05 mmol), Cs_2CO_3 (652 mg), and dioxane (10 mL) were added into a dry flask (25 mL). The reaction mixture was stirred under reflux for 5–10 h before completion, which was monitored by TLC. The solid was removed by a hot and immediate filtration. The filtrate was allowed to cool down to room temperature, and the product **3** was precipitated as solid and obtained by filtration.

*4.2.1. 1,2-Diphenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3a**).* Yield 89% (300 mg). Pale yellow solid, mp: 257–258 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.23 (d, *J*=8.0 Hz, 1H), 7.76–7.73 (m, 2H), 7.57–7.55 (m, 2H), 7.41–7.35 (m, 5H), 7.34–7.30 (m, 4H), 6.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.8, 156.5, 152.1, 149.7, 140.1, 133.9, 130.7, 129.6, 129.0, 128.9, 128.8, 128.0, 126.5, 126.3, 124.1, 118.0, 102.0. IR (KBr): ν 3065, 1679, 1614, 1589, 1548, 1489, 1463, 1360, 1321, 1255, 1228, 1201, 1179, 1100, 1064, 1025, 964, 914, 809, 773, 760, 690 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{22}H_{16}N_3O$ $[M+H]^+$ 338.1293, found 338.1291.

*4.2.2. 1-(4-Chlorophenyl)-2-phenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3b**).* Yield 92% (342 mg). Pale yellow solid, mp: 220–221 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.23 (d, *J*=8.0 Hz, 1H), 7.78–7.72 (m, 2H), 7.56–7.54 (m, 2H), 7.43–7.38 (m, 3H), 7.37–7.33 (m, 3H), 7.27 (d, *J*=8.0 Hz, 2H), 6.66 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.7, 156.5, 151.9, 149.6, 138.7, 135.4, 134.1, 130.9, 129.3, 129.2, 129.0, 128.9, 127.7, 126.44, 126.42, 124.4, 118.0, 102.4. IR (KBr): ν 3031, 1681, 1616, 1589, 1550, 1485, 1467, 1362, 1325, 1257, 1229, 1202, 1180, 1097, 1063, 1017, 967, 922, 838, 803, 774, 760, 690 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{22}H_{15}N_3OCl$ $[M+H]^+$ 372.0904, found 372.0905.

*4.2.3. 2-Phenyl-1-(p-tolyl)pyrazolo[5,1-b]quinazolin-9(1H)-one (**3c**).* Yield 86% (302 mg). Pale yellow solid, mp: 273–274 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.24 (d, *J*=8.0 Hz, 1H), 7.76–7.72 (m, 2H), 7.58–7.56 (m, 2H), 7.37–7.31 (m, 4H), 7.27 (d, *J*=8.4 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 2H), 6.63 (s, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.7, 156.6, 152.0, 149.6, 139.7, 137.4, 133.9, 130.6, 129.5, 129.0, 128.8, 128.1, 127.8, 126.5, 126.3, 124.0, 118.0, 101.7, 21.3. IR (KBr): ν 3030, 1681, 1616, 1588, 1548, 1505, 1466, 1363, 1326, 1258, 1229, 1201, 1180, 1063, 1021, 966, 923, 879, 804, 778, 757, 690 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{23}H_{18}N_3O$ $[M+H]^+$ 352.1450, found 352.1450.

*4.2.4. 7-Methyl-1,2-diphenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3d**).* Yield 90% (316 mg). Pale yellow solid, mp: 238–239 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.94 (s, 1H), 7.59 (d, *J*=8.4 Hz, 1H), 7.50–7.48 (m, 3H), 7.33–7.27 (m, 4H), 7.25–7.22 (m, 3H), 7.19 (s, 1H), 6.56 (s, 1H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 157.5, 155.4, 150.5, 146.6, 139.3, 134.6, 133.1, 129.6, 128.4, 127.9, 127.8, 127.7, 127.1, 126.9, 125.1, 124.6, 116.8, 101.1, 20.2. IR (KBr): ν 3057, 1683, 1584, 1542, 1483, 1445, 1342, 1318, 1260, 1212, 1116, 1077, 1026, 830, 807, 776, 760, 689 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{23}H_{18}N_3O$ $[M+H]^+$ 352.1450, found 352.1452.

*4.2.5. 7-Methyl-2-Phenyl-1-(p-tolyl)pyrazolo[5,1-b]quinazolin-9(1H)-one (**3e**).* Yield 85% (310 mg). Pale yellow solid, mp: 272–273 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.02 (s, 1H), 7.63 (d, *J*=8.4 Hz, 1H), 7.58–7.54 (m, 3H), 7.37–7.33 (m, 3H), 7.26 (d, *J*=8.0 Hz, 2H), 7.08 (d, *J*=8.0 Hz, 2H), 6.62 (s, 1H), 2.44 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.5, 156.5, 151.5, 147.7, 139.5, 137.6, 135.6, 134.0, 130.5, 129.5, 129.0, 128.8, 128.2, 127.7, 126.1, 125.7, 117.8, 101.8, 21.244, 21.236. IR (KBr): ν 3012, 1678, 1624, 1595, 1506, 1484, 1448, 1358, 1308, 1258, 1209, 1121, 1109, 1061, 1020, 837, 801, 758, 719, 692 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{24}H_{20}N_3O$ $[M+H]^+$ 366.1606, found 366.1607.

*4.2.6. 7-Bromo-1,2-diphenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3f**).* Yield 86% (358 mg). Pale yellow solid, mp: 259–260 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.26 (d, *J*=1.6 Hz, 1H), 7.72–7.69 (m, 1H), 7.52 (d, *J*=8.8 Hz, 1H), 7.48 (d, *J*=8.0 Hz, 2H), 7.32–7.27 (m, 5H), 7.25–7.19 (m, 3H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 157.9, 154.3, 151.2, 147.4, 138.7, 136.0, 129.8, 128.7, 128.0, 127.91, 127.86, 127.8, 127.1, 127.0, 126.8, 118.2, 115.9, 100.7. IR (KBr): ν 3051, 1674, 1606, 1585, 1537, 1489, 1461, 1367, 1334, 1309, 1246, 1211, 1120, 1068, 1027, 981, 819, 802, 763, 694 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{22}H_{15}N_3OBr$ $[M+H]^+$ 416.0398, found 416.0373.

*4.2.7. 7-Bromo-1-(4-chlorophenyl)-2-phenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3g**).* Yield 90% (405 mg). Pale yellow solid, mp:

217–218 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.33 (d, J=1.2 Hz, 1H), 7.79 (dd, J=8.8 Hz, J'=1.2 Hz, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.54 (d, J=8.0 Hz, 2H), 7.44–7.37 (m, 3H), 7.34–7.29 (m, 4H), 6.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.9, 155.3, 152.0, 148.4, 138.3, 137.2, 135.6, 131.0, 129.4, 129.2, 129.0, 128.9, 128.8, 128.2, 127.5, 119.2, 117.2, 102.2. IR (KBr): ν 3055, 1683, 1609, 1588, 1541, 1487, 1461, 1402, 1355, 1261, 1226, 1088, 1015, 821, 807, 767, 692 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{22}H_{14}N_3OBrCl$ $[M+H]^+$ 450.0009, found 449.9995.

*4.2.8. 7-Bromo-2-phenyl-1-(p-tolyl)pyrazolo[5,1-b]quinazolin-9(1H)-one (**3h**).* Yield 89% (383 mg). Pale yellow solid, mp: 240–241 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.34 (s, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 7.55 (d, J=7.6 Hz, 2H), 7.41–7.35 (m, 3H), 7.25 (d, J=7.2 Hz, 2H), 7.10 (d, J=8.0 Hz, 2H), 6.62 (s, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.9, 155.3, 152.2, 148.5, 139.9, 137.00, 136.96, 130.7, 129.6, 129.0, 128.9, 128.8, 128.1, 127.9, 127.8, 119.2, 116.8, 101.5, 21.3. IR (KBr): ν 3060, 3033, 1686, 1610, 1584, 1539, 1506, 1461, 1447, 1360, 1322, 1306, 1243, 1208, 1132, 1117, 1060, 1020, 976, 900, 835, 758, 691 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{23}H_{17}N_3OBr$ $[M+H]^+$ 430.0550, found 430.0538.

*4.2.9. 7-Chloro-1,2-diphenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3i**).* Yield 84% (312 mg). Pale yellow solid, mp: 237–238 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.17 (s, 1H), 7.68–7.63 (m, 2H), 7.55 (d, J=7.6 Hz, 2H), 7.38–7.35 (m, 5H), 7.32–7.31 (m, 3H), 6.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.9, 155.4, 152.1, 148.2, 139.8, 134.4, 130.8, 129.7, 129.4, 129.0, 128.9, 128.8, 128.03, 127.98, 127.8, 125.6, 118.8, 101.7. IR (KBr): ν 3060, 1675, 1611, 1583, 1540, 1490, 1465, 1448, 1365, 1337, 1309, 1248, 1211, 1174, 1132, 1065, 1027, 831, 764, 694 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{22}H_{15}N_3OCl$ $[M+H]^+$ 372.0904, found 372.0903.

*4.2.10. 6-Chloro-1,2-diphenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3j**).* Yield 90% (334 mg). Pale yellow solid, mp: 246–247 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.13 (d, J=8.8 Hz, 1H), 7.70 (s, 1H), 7.54 (d, J=7.6 Hz, 2H), 7.40–7.35 (m, 5H), 7.33–7.31 (m, 3H), 7.26 (d, J=7.6 Hz, 1H), 6.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.9, 156.0, 152.8, 150.6, 140.1, 139.7, 130.8, 129.7, 129.0, 128.9, 128.8, 128.1, 128.0, 127.8, 125.6, 124.7, 116.3, 101.7. IR (KBr): ν 3074, 1692, 1582, 1539, 1489, 1453, 1432, 1362, 1338, 1282, 1249, 1211, 1158, 1108, 1067, 1025, 969, 920, 876, 812, 760, 691 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{22}H_{15}N_3OCl$ $[M+H]^+$ 372.0904, found 372.0892.

*4.2.11. 6-Chloro-2-Phenyl-1-(p-tolyl)pyrazolo[5,1-b]quinazolin-9(1H)-one (**3k**).* Yield 91% (351 mg). Pale yellow solid, mp: 253–254 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.14 (d, J=8.8 Hz, 1H), 7.69 (d, J=2.0 Hz, 1H), 7.56–7.53 (m, 2H), 7.41–7.34 (m, 3H), 7.27–7.24 (m, 3H), 7.10 (d, J=8.0 Hz, 2H), 6.62 (s, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.9, 156.0, 152.7, 150.6, 140.0, 139.7, 137.0, 130.7, 129.6, 129.0, 128.8, 128.0, 127.9, 125.5, 124.5, 116.3, 101.4, 21.6. IR (KBr): ν 3032, 1683, 1605, 1579, 1538, 1506, 1455, 1433, 1364, 1338, 1283, 1230, 1212, 1108, 1076, 1064, 918, 807, 768, 759, 692 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{23}H_{17}N_3OCl$ $[M+H]^+$ 386.1060, found 386.1060.

*4.2.12. 6-Chloro-1-(4-chlorophenyl)-2-phenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3l**).* Yield 88% (357 mg). Pale yellow solid, mp: 260–261 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.13 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.53 (d, J=7.2 Hz, 2H), 7.42–7.37 (m, 3H), 7.33 (d, J=8.8 Hz, 2H), 7.29–7.27 (m, 3H), 6.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.9, 156.0, 152.6, 150.5, 140.2, 138.3, 135.6, 131.0, 129.4, 129.2, 129.01, 128.95, 127.9, 127.5, 125.7, 124.9, 116.3, 102.2. IR (KBr): ν 3084, 1682, 1609, 1585, 1540, 1489, 1455, 1433, 1358, 1339, 1254, 1211, 1088, 1066, 1017, 972, 919, 868, 804, 761, 744, 692 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{22}H_{14}N_3OCl_2$ $[M+H]^+$ 406.0514, found 406.0506.

*4.2.13. 5,6-Dimethyl-1,2-diphenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3m**).* Yield 85% (310 mg). Pale yellow solid, mp: 152–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.01 (d, J=8.4 Hz, 1H), 7.57–7.54 (m, 2H), 7.39–7.33 (m, 5H), 7.30–7.25 (m, 3H), 7.16 (d, J=8.4 Hz, 1H), 6.70 (s, 1H), 2.64 (s, 3H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 158.4, 156.9, 151.1, 148.3, 142.3, 140.5, 132.2, 130.5, 129.4, 128.9, 128.8, 128.7, 128.3, 128.0, 126.6, 123.3, 116.1, 102.6, 21.0, 13.5. IR (KBr): ν 3107, 3056, 2913, 1672, 1591, 1556, 1487, 1448, 1412, 1361, 1291, 1217, 1135, 1071, 1027, 980, 948, 814, 775, 761, 689 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{24}H_{20}N_3O$ $[M+H]^+$ 366.1606, found 366.1605.

*4.2.14. 7-Chloro-2-Methyl-1-phenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3n**).* Yield 86% (266 mg). Pale yellow solid, mp: 188–189 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.14 (s, 1H), 7.63–7.62 (m, 2H), 7.52–7.47 (m, 3H), 7.30–7.25 (m, 2H), 6.24 (s, 1H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 155.0, 154.2, 151.8, 148.2, 138.0, 134.3, 129.5, 129.3, 128.8, 127.9, 125.9, 125.5, 117.9, 99.9, 13.1. IR (KBr): ν 3061, 3013, 1693, 1614, 1591, 1542, 1488, 1468, 1422, 1383, 1357, 1330, 1299, 1252, 1215, 1174, 1138, 1113, 1071, 1029, 993, 890, 828, 788, 767, 695 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{17}H_{13}N_3OCl$ $[M+H]^+$ 310.0747, found 310.0748.

*4.2.15. 7-Bromo-1-(4-chlorophenyl)-2-methylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3o**).* Yield 89% (345 mg). Pale yellow solid, mp: 215–216 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.30–8.28 (m, 1H), 7.78–7.75 (m, 1H), 7.57–7.54 (m, 1H), 7.45 (dd, J=8.4 Hz, J'=1.2 Hz, 2H), 7.23–7.20 (m, 2H), 6.25 (s, 1H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 154.9, 154.1, 151.7, 148.4, 137.0, 136.5, 135.5, 129.6, 128.7, 128.1, 127.2, 118.3, 116.5, 100.5, 13.0. IR (KBr): ν 3060, 1672, 1608, 1591, 1538, 1489, 1463, 1385, 1358, 1335, 1305, 1278, 1218, 1174, 1133, 1089, 1016, 970, 882, 832, 817, 777, 740, 690 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{17}H_{12}N_3OBrCl$ $[M+H]^+$ 387.9852, found 387.9852.

*4.2.16. 6-Chloro-2-Methyl-1-phenylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3p**).* Yield 84% (260 mg). Pale yellow solid, mp: 212–213 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.10 (d, J=8.8 Hz, 1H), 7.67 (d, J=2.0 Hz, 1H), 7.52–7.46 (m, 3H), 7.29–7.27 (m, 2H), 7.23 (dd, J=8.8 Hz, J'=2.0 Hz, 1H), 6.24 (s, 1H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 155.5, 154.2, 152.4, 150.6, 139.9, 138.0, 129.5, 129.3, 127.9, 126.0, 125.4, 124.1, 115.4, 99.8, 13.0. IR (KBr): ν 3072, 3033, 1690, 1581, 1537, 1488, 1455, 1433, 1354, 1336, 1275, 1216, 1185, 1099, 1070, 996, 918, 871, 829, 768, 692 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{17}H_{13}N_3OCl$ $[M+H]^+$ 310.0747, found 310.0748.

*4.2.17. 6-Chloro-1-(4-chlorophenyl)-2-methylpyrazolo[5,1-b]quinazolin-9(1H)-one (**3q**).* Yield 90% (309 mg). Pale yellow solid, mp: 202–203 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.10 (d, J=8.8 Hz, 1H), 7.67 (d, J=2.0 Hz, 1H), 7.48–7.46 (m, 1H), 7.45–7.44 (m, 1H), 7.26–7.23 (m, 2H), 7.22–7.21 (m, 1H), 6.25 (s, 1H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 155.5, 154.1, 152.3, 150.5, 140.1, 136.5, 135.5, 129.6, 127.8, 127.3, 125.5, 124.4, 115.4, 100.4, 13.0. IR (KBr): ν 3082, 1677, 1636, 1595, 1538, 1483, 1456, 1434, 1388, 1355, 1280, 1221, 1087, 1073, 1012, 992, 922, 870, 844, 810, 768, 684 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{17}H_{12}N_3OCl_2$ $[M+H]^+$ 344.0357, found 344.0356.

*4.2.18. 7-Bromo-1-(4-chlorophenyl)pyrazolo[5,1-b]quinazolin-9(1H)-one (**3r**).* Yield 82% (307 mg). Pale yellow solid, mp: 223–224 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.55 (s, 1H), 8.54 (s, 1H), 8.29 (d, J=2.4 Hz, 1H), 8.12–8.09 (m, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 159.0, 150.9, 147.1, 146.6, 138.1, 130.5, 129.5, 129.4, 128.8, 124.8, 124.5, 120.4, 115.2, 114.7. IR (KBr): ν 3034, 1698, 1672, 1607, 1578, 1541, 1488, 1463, 1300, 1251, 1212, 1176, 1090, 1016, 827, 819, 766,

692 cm^{-1}. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{16}H_8N_3OBrCl$ $[M-H]^-$ 371.9539, found 371.9538.

4.3. Syntheses of 3-(phenylamino)-2-(phenylethynyl)-2,3-dihydroquinazolin-4(1*H*)-one 4

2-Amino-*N*′-phenylbenzohydrazide **1a** (227 mg, 1.0 mmol), 3-phenylpropynal diethyl acetal (204 mg, 1.0 mmol), CuBr (7 mg, 0.05 mmol), and dioxane (10 mL) was added into a dry flask (25 mL). The reaction mixture was stirred at room temperature for 3 h and the product **4** was obtained by filtration.

*4.3.1. 3-(Phenylamino)-2-(phenylethynyl)-2,3-dihydroquinazolin-4(1H)-one (**4**).* Yield 90% (305 mg). Pale yellow solid, mp: 154–155 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.99 (dd, J=8.0 Hz, J'=1.6 Hz, 1H), 7.43–7.38 (m, 1H), 7.33–7.29 (m, 3H), 7.28–7.23 (m, 4H), 7.03 (d, J=7.6 Hz, 2H), 6.98–6.92 (m, 2H), 6.81 (d, J=8.0 Hz, 1H), 6.74 (s, 1H), 5.76 (d, J=2.8 Hz, 1H), 4.81 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 164.3, 146.6, 145.5, 134.2, 132.0, 129.3, 129.0, 128.9, 128.3, 121.7, 121.3, 120.3, 115.42, 115.39, 113.9, 85.3, 84.1, 64.8. HRMS (TOF, ESI, *m*/*z*): calcd for $C_{22}H_{17}N_3ONa$ $[M+Na]^+$ 362.1269, found 362.1267.

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References and notes

1. (a) Rewcastle, G. W.; Palmer, B. D.; Bridges, A. J.; Showalter, H. D. H.; Sun, L.; Nelson, J.; McMichael, A.; Kraker, A. J.; Fry, D. W.; A Denny, W. *J. Med. Chem.* **1996**, *39*, 918–928; (b) Palmer, B. D.; Trumpp-Kallmeyer, S.; Fry, D. W.; Nelson, J. M.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 1519–1529; (c) Eibl, J. K.; Strasser, B. C.; Ross, G. M. *Eur. J. Pharmacol.* **2013**, *708*, 30–37; (d) Mount, H. T. J.; Elkabes, S.; Dreyfus, C. F.; Black, I. B. *J. Neurochem.* **1998**, *70*, 1045–1053; (e) Spiegel, K.; Agrafiotis, D.; Caprathe, B.; Davis, R. E.; Dickerson, M. R.; Fergus, J. H.; Hepburn, T. W.; Marks, J. S.; Vandorf, M.; Wieland, D. M.; Jaen, J. C. *Biochem. Biophys. Res. Commun.* **1995**, *217*, 488–494.
2. Caldarelli, M.; Angiolini, M.; Disingrini, T.; Donati, D.; Guanci, M.; Nuvoloni, S.; Posteri, H.; Quartieri, F.; Silvagni, M.; Colombo, R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4507–4511.
3. Asproni, B.; Murineddu, G.; Pau, A.; Pinna, G. A.; Langgard, M.; Christoffersen, C. T.; Nielsen, J.; Kehler, J. *Bioorg. Med. Chem.* **2011**, *19*, 642–649.
4. Beria, I.; Ballinari, D.; Bertrand, J. A.; Borghi, D.; Bossi, R. T.; Brasca, M. G.; Cappella, P.; Caruso, M.; Ceccarelli, W.; Ciavolella, A.; Cristiani, C.; Croci, V.; Ponti, A. D.; Fachin, G.; Ferguson, R. D.; Lansen, J.; Moll, J. K.; Pesenti, E.; Posteri, H.; Perego, R.; Rocchetti, M.; Storici, P.; Volpi, D.; Valsasina, B. *J. Med. Chem.* **2010**, *53*, 3532–3551.
5. Traquandi, G.; Ciomei, M.; Ballinari, D.; Casale, E.; Colombo, N.; Croci, V.; Fiorentini, F.; Isacchi, A.; Longo, A.; Mercurio, C.; Panzeri, A.; Pastori, W.; Pevarello, P.; Volpi, D.; Roussel, P.; Vulpetti, A.; Brasca, M. G. *J. Med. Chem.* **2010**, *53*, 2171–2187.
6. Varano, F.; Catarzi, D.; Colotta, V.; Filacchioni, G.; Galli, A.; Costagli, C.; Carla, V. *J. Med. Chem.* **2002**, *45*, 1035–1044.
7. Catarzi, D.; Colotta, V.; Varano, F.; Poli, D.; Squarcialupi, L.; Filacchioni, G.; Varani, K.; Vincenzi, F.; Borea, P. A.; Dal Ben, D.; Lambertucci, C.; Cristalli, G. *Bioorg. Med. Chem.* **2013**, *21*, 283–294.
8. (a) Yang, X.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *RSC Adv.* **2012**, *2*, 11061–11066; (b) Al-Etaibi, A.; John, E.; Ibrahim, M. R.; Al-Awadi, N. A.; Ibrahim, Y. A. *Tetrahedron* **2011**, *67*, 6259–6274; (c) Ghotekar, B. K.; Jachak, M. N.; Toche, R. B. *J. Heterocycl. Chem.* **2009**, *46*, 708–713; (d) Ibrahim, Y. A.; Al-Awadi, N. A.; John, E. *Tetrahedron* **2008**, *64*, 10365–10374; (e) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 5110–5118; (f) El-Khamry, A. A.; Shiba, S. A.; Shalaby, A. A.; Abd Alaha, A. A. *J. Heterocycl. Chem.* **2006**, *43*, 1189–1193; (g) Yang, X.-J.; Liu, J.-T.; Lu, H.-J. *Tetrahedron* **2004**, *60*, 2897–2902; (h) Sofan, M. A.-M.; Abdel-Aziz El-Taweel, F. M.; El-Maati, T. A.; Ali El-Agamey, A.-G. *Indian J. Chem. B* **1994**, *33B*, 738–741; (i) Augusti, R.; Kascheres, C. *J. Org. Chem.* **1993**, *58*, 7079–7083; (j) Schweizer, E. E.; Hayes, J. E. *J. Org. Chem.* **1988**, *53*, 5562–5564; (k) Schweizer, E. E.; Hayes, J. E.; Rheingold, A.; Xu, W. *J. Org. Chem.* **1987**, *52*, 1810–1816; (l) Sircar, J. C.; Capiris, T.; Kesten, S. J. *J. Heterocycl. Chem.* **1981**, *18*, 117–121; (m) Maity, P.; Lepore, S. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 8338–8341; (n) Zora, M.; Kivrak, A. *J. Org. Chem.* **2011**, *76*, 9379–9390; (o) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326–329; (p) Liu, P.; Pan, Y. M.; Xu, Y. L.; Wang, H. S. *Org. Biomol. Chem.* **2012**, *10*, 4696–4698; (q) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641–652.
9. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971; (c) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552–2555; (d) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012**, *14*, 3894–3897; (e) Kavala, V.; Wang, C. C.; Barange, D. K.; Kuo, C. W.; M Lei, P.; Yao, C. F. *J. Org. Chem.* **2012**, *77*, 5022–5029; (f) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326–14329; (g) Jiang, M.; Li, M.; Wang, F.; Zhao, Y.; Zhao, F.; Dong, X.; Zhao, W. *Org. Lett.* **2012**, *14*, 1420–1423; (h) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936–7938; (i) Feng, Z.; Chen, F.; Zhang, X. *Org. Lett.* **2012**, *14*, 1938–1941; (j) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, 5623–5625; (k) Aljaar, N.; Malakar, C. C.; Conrad, J.; Strobel, S.; Schleid, T.; Beifuss, U. *J. Org. Chem.* **2012**, *77*, 7793–7803; (l) Liu, Y.; Wan, J.-P. *Chem.–Asian J.* **2012**, *7*, 1488–1501.
10. Chen, D. S.; Dou, G. L.; Li, Y. L.; Liu, Y.; Wang, X. S. *J. Org. Chem.* **2013**, *78*, 5700–5704.
11. (a) Muller, T. E.; C Hultzsch, K.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892; (b) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423–1427; (c) Han, J.-B.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 916–917; (d) Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Reddy, K. S. K.; Danodia, A. *J. Org. Chem.* **2012**, *77*, 8191–8205; (e) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3116–3120; (f) Joshi, M.; Patel, M.; Tiwari, R.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 5633–5645; (g) Tokimizu, Y.; Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Tetrahedron* **2011**, *67*, 5168–5175; (h) Wang, H.-F.; Yang, T.; Xu, P.-F.; Dixon, D. J. *Chem. Commun.* **2009**, 3916–3918; (i) Zhou, L.; Bohle, D. S.; Jiang, H.-F.; Li, C.-J. *Synlett* **2009**, 937–940; (j) Peng, C.; Cheng, J.; Wang, J. *Adv. Synth. Catal.* **2008**, *350*, 2359–2364; (k) Krasnova, L. B.; Hein, J. E.; Fokin, V. V. *J. Org. Chem.* **2010**, *75*, 8662–8665; (l) Ackermann, L.; Barfuesser, S.; Potukuchi, H. K. *Adv. Synth. Catal.* **2009**, *351*, 1064–1072.
12. Shemchuk, L. A.; Chernykh, V. P.; Krys'kiv, O. S. *Russ. J. Org. Chem.* **2008**, *44*, 1006–1008.