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Copper-Catalyzed Multicomponent Domino Reaction of 2-Bromoaldehydes, Benzylamines, and Sodium Azide for the Assembly of Quinazoline Derivatives

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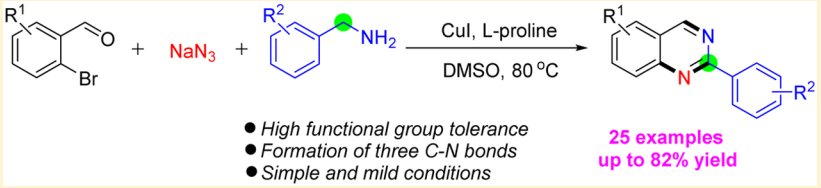
Supporting Information

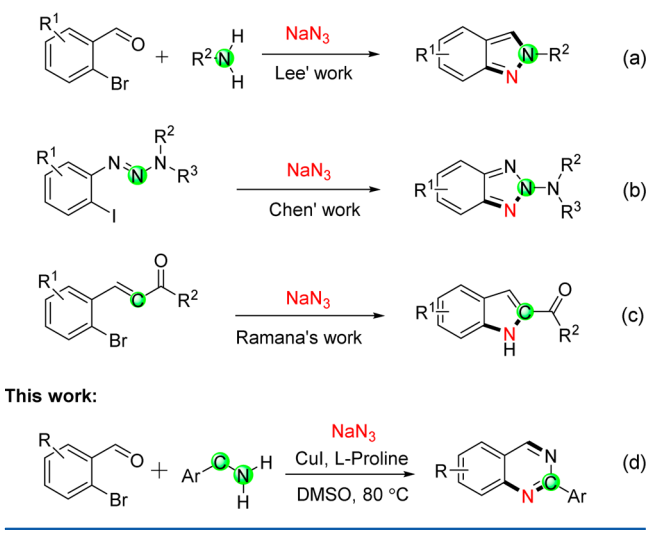


ABSTRACT: An efficient three-component domino reaction of 2-bromoaldehydes, benzylamines, and sodium azide has been developed for the synthesis of quinazoline derivatives. This domino process involves copper-catalyzed S_NAr, oxidation/cyclization, and denitrogenation sequences. The mild catalytic system enabled the effective construction of three C−N bonds in one operation.

In the past years, aryl azides have emerged as powerful synthons and exhibited enormous potential in metal-catalyzed N atom transfer reactions for the assembly of nitrogen-containing frameworks.[1] Since pioneering examples were demonstrated by Driver to realize the construction of *N*-heterocycles through intramolecular C−N or N−N bond formation from *ortho*-substituted aryl azides,[2] continued attention has been focused on this fascinating research area. However, in most cases, these elaborative designs implied a multistep process for the preparation of *ortho*-functionalized aryl azides. To address this gap, copper-catalyzed coupling[3] of *ortho*-substituted haloarenes with NaN_3 was combined with subsequent intramolecular N−N or C−N bond formation.[4−7] For instance, in 2011, Lee's group described a copper-catalyzed one-pot three-component synthesis of 2*H*-indazole via consecutive condensation, C−N and N−N bond formations (Scheme 1a).[4] Recently, Chen and co-workers developed a new strategy to form 2*H*-benzotriazoles via copper-catalyzed C−N coupling and intramolecular addition of nitrene to N=N bonds (Scheme 1b).[5] Moreover, Ramana introduced a simple procedure for the synthesis of 2-aroylindole derivatives, which consisted of a one-pot CuI-catalyzed S_NAr reaction of *o*-bromochalcones with sodium azide and subsequent intramolecular cyclization through nitrene C−H insertion (Scheme 1c).[6] Despite these limited examples, the strategy of using *in situ* generated aryl azides as key intermediates can still provide new valuable transformations for the facile synthesis of other N-containing heterocycles.

Quinazoline represents a fundamental and abundant class of nitrogen-containing heterocycles. Many compounds that contain the quinazoline motif possess a wide range of remarkable biological and medicinal activities including anticancer,[8] antiviral,[9] antitubercular,[10] and antimalarial properties.[11] The growing importance of quinazoline and its derivatives is also highlighted by the huge sales of commercially available drugs (e.g., Erlotinib,[12] Prazosin,[13] Iressa[14]). Because of their great value, the synthesis of quinazolines has always attracted much attention.[15−19] However, traditional condensa-

Scheme 1. Synthesis of *N*-Heterocycles via Copper-Catalyzed Domino Reactions of *ortho*-Functionalized Aryl Halides and Sodium Azide



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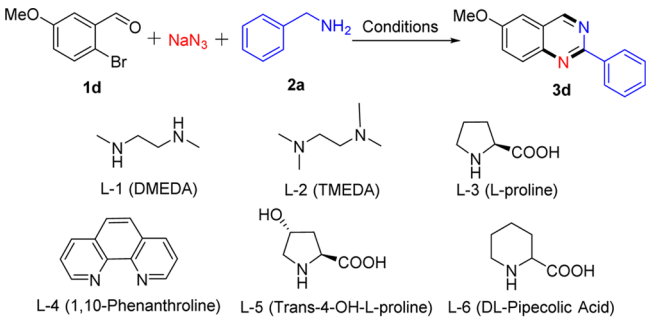
tion/oxidation sequences generally required the assistance from stoichiometric or large excess amounts of strong oxidants such as DDQ,[16a] NaClO,[16b] or MnO_2,[16c] therefore limiting functional group tolerance of these procedures. Although some improved methods for the synthesis of quinazolines have been proposed,[17−19] it is still highly desirable to search for a more convenient and efficient approach. Sodium azide (NaN_3) has been widely applied as a convenient nitrogen source in various chemical transformations.[4−7,20,21] As part of our ongoing efforts toward the development of novel copper-catalyzed domino reactions related to sodium azide,[21] herein we present another protocol for efficient synthesis of quinazoline derivatives from commercially available 2-bromobenzoaldehydes, benzylamines, and sodium azide under mild conditions. Notably, the C−N bond formation, not the N−N bond formation,[4] is followed by the copper-catalyzed C−N coupling (Scheme 1d).

Our initial efforts were focused on the optimization of the reaction conditions by using 2-bromo-5-methoxybenzaldehyde (**1d**), benzylamine (**2a**), and sodium azide as model substrates. Delightfully, the desired product 6-methoxy-2-phenylquinazoline (**3d**) was obtained in 42% yield using 10 mol % CuI catalyst at 100 °C in DMSO for 15 h (Table 1, entry 1). To further improve the yield, various reaction parameters such as ligands, copper salts, solvents, and temperatures were evaluated systematically. The results are summarized in Table 1. A range of ligands such as DMEDA, TMEDA, L-proline, 1,10-phenanthroline, *trans*-4-OH-L-proline, and DL-pipecolic acid were first screened (Table 1, entries 2−7), and L-proline showed the highest efficiency (Table 1, entry 4). Then, various copper salts were evaluated (Table 1, entries 8−14), and the results suggested that the use of CuI as a catalyst provided the optimum result. This transformation was also performed with several other solvents (Table 1, entries 15−18), and DMSO proved to be the most compatible (compare entries 4 and 15−18). An improvement of the yield was observed for decreasing temperature from 100 to 80 °C; subsequent increases or decreases in the temperature did not enhance the outcome of the reaction any further (Table 1, entries 19−21). The Cu/L ratio for this transformation was also investigated; reaction with CuI/L-proline (1:2) gave the best result (Supporting Information, Table S2). Eventually, the optimized reaction conditions were determined as **1d** (0.5 mmol), 1.0 equiv of **2a**, 2.0 equiv of sodium azide, 10 mmol % of CuI, and 20 mmol % of L-proline in 3 mL of DMSO at 80 °C in a sealed vessel under air.

Having identified the optimized reaction conditions, the substrate scope of this copper-catalyzed process was explored with a range of different 2-bromoaldehydes (Table 2). To our delight, 2-bromoaldehydes bearing both electronically neutral (4-H, 5-Me, 4-Me) and electron-donating (5-OMe, 4,5-$(OMe)_2$, 4,5-OCH_2O) substituents proceeded smoothly to afford the corresponding products in moderate to good yields (Table 2, 62−81%, **3a**−**3f**). Gratifyingly, halo-substituted aldehydes were also successfully converted into the corresponding products (Table 2, 36−58%, **3g**−**3k**), therefore providing the possibility for further derivatization. This method was further extended to several representative heteroaryl aldehydes such as 2-bromonicotinaldehyde and 3-bromothiophene-2-

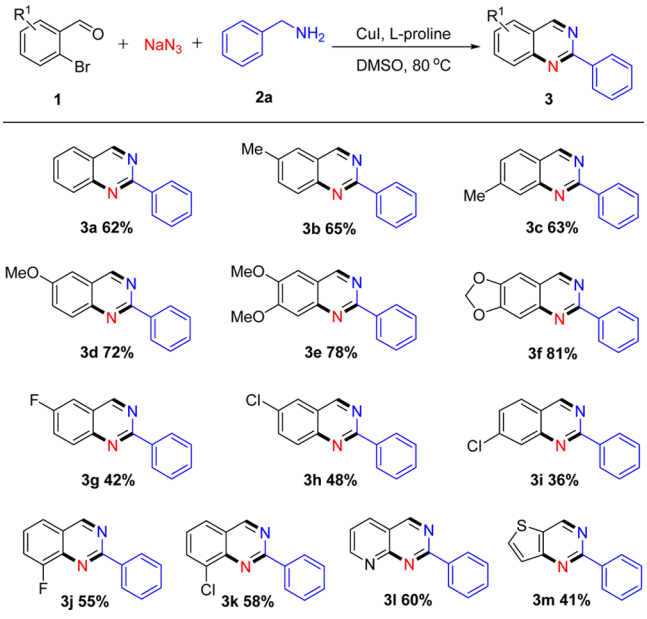
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	solvent	temp (°C)	yield[b] (%)
1	CuI		DMSO	100	42
2	CuI	L-1	DMSO	100	48
3	CuI	L-2	DMSO	100	58
4	CuI	L-3	DMSO	100	63
5	CuI	L-4	DMSO	100	55
6	CuI	L-5	DMSO	100	56
7	CuI	L-6	DMSO	100	61
8	CuCl	L-3	DMSO	100	40
9	CuBr	L-3	DMSO	100	42
10	Cu_2O	L-3	DMSO	100	36
11	$CuCl_2$	L-3	DMSO	100	23
12	$CuBr_2$	L-3	DMSO	100	26
13	$Cu(OAc)_2$	L-3	DMSO	100	30
14	$Cu(OTf)_2$	L-3	DMSO	100	33
15	CuI	L-3	DMF	100	45
16	CuI	L-3	1,4-dioxane	100	trace
17	CuI	L-3	toluene	100	trace
18	CuI	L-3	CH_3CN	100	12
19	**CuI**	**L-3**	**DMSO**	**80**	**72**
20	CuI	L-3	DMSO	120	35
21	CuI	L-3	DMSO	60	53

[a]Reactions conditions: **1d** (0.5 mmol), **2a** (0.5 mmol), NaN_3 (1.0 mmol), catalyst (10%), and ligand (20%) were heated in 3 mL of solvent in a sealed vessel for 15 h. [b]Isolated yields.

Table 2. Scope of 2-Bromoaldehydes[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), NaN_3 (1.0 mmol), CuI (0.05 mmol), and L-proline (0.1 mmol) in DMSO (3 mL) at 80 °C in a sealed vessel for 15 h. [b]Isolated yields.

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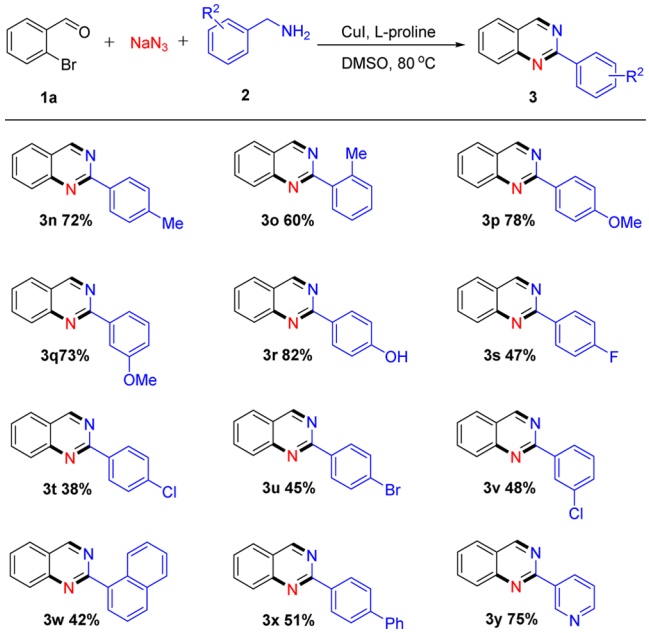
carbaldehyde. Much to our satisfaction, the optimized conditions were mild enough for the conversion to these new medicinally relevant molecules that may possess distinct biological activity (Table 2, 41−60%, **3l**−**3m**).

Inspired by these results, we further extended the scope of this reaction to various benzylamines. It was noticed that the electronic properties of benzylamines had a significant influence on the reaction efficiency. For example, benzylamines with electronically neutral (4-Me, 2-Me) and electron-donating (4-OMe, 3-OMe, 4-OH) groups attached to the aryl ring gave good yields (Table 3, 60−82%, **3n**−**3r**). However, when electron-deficient substrates were used, the reactivity was largely decreased to deliver the desired products in lower yields (Table 3, 38−48%, **3s**−**3v**). In addition, naphthalen-1-ylmethanamine and [1,1′-biphenyl]-4-ylmethanamine only proceeded to the products in moderate yields, which might be owing to steric effects (Table 3, 42−51%, **3w**−**3x**). A heteroaryl substrate such as pyridin-3-ylmethanamine also proceeded in good yield (Table 3, 75%, **3y**). Furthermore, the structure of **3u** was unambiguously determined by X-ray crystallographic analysis (see the Supporting Information).

Table 3. Scope of Benzylamines[a,b]

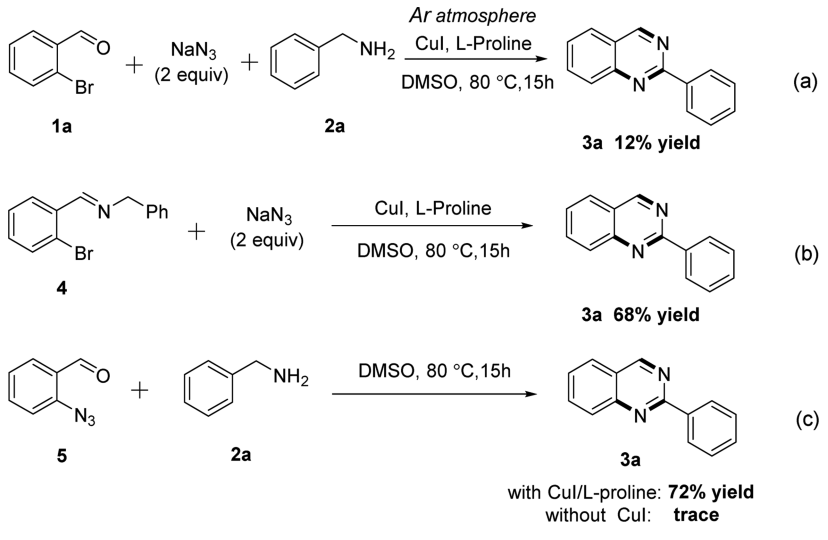


[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), NaN_3 (1.0 mmol), CuI (0.05 mmol), and L-proline (0.1 mmol) in DMSO (3 mL) at 80 °C in a sealed vessel for 15 h; [b]Isolated yields.

With the scope of the method established, we then turned our attention to evaluate the reaction mechanism. It is noticed that the yield of product 2-phenylquinazoline (**3a**) decreased significantly when the reaction was performed under an argon atmosphere, thus suggesting that oxygen is essential for this Cu-catalyzed multicomponent reaction (Scheme 2a). When treatment of the presynthesized (*E*)-*N*-benzyl-1-(2-bromophenyl)methanimine (**4**)[22] with sodium azide (2.0 equiv) was performed under the standard conditions for 15 h, 2-phenylquinazoline (**3a**) was obtained in 68% yield (Scheme 2b). This result showed that **4** may be an intermediate in this transformation. Considering that the *ortho*-halogenated substrates may transform to the corresponding aryl azides through a copper-catalyzed S_NAr sequence, 2-azidobenzaldehyde (**5**) was applied to gain insight into the subsequent denitrogenation process. In the following experiments, 2-azidobenzaldehyde (**5**) and benzylamine (**2a**), together with 2.0 equiv of sodium azide, were reacted under the optimal conditions, and the desired product (**3a**) was generated in 72% yield. In contrast, only a trace amount of **3a** was observed in the absence of CuI (Scheme 2c). The results indirectly indicated that the catalytic amount of CuI may play a dual role in both the S_NAr process and the subsequent intramolecular C−N bond formation.

Although the mechanistic details are not completely clear at this stage, on the basis of our experimental observations and previous literature reports,[2,3,23] a tentative mechanism for the copper-catalyzed domino sequence was proposed by using 2-bromobenzaldehyde (**1a**), benzylamine (**2a**), and sodium azide as an example (Scheme 3). Initially, 2-bromobenzaldehyde (**1a**) condensed with benzylamine (**2a**) to generate the resultant Schiff base **4** *in situ*. Subsequently, copper-catalyzed S_NAr of Schiff base **4** with NaN_3 proceeded to give the azido intermediate **A**. In the presence of Cu/O_2, **A** could be further oxidated to ion intermediate **B**,[23] which would undergo intramolecular cyclization via nucleophilic attack by the

Scheme 2. Mechanistic Studies



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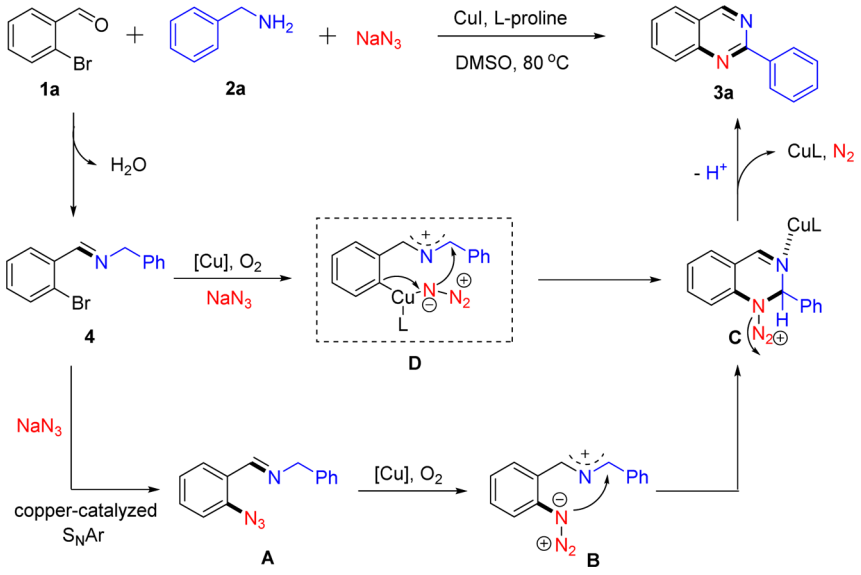
Scheme 3. A Possible Mechanism



pendant azide to furnish the C−N bond formation.[2d,7c] After extrusion of N_2 and proton elimination of **C**, the desired product 2-phenylquinazoline (**3a**) was finally obtained. A concerted procedure is also taken into consideration, whereby the cyclization of complex **D** directly converted to **C** without the formation of azido intermediate **A**. However, in view of the earlier works of Driver where the intramolecular C−N bonding may involve a nitrene-mediated sp^3 C−H insertion,[2a−c] an analogous reaction pathway cannot be overlooked for this Cu-catalyzed quinazoline synthesis (Supporting Information, Scheme S1).

In summary, we have developed an efficient and practical Cu-catalyzed domino protocol for the synthesis of quinazoline derivatives from simple and readily available 2-bromoaldehydes, benzylamines, and sodium azide under mild conditions. CuI was used as a tandem catalyst to trigger the S_NAr and to promote the subsequent denitrogenation/cyclization sequences. Further studies on the development of new domino reactions related to NaN_3 for the construction of other fascinating *N*-heterocycles are underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all starting materials and catalysts were obtained from commercial suppliers and used without further purification. All new compounds were fully characterized. TLC analysis was performed using precoated glass plates. Column chromatography was performed using silica gel (200−300 mesh). IR spectra were recorded as KBr pellets with absorption in cm^{-1}. ^1H spectra were recorded in $CDCl_3$ on 600 MHz spectrometers, and resonances (δ) are given in ppm relative to TMS (internal standard). ^{13}C spectra were recorded in $CDCl_3$ or DMSO-d_6 on 100/150 MHz NMR spectrometers. HRMS were obtained on a 7.0T FTMS equipped with ESI. Melting points were determined using an electrothermal capillary melting point apparatus and not corrected.

General Procedures for the Synthesis of the Products 3 (3a as an Example). A sealed tube was charged with 2-bromobenzaldehyde **1a** (92.5 mg, 0.50 mmol), benzylamine **2a** (53.5 mg, 0.50 mmol), NaN_3 (65.0 mg, 1.0 mmol), CuI (9.5 mg, 0.05 mmol), and L-proline (11.5 mg, 0.10 mmol) at room temperature, and then solvent DMSO (3 mL) was added. The resulting mixture was stirred at 80 °C for 15 h. After disappearance of the reactant (monitored by TLC), 50 mL of water was added to the mixture, which was then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 30% NaCl solution (V/V), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE-EtOAc, 5:1) to yield the desired product **3a**.

Experimental Procedure for Preparation of 4. (*E*)-*N*-Benzyl-1-(2-bromophenyl)methanimine (**4**) was prepared according to the related literature.[22] The mixture of (2-bromophenyl)methanol (412 mg, 2.2 mmol), benzylamine (214 mg, 2 mmol), CuI (3.8 mg, 0.02 mmol, 1 mol %), 2,2′-Bipy (3.1 mg, 0.02 mmol, 1 mol %), and TEMPO (6.3 mg, 0.04 mmol, 2 mol %) was stirred in open air at room temperature (ca. 25−30 °C) and monitored by TLC. The reaction mixture was then directly purified (without any workup) by column chromatography on neutral alumina gel (petroleum ether/ethyl acetate/triethylamine 100:10:1) to afford **4** in 90% isolated yield.

Analytical Data for Products 3 and 4. *2-Phenylquinazoline (**3a**).*[17a] Yellow solid; 63.9 mg (yield 62%); IR (KBr): 3060, 2924, 1613, 1583, 1548, 1480, 1397, 1206, 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.62 (d, J = 7.2 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.94−7.89 (m, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.56−7.50 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 160.5, 150.7, 137.9, 134.1, 130.6, 128.59, 128.56, 128.52, 127.2, 127.1, 123.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{11}N_2$: 207.0917; found: 207.0918.

*6-Methyl-2-phenylquinazoline (**3b**).*[17c] Yellow solid; 71.6 mg (yield 65%); IR (KBr): 3060, 2918, 1555, 1490, 1422, 1371, 1163, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.59 (d, J = 7.2 Hz, 2H), 7.97(d, J = 8.4 Hz, 1H), 7.71(d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.55−7.49 (m, 3H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 159.7, 149.3, 138.1, 137.4, 136.4, 130.4, 128.6, 128.4, 128.2, 125.8, 123.5, 21.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1074.

*7-Methyl-2-phenylquinazoline (**3c**).*[19a] White solid; 69.4 mg (yield 63%); IR (KBr): 2922, 1622, 1547, 1489, 1453, 1379, 1243, 1052 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.60 (d, J = 7.2 Hz, 2H), 7.86 (s, 1H), 7.79(d, J = 8.4 Hz, 1H), 7.55−7.48 (m, 3H), 7.42 (d, J = 8.4 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 159.8, 151.0, 145.2, 138.1, 130.5, 129.5, 128.6, 128.5, 127.5, 126.7, 121.8, 22.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1074.

*6-Methoxy-2-phenylquinazoline (**3d**).*[18b] Yellow solid; 85.1 mg (yield 72%); IR (KBr): 2921, 1691, 1556, 1490, 1349, 1221, 1163, 1024 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.57 (d, J = 7.2 Hz, 2H), 7.98 (d, J = 9.0 Hz, 1H), 7.52 (t, J = 7.8 Hz, 3H), 7.48 (t, J = 7.2 Hz, 1H), 7.12 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 158.7, 158.1, 146.9, 138.1, 130.1, 130.0, 128.6, 128.1, 127.1, 124.4, 103.8, 55.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1022; found: 237.1024.

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*6,7-Dimethoxy-2-phenylquinazoline (**3e**).*[18a] White solid; 103.9 mg (yield 78%); IR (KBr): 2921, 1619, 1581, 1498, 1452, 1407, 1343, 1229, 1155, 1004 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.54 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.37 (s, 1H), 7.10 (s, 1H), 4.08 (s, 3H), 4.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 157.0, 156.1, 150.3, 148.5, 138.2, 130.1, 128.5, 128.1, 119.3, 106.8, 103.9, 56.4, 56.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1128; found: 267.1130.

*6-Phenyl-[1,3]dioxolo[4,5-g]quinazoline (**3f**).*[18b] White solid; 101.4 mg (yield 81%); IR (KBr): 3048, 2920, 1612, 1565, 1455, 1337, 1219, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.53 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.8 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.31 (s, 1H), 7.07 (s, 1H), 6.11 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 157.3, 154.1, 150.2, 148.2, 138.0, 130.2, 128.5, 128.1, 120.6, 104.9, 102.1, 101.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{11}N_2O_2$: 251.0815; found: 251.0817.

*6-Fluoro-2-phenylquinazoline (**3g**).*[18b] Yellow solid; 47.1 mg (yield 42%); IR (KBr): 3068, 1626, 1591, 1555, 1488, 1434, 1378, 1349, 1209, 1143, 1019 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.59 (d, J = 7.2 Hz, 2H), 8.11−8.08 (m, 1H), 7.66 (t, J = 9.0 Hz, 1H), 7.55−7.51 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 160.6, 159.8, 159.5, 147.9, 137.6, 131.4, 130.7, 128.7, 128.4, 124.6, 124.4, 123.8, 110.2, 110.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0823; found: 225.0824.

*6-Chloro-2-phenylquinazoline (**3h**).*[17c] White solid; 57.8 mg (yield 48%); IR (KBr): 2922, 1573, 1547, 1475, 1428, 1383, 1342, 1275, 1179, 1076 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.58 (d, J = 7.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.54−7.50 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 159.4, 149.1, 137.5, 135.0, 132.7, 130.8, 130.3, 128.7, 128.5, 125.8, 123.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0527; found: 241.0529.

*7-Chloro-2-phenylquinazoline (**3i**).* White solid; 43.3 mg (yield 36%); mp 142−144 °C; IR (KBr): 3451, 2923, 1660, 1610, 1541, 1474, 1450, 1397, 1328, 1276, 1236, 1186, 1069, 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.58 (d, J = 6.6 Hz, 2H), 8.05 (s, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.53−7.50 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 160.1, 151.2, 140.3, 137.5, 130.9, 128.6, 128.3, 127.7, 121.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0527; found: 241.0529.

*8-Fluoro-2-phenylquinazoline (**3j**).* White solid; 61.7 mg (yield 55%); mp 137−139 °C; IR (KBr): 3066, 1626, 1560, 1442, 1407, 1379, 1302, 1245, 1081, 1022 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.56−7.46 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 160.1, 158.0, 156.3, 141.1, 141.0, 137.4, 130.9, 128.7, 128.6, 126.92, 126.87, 124.7, 122.70, 122.67, 118.1, 118.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0823; found: 225.0825.

*8-Chloro-2-phenylquinazoline (**3k**).* Yellow solid; 69.8 mg (yield 58%); mp 111−113 °C; IR (KBr): 3022, 1609, 1573, 1544, 1464, 1402, 1321, 1205, 1166, 1067, 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.68 (d, J = 6.6 Hz, 2H), 7.95 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.56−7.50 (m, 3H), 7.47 (t, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 160.7, 147.2, 137.5, 133.8, 133.1, 131.0, 128.8, 128.6, 127.0, 125.9, 124.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0527; found: 241.0534.

*2-Phenylpyrido[2,3-d]pyrimidine (**3l**).* Yellow solid; 62.2 mg (yield 60%); mp 201−203 °C; IR (KBr): 3080, 1603, 1593, 1582, 1545, 1460, 1366, 1358, 1312, 1155, 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.25 (s, 1H), 8.74−8.72 (m, 2H), 8.28 (d, J = 8.4 Hz, 1H), 7.55−7.52 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 161.8, 158.6, 158.1, 136.9, 136.2, 131.4, 129.1, 128.5, 122.7, 118.0; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_9N_3Na$: 230.0689; found: 230.0690.

*2-Phenylthieno[3,2-d]pyrimidine (**3m**).* Yellow solid; 43.5 mg (yield 41%); mp 118−120 °C; IR (KBr): 3090, 1561, 1543, 1521, 1511, 1387, 1298, 1275, 1240, 1105, 1046 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.54−8.52 (m, 2H), 8.00 (d, J = 5.4 Hz, 1H), 7.60 (d, J = 5.4 Hz, 1H), 7.54−7.47 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 160.9, 151.7, 137.9, 136.5, 130.3, 129.0, 128.6, 128.2, 124.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_9N_2S$: 213.0481; found: 213.0483.

*2-(p-Tolyl)quinazoline (**3n**).*[17a] Yellow solid; 79.3 mg (yield 72%); IR (KBr): 2919, 1613, 1584, 1549, 1484, 1401, 1169, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.51 (d, J = 7.8 Hz, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.85 (t, J = 7.8 Hz, 2H), 7.54 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.4, 150.7, 140.8, 135.3, 133.9, 129.3, 128.48, 128.47, 127.0, 126.9, 123.4, 21.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1074.

*2-(o-Tolyl)quinazoline (**3o**).*[18a] Yellow solid; 66.1 mg (yield 60%); IR (KBr): 3065, 2922, 1619, 1551, 1483, 1446, 1378, 1289, 1140, 1035 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.93−7.89 (m, 3H), 7.64−7.61 (m, 1H), 7.38−7.32 (m, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 159.9, 150.2, 138.4, 137.2, 133.9, 131.1, 130.5, 129.1, 128.3, 127.3, 126.9, 125.8, 122.7, 21.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1073.

*2-(4-Methoxyphenyl)quinazoline (**3p**).*[17a] White solid; 92.2 mg (yield 78%); IR (KBr): 2914, 2834, 1609, 1586, 1548, 1399, 1248, 1163, 1026 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.58 (d, J = 9.0 Hz, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.86 (t, J = 8.4 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 160.7, 160.2, 150.7, 133.9, 130.6, 130.1, 128.2, 127.0, 126.6, 123.2, 113.8, 55.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1022; found: 237.1023.

*2-(3-Methoxyphenyl)quinazoline (**3q**).*[18a] White solid; 86.2 mg (yield 73%); IR (KBr): 3001, 2953, 2829, 1615, 1548, 1487, 1395, 1339, 1227, 1037 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.87 (t, J = 7.8 Hz, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 160.3, 159.9, 150.6, 139.4, 134.0, 129.6, 128.5, 127.2, 127.0, 123.5, 121.1, 117.2, 112.9, 55.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{12}N_2NaO$: 259.0842; found: 259.0859.

*4-(Quinazolin-2-yl)phenol (**3r**).*[16c] Yellow solid; 91.1 mg (yield 82%); IR (KBr): 3066, 2800, 2676, 1608, 1577, 1407, 1340, 1237, 1166, 1054 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.88 (s, 1H), 6.80 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 7.8 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 6.24 (t, J = 7.8 Hz, 1H), 5.92 (t, J = 7.8 Hz, 1H), 5.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 160.2, 160.0, 150.0, 134.4, 130.1, 128.5, 127.62, 127.60, 126.8, 122.9, 115.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{11}N_2O$: 223.0866; found: 223.0867.

*2-(4-Fluorophenyl)quinazoline (**3s**).*[17a] Yellow solid; 52.7 mg (yield 47%); IR (KBr): 3052, 1600, 1508, 1405, 1340, 1220, 1145, 1007 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.60 (t, J = 6.6 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 7.86 (t, J = 7.2 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 163.4, 160.4, 160.0, 150.6, 134.1, 130.7, 130.6, 128.4, 127.2, 127.0, 123.4, 115.5, 115.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0823; found: 225.0823.

*2-(4-Chlorophenyl)quinazoline (**3t**).*[17a] White solid; 45.7 mg (yield 38%); IR (KBr): 3053, 1618, 1582, 1548, 1487, 1404, 1289, 1082, 1007 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.55 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 9.0 Hz, 1H), 7.89 (t, J = 7.2 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.7, 150.4, 136.6, 136.3, 134.0, 129.7, 128.6, 128.4, 127.2, 126.9, 123.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0527; found: 241.0529.

*2-(4-Bromophenyl)quinazoline (**3u**).*[17c] White solid; 64.1 mg (yield 45%); IR (KBr): 3054, 2924, 1616, 1579, 1546, 1485, 1402, 1288, 1062, 1003 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.48 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 9.0 Hz, 1H), 7.90−7.87 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.8, 150.4, 136.8, 134.0, 131.6, 130.0, 128.4, 127.3, 127.0, 125.2, 123.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}BrN_2$: 285.0022; found: 285.0024.

*2-(3-Chlorophenyl)quinazoline (**3v**).*[17a] White solid; 57.8 mg (yield 48%); IR (KBr): 2923, 1617, 1584, 1549, 1455, 1402, 1339,

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1241, 1143, 1057 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.63 (s, 1H), 8.51 (d, J = 6.6 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.95−7.91 (m, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 160.5, 159.6, 150.6, 139.7, 134.7, 134.4, 130.6, 129.8, 128.6, 127.7, 127.2, 126.6, 123.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0527; found: 241.0529.

*2-(Naphthalen-1-yl)quinazoline (**3w**).*[16b] White solid; 53.8 mg (yield 42%); IR (KBr): 3047, 1618, 1550, 1480, 1379, 1287, 1242, 1186, 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.93−7.88 (m, 3H), 7.63−7.59 (m, 2H), 7.56−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 160.3, 150.4, 136.2, 134.2, 134.1, 131.1, 130.3, 129.6, 128.5, 128.4, 127.6, 127.0, 126.7, 125.9, 125.8, 125.2, 123.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{13}N_2$: 257.1073; found: 257.1074.

*2-([1,1′-Biphenyl]-4-yl)quinazoline (**3x**).*[19b] White solid; 72.0 mg (yield 51%); IR (KBr): 3030, 1615, 1581, 1545, 1484, 1407, 1342, 1287, 1177, 1064 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.71−8.68 (m, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.89 (t, J = 7.2 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.62−7.57 (m, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 160.3, 150.7, 143.1, 140.5, 136.9, 134.0, 128.97, 128.95, 128.7, 128.5, 127.6, 127.2, 127.1, 127.0, 123.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{15}N_2$: 283.1230; found: 283.1232.

*2-(Pyridin-3-yl)quinazoline (**3y**).*[17a] Yellow solid; 77.7 mg (yield 75%); IR (KBr): 3050, 1618, 1583, 1550, 1487, 1400, 1380, 1291, 1242, 1068, 1022 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 9.45 (s, 1H), 8.85 (d, J = 7.8 Hz, 1H), 8.74 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.92 (t, J = 7.8 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.46−7.43 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.5, 159.0, 151.1, 150.5, 150.2, 135.7, 134.3, 133.4, 128.5, 127.7, 127.1, 123.7, 123.3; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_9N_3Na$: 230.0689; found: 230.0698.

*(E)-N-Benzyl-1-(2-bromophenyl)methanimine (**4**).* Yellow liquid; 493 mg (yield 90%); IR (KBr): 3457, 3062, 3028, 2887, 1696, 1635, 1587, 1564, 1494, 1435, 1374, 1341, 1270, 1213, 1158, 1116, 1025 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.34−7.31 (m, 4H), 7.29 (t, J = 7.8 Hz, 1H), 7.27−7.24 (m, 1H), 7.22 (t, J = 7.8 Hz, 1H), 4.84 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.8, 138.9, 134.3, 132.9, 131.8, 128.8, 128.4, 127.9, 127.5, 127.0, 125.0, 65.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{13}BrN$: 274.0226; found: 274.0229.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02843.

Crystallographic data and copies of the ^1H and ^{13}C NMR spectra (PDF)

Crystallographic data for **3u** (CIF)

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Notes

The authors declare no competing financial interest.

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