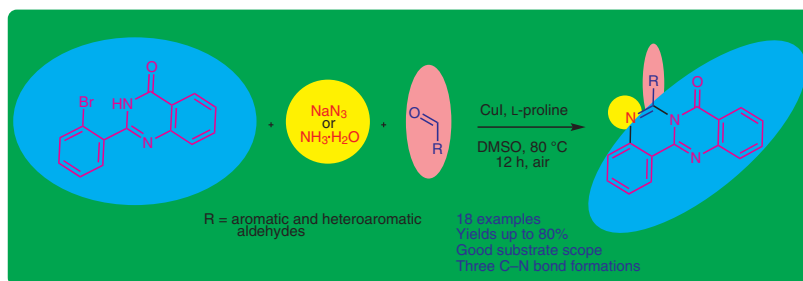


An Efficient One-Pot Multicomponent Synthesis of Tetracyclic Quinazolino[4,3-*b*]quinazolines by Sequential C–N Bond Formation and Copper-Mediated Aerobic Oxidative Cyclization

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Abstract An efficient one-pot synthesis of quinazolino[4,3-*b*]quinazoline derivatives has been accomplished, starting from 2-(2-bromophenyl)quinazolin-4(3*H*)-one, aldehydes, and various nitrogen sources under aerobic conditions. The multicomponent protocol is mediated by copper(I) salts and involves amination of 2-(2-bromophenyl)quinazolin-4(3*H*)-one, followed by condensation with the aldehyde and an oxidative cyclization to give the target compounds in moderate to good yields.

Key words quinazolinoquinazoline, copper catalysis, oxidative cyclization, C–N bond formation.

The synthesis of N-fused polycyclic heterocycles and their analogues has attracted much attention, not only because of their presence in many bioactive natural products, but also due to their status as privileged scaffolds in drug design.¹ Among these compounds, tetracyclic benzimidazole and quinazoline compounds containing a bridgehead nitrogen atom are frequently encountered in pharmaceuticals.² Molecules containing the quinazoline core have been known to bind to an array of receptors with enhanced affinity.³ Therapeutic applications of quinazolines cover a wide range of disease states,⁴ and the compounds show anti-inflammatory, antihypertensive, anticancer, antibacterial, and analgesic properties.^{5–7} Many potential drug molecules and natural products possessing the quinazolinone moiety in a tetracyclic framework, such as luotonin A,⁸ batracylin,⁹ tryptanthrin,¹⁰ ophiuroidine,¹¹ and auranthine¹² have been reported (Figure 1).

C–N bond formation plays a vital role in the construction of such tetracyclic bridgehead-nitrogen molecules.¹³ The coupling is usually carried out in the presence of palladium derivatives as catalysts. Recently, copper-mediated C–N bond formation has received attention owing to the

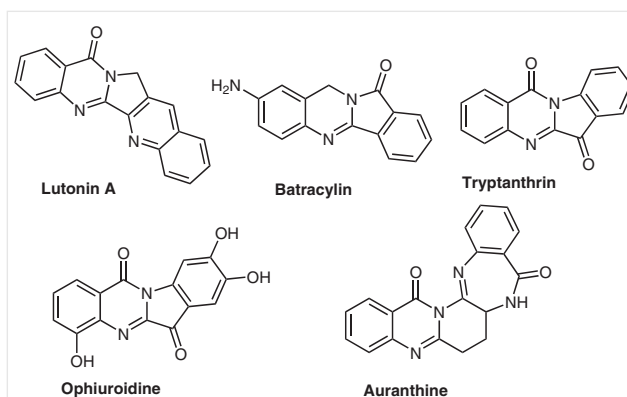


Figure 1 Representative examples of natural products and biologically active quinazolinone derivatives

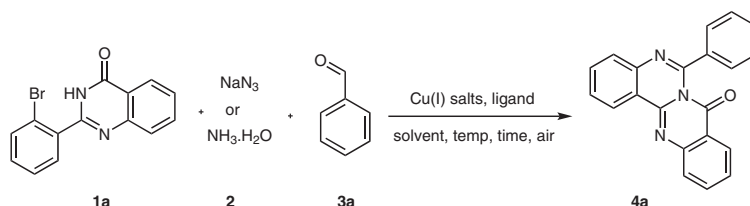
better toxicity profile and the lower cost of the metal. Our recent account on the convenient amination of the dihalide of Tröger's base¹⁴ by a copper-catalyzed protocol is an example. This inspired us to probe the feasibility of a C–N bond-formation protocol for the construction of tetracyclic quinazolino[4,3-*b*]quinazolines. The present study explored optimal conditions, suitable nitrogen sources, and the scope of copper-catalyzed construction of quinazolino[4,3-*b*]quinazolines from 2-(2-bromophenyl)quinazolin-4(3*H*)-one and various aldehydes through oxidative C–N bond formation.¹⁵

The optimum conditions for the protocol were assessed by using 2-(2-bromophenyl)quinazolin-4(3*H*)-one (**1a**) and benzaldehyde (**3a**) as model substrates together with various nitrogen sources **2**, including sodium azide (NaN₃), aqueous ammonia, and benzylamine. Initially the screening was carried out with NaN₃ as the nitrogen source, copper iodide (CuI) as the catalyst, L-proline (L-Pro) as the ligand, and DMSO as the solvent. The reaction proceeded at 80 °C

during 12 hours without the need for a base to yield the desired quinazolino[4, 3-*b*]quinazoline **4a** in 80% yield (Table 1, entry 1). Increasing the reaction time to 24 hours or the reaction temperature to 100 °C did not alter the product yield appreciably (entries 2 and 3). The reaction proceeded more effectively in DMSO than in DMF, acetonitrile, or toluene (entries 4–6). The efficiency of the copper salts CuBr, CuCl, (CuOAc)₂, and CuOAc was then examined (entries 8–11) but CuI was found to give the best results. The reaction did not proceed in the absence of a catalyst (entry 12). L-Proline was found to be a more effective ligand than *N,N'*-dimethylethane-1,2-diamine (DMEDA) (entries 13 and 14), and the reaction yield fell in the absence of a ligand (entry 15).

When aqueous ammonia was used as the nitrogen source, the reaction did not proceed under the standard conditions. Modification of the reaction conditions by employing a base and heating the reaction in a sealed tube (K₂CO₃, DMSO, 100 °C, 24 h), followed by aerial heating, gave **4a** in 61% yield (Table 1, entry 16). This version of the reaction therefore takes longer, requires harsher conditions, and gives a poorer yield compared with the use of NaN₃ as nitrogen source. The catalyst efficiency was also investigated (entries 18–20); again, CuI was found to be the best catalyst. Subsequently, we examined the use of benzylamine as the nitrogen source (K₂CO₃, DMSO, 80 °C; entry 21). However, the reaction yield was even lower (51%). Therefore, the

Table 1 Synthesis of **4a** by Employing Various Reaction Parameters^a



Entry	Catalyst	Ligand	N Source	Base	Temp (°C)	Solvent	Time (h)	Yield (%)
1	CuI	L-Pro	NaN₃	–	80	DMSO	12	80
2	CuI	L-Pro	NaN ₃	–	80	DMSO	24	80
3	CuI	L-Pro	NaN ₃	–	100	DMSO	12	80
4	CuI	L-Pro	NaN ₃	–	80	DMF	12	62
5	CuI	L-Pro	NaN ₃	–	80	MeCN	12	trace
6	CuI	L-Pro	NaN ₃	–	80	toluene	12	trace
7	CuI	L-Pro	NaN ₃	–	r.t.	DMSO	24	trace
8	CuBr	L-Pro	NaN ₃	–	80	DMSO	12	56
9	CuCl	L-Pro	NaN ₃	–	80	DMSO	12	51
10	Cu(OAc) ₂	L-Pro	NaN ₃	–	80	DMSO	12	41
11	CuOAc	L-Pro	NaN ₃	–	80	DMSO	12	36
12	–	L-Pro	NaN ₃	–	80	DMSO	12	NR ^b
13	CuI	DMEDA	NaN ₃	–	80	DMSO	12	48
14	CuI	DMEDA	NaN ₃	–	80	DMSO	12	45
15	CuI	–	NaN ₃	–	80	DMSO	12	34
16	CuI	L-Pro	NH ₃ ·H ₂ O	K ₂ CO ₃	100	DMSO	24	61
17	–	L-Pro	NH ₃ ·H ₂ O	K ₂ CO ₃	100	DMSO	24	NR ^b
18	CuCl	L-Pro	NH ₃ ·H ₂ O	K ₂ CO ₃	100	DMSO	24	32
19	CuBr	L-Pro	NH ₃ ·H ₂ O	K ₂ CO ₃	100	DMSO	24	36
20	Cu(OAc) ₂	L-Pro	NH ₃ ·H ₂ O	K ₂ CO ₃	100	DMSO	24	31
21 ^c	CuI	L-Pro	BnNH ₂	K ₂ CO ₃	80	DMSO	24	51

^a Reaction conditions: (Entries 1–15) **1** (1.66 mmol), PhCHO (**3a**; 2 mmol), CuI (10 mol%), ligand (20 mol%), NaN₃ (3 mmol), DMSO (5 mL), 80 °C, air;¹⁶ (Entries 16–20) **1** (1.66 mmol), PhCHO (**3a**; 2 mmol), CuI (10 mol%), ligand (20 mol%), 25% aq NH₃ (1 mL), K₂CO₃ (5 mmol), DMSO (5 mL), 100 °C, sealed tube then air.¹⁶

^b No reaction.

^c No aldehyde was used.

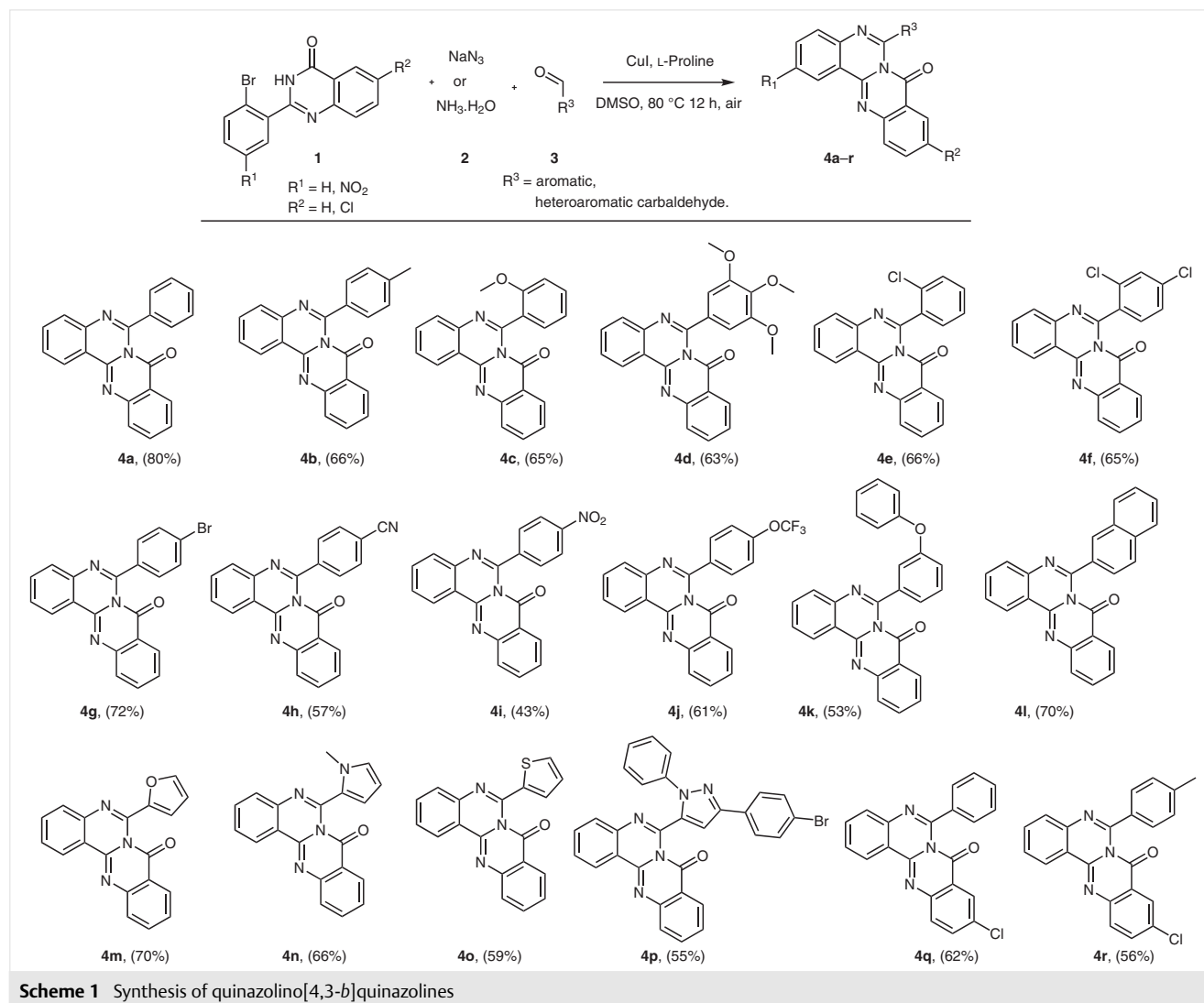
preferred nitrogen source for this multicomponent protocol is sodium azide (Scheme 1).

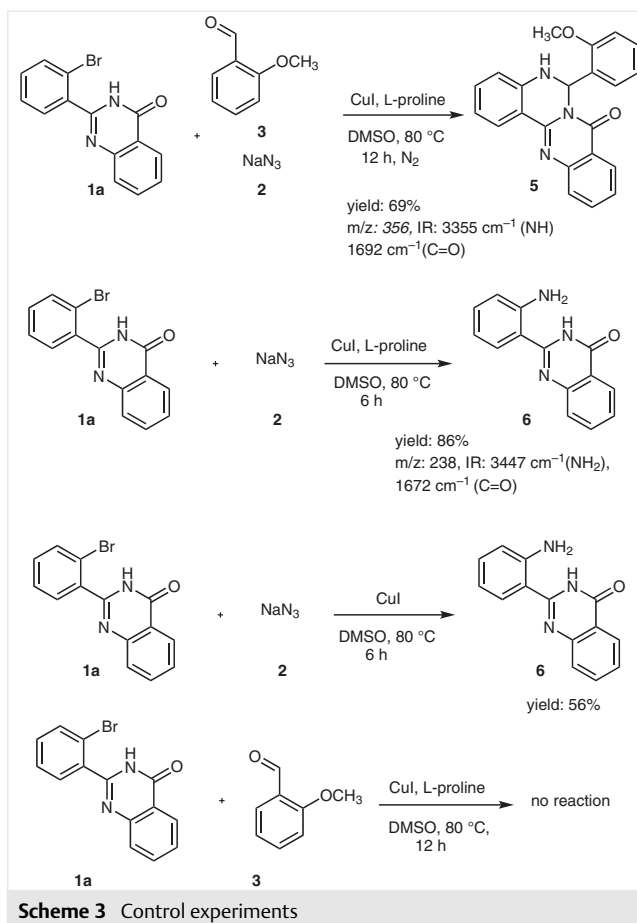
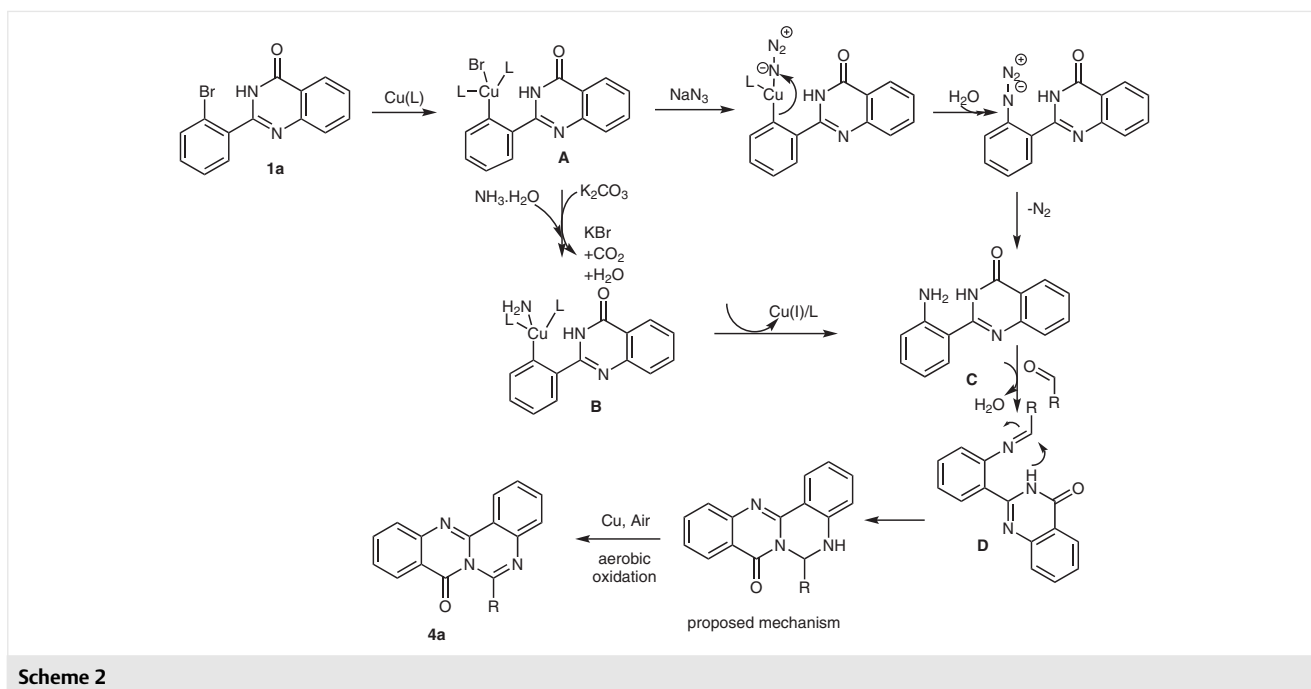
Having successfully established optimal reaction conditions, we examined the scope of the protocol with various aldehydes. The reaction proceeded smoothly with a range of aromatic and heteroaromatic aldehydes (Scheme 1; **4a–r**), giving yields of 43–80%. In general, aryl aldehydes (**4a–l**) were more reactive than heteroaryl aldehydes (**4m–o**). Use of a bulkier aldehyde (**4p**) had a negative influence on reaction yield, probably due to steric crowding. Substituents on the aryl ring also influenced the reaction yields; aromatic aldehydes with electron-donating substituents seem to be preferred compared with those with electron-withdrawing substituents. This explains why the lowest yield was obtained in case of 4-nitrobenzaldehyde (**4i**; 43%). The reaction did not proceed with **1** ($R^1 = \text{NO}_2$). Aliphatic and unsaturated aldehydes did not undergo the copper-mediated coupling reaction.

We assumed that the reaction proceeds mainly by a copper-catalyzed Ullmann-type aryl amination, followed by sequential C–N bond formations and aerobic oxidative cyclization (Scheme 2).

To confirm the salient features of the pathway, we performed a series of control experiments (Scheme 3). First, we proved beyond doubt that aerobic oxidation indeed occurs, as experiments performed under a nitrogen atmosphere with all three nitrogen sources gave the nonoxidized product **5**.

In the case of benzylamine, the reaction seems to proceed by an Ullmann-type N-arylation¹⁷ in the presence of CuI, L-proline, and K_2CO_3 . The arylated product undergoes C–H amidation, followed by oxidative cyclization.¹⁸ With aqueous ammonia as the nitrogen source, the CuI-catalyzed ligand-assisted arylation¹⁹ of NH_3 affords intermediate **C**, probably via intermediates **A** and **B**. This is followed by a second C–N bond formation between the newly formed an-





iline and the aldehyde, resulting in formation of imine **D**. Cyclization through a third C–N bond formation, followed by aerial oxidation results in the formation of the target compound (Scheme 2).

On the other hand, the reaction with NaN_3 is probably initiated by disproportionation of NaN_3 between CuI and *L*-proline, resulting in the formation of CuN_3 and the sodium salt of *L*-proline. This is followed by coupling of CuN_3 with the aryl bromide and elimination of Br^- . Subsequent loss of nitrogen from the aryl azide followed by reduction (with the assistance of trace amounts of water in the DMSO) leads to corresponding aniline.²⁰ Control experiments with the substrate and sodium azide in the presence of a copper salt and *L*-proline resulted in the formation of aniline **6** (Scheme 3).²¹ Only traces of the aniline **6** were found in the absence of *L*-proline. The second C–N bond formed between the aldehyde and the resulting aniline affords the corresponding imine. Nucleophilic attack by the quinazoliny *N*-H moiety forms the third C–N bond, resulting in the dihydro product. Aerobic oxidation assisted by the metal affords the aza-fused polycyclic target (Scheme 2).

In conclusion, a facile method for the construction of tetracyclic quinazolino[4,3-*b*]quinazolines through copper-catalyzed C–N bond formation has been developed. Three nitrogen sources were explored for the initial *N*-arylation, and the optimal conditions for the transformation were established. This one-pot multicomponent reaction is successful for various *N*-nucleophiles and for a range of aryl or heteroaryl aldehydes, with good functional-group toler-

ance. The protocol uses simple substrates and reagents and this, coupled with its generality, make it a valuable tool for the synthesis of aza-fused polycyclic heterocycles.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1591578>.

References

- (1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.
- (2) (a) Göker, H.; Özden, S.; Yilidiz, S.; Boykin, D. W. *Eur. J. Med. Chem.* **2005**, *40*, 1062. (b) Malecki, N.; Carato, P.; Rigo, B.; Goossens, J.-F.; Houssin, R.; Bailly, C.; Hénichart, J.-P. *Bioorg. Med. Chem.* **2014**, *12*, 641.
- (3) Colotta, V.; Catarzi, D.; Varano, F.; Lenzi, O.; Filacchioni, G.; Costagli, G.; Galli, A.; Ghelardini, C.; Galeotti, N.; Gratteri, P.; Sgrignani, J.; Deflorian, F.; Moro, S. *J. Med. Chem.* **2006**, *49*, 6015.
- (4) (a) Maggio, B.; Daidone, G.; Raffa, D.; Plescia, S.; Mantione, L.; Catena Cutuli, V. A.; Mangano, N. G.; Caruso, A. *Eur. J. Med. Chem.* **2001**, *36*, 737. (b) Laddha, S. L.; Bhatnagar, S. P. *Bioorg. Med. Chem.* **2009**, *17*, 6796. (c) Aly, M. M.; Mohamed, Y. A.; El-Bayouki, K. A. M.; Basyouni, W. M.; Abbas, S. Y. *Eur. J. Med. Chem.* **2010**, *45*, 3365. (d) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Eur. J. Med. Chem.* **2014**, *76*, 193. (e) Ugale, V. G.; Bari, S. B. *Eur. J. Med. Chem.* **2014**, *80*, 447. (f) Maurya, H. K.; Verma, R.; Alam, S.; Pandey, S.; Pathak, V.; Sharma, S.; Srivastava, K. K.; Negi, A. S.; Gupta, A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5844.
- (5) Latermann, A. B.; Chen, D.; McCutcheon, K.; Hoffman, G.; Frias, E.; Ruddy, D.; Rakiec, D.; Korn, J.; McAllister, G.; Stegmeier, F.; Meyer, M. J.; Sharma, S. V. *Cancer Res.* **2015**, *75*, 4937.
- (6) Chen, C.-H.; Statt, S.; Chiu, C.-L.; Thai, P.; Arif, M.; Adler, K. B.; Wu, R. *Am. J. Respir. Crit. Care Med.* **2014**, *190*, 1127.
- (7) Ayala-Ramirez, M.; Feng, L.; Habra, M. A.; Dickson, P. V.; Perreier, N.; Phan, A.; Waguespack, S.; Patel, S.; Jimenez, C. *Cancer* **2012**, *118*, 2804.
- (8) Tseng, M. C.; Chu, Y.-W.; Tasi, H.-P.; Lin, C.-M.; Hwang, J.; Chu, Y.-H. *Org. Lett.* **2011**, *13*, 920.
- (9) Dzierzbicka, K.; Trzonokowski, P.; Sewerynek, P. L.; Myśliwski, A. *J. Med. Chem.* **2003**, *46*, 978.
- (10) Li, H.; Li, W.; Spannenberg, A.; Baumann, W.; Neumann, H.; Beller, M.; Wu, X.-F. *Chem. Eur. J.* **2014**, *20*, 8541.
- (11) (a) Utkina, N. K.; Denisenko, V. *Tetrahedron Lett.* **2007**, *48*, 4445. (b) Mason, J. J.; Janosik, T.; Bergman, J. *Synthesis* **2009**, 3642.
- (12) Kshirsagar, U. A.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 2702.
- (13) (a) Alexandre, F. R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413. (b) Adepu, R.; Sunke, R.; Meda, C. L. T.; Ramudu, D.; Krishna, G. R.; Reddy, C. M.; Deora, G. S.; Parsa, K. V. L.; Pal, M. *Chem. Commun.* **2013**, *49*, 190. (c) Saha, B.; Kumar, R.; Maulik, P. R.; Kundu, B. *Tetrahedron Lett.* **2006**, *47*, 2765. (d) Cai, Q.; Li, Z.; Wei, J.; Fu, L.; Ha, C.; Pei, D.; Ding, K. *Org. Lett.* **2010**, *12*, 1500. (e) Tyagi, V.; Khan, S.; Bajpai, V.; Gauniyal, H. M.; Kumar, B.; Chauhan, P. M. S. *J. Org. Chem.* **2012**, *77*, 1414.
- (14) Reddy, M. B.; Reddy, P. G.; Shailaja, M.; Manjula, A.; Rao, T. P. *RSC Adv.* **2016**, *6*, 98297.
- (15) Xu, C.; Jia, F. C.; Zhou, Z.-W.; Zheng, S.-J.; Li, H.; Wu, A.-X. *J. Org. Chem.* **2016**, *81*, 3000.
- (16) **Quinazolino[4,3-b]quinazolines 4a-r; General Procedures**
Method 1 (NaN₃ as the nitrogen source): CuI (10 mol%), L-proline (20 mol %), and NaN₃ (3 mmol) were added to a solution of quinazolinone **1** (1.66 mmol) in DMSO (5 mL) at r.t., and a blue complex formed. The appropriate aldehyde (2 mmol) was added, and the mixture was stirred at 80 °C for 12 h until the reaction was complete (TLC). The mixture was cooled then partitioned between ice-cold H₂O (25 mL) and EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The organic layers were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrate in vacuo. The residue was purified by column chromatography (silica gel).
Method 2 (aq NH₃ as the nitrogen source): CuI (10 mol %), L-proline (20 mol %), 25% aq NH₃ (1 mL), K₂CO₃ (5 mmol), and the appropriate aldehyde (2 mmol) were added to a solution of quinazolinone **1**²² (1.66 mmol) in DMSO (5 mL), and mixture was stirred at 100 °C for 6 h in a sealed tube. The mixture was then heated for 18 h open to the air until the reaction was complete (TLC). The mixture was cooled to r.t. then partitioned between ice-cold H₂O (25 mL) and EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The organic layers were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel).
6-(4-Bromophenyl)-8H-quinazolino[4,3-b]quinazolin-8-one (4g)
White solid; yield: 482 mg (72%); mp 270–272 °C. IR (KBr): 1696 (C=O) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.81 (d, J = 8.0 Hz, 1 H), 8.24 (d, J = 7.9 Hz, 1 H), 7.88 (d, J = 3.5 Hz, 2 H), 7.85–7.78 (m, 2 H), 7.66–7.63 (m, 1 H), 7.62–7.59 (m, 2 H), 7.52–7.50 (m, 1 H), 7.49 (d, J = 8.2 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 160.54 (C=O), 148.96, 146.92, 146.15, 144.21, 142.28, 135.96, 135.58, 133.70, 131.40, 128.62, 127.99, 127.40, 127.18, 126.52, 126.01, 124.01, 121.42, 120.29. LC-MS (positive-ion mode): m/z = 402 [M + H]⁺; HRMS (EI): m/z [M + H]⁺ calcd for C₂₁H₁₃BrN₃O: 402.02404; found: 402.02365.
6-(4-Nitrophenyl)-8H-quinazolino[4,3-b]quinazolin-8-one (4i)
Yellow solid; yield: 246 (43%); mp 288–290 °C. IR (KBr): 1692 (C=O) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.85 (d, J = 8.0 Hz, 1 H), 8.35 (d, J = 8.7 Hz, 2 H), 8.23 (d, J = 7.9 Hz, 1 H), 7.91 (d, J = 2.3 Hz, 2 H), 7.85 (d, J = 6.5 Hz, 2 H), 7.75 (d, J = 8.7 Hz, 2 H), 7.69 (t, J = 7.3 Hz, 1 H), 7.55–7.50 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 160.33 (C=O), 147.97, 147.81, 146.92, 145.70, 143.27, 141.97, 135.89, 133.91, 129.39, 128.26, 127.94, 127.37, 126.83, 126.13, 123.50, 121.39, 119.97. LC-MS (positive-ion mode): m/z = 369 [M + H]⁺; HRMS (EI): m/z [M + H]⁺ calcd for C₂₁H₁₃N₄O₃: 369.0988; found: 369.0986.
- (17) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012**, *14*, 3894.
- (18) Kotipalli, T.; Kavala, V.; Janreddy, D.; Bandi, V.; Kuo, C. W.; Yao, C. F. *Eur. J. Org. Chem.* **2016**, 1182.
- (19) (a) Li, B.; Zhang, B.; Zhang, X.; Fan, X. *J. Org. Chem.* **2016**, *81*, 9530. (b) Guo, S.; Li, Y.; Tao, L.; Zhang, W.; Fan, X. *RSC Adv.* **2014**, *4*, 59289.

- (20) (a) Jia, F.-C.; Zhou, Z.-W.; Xu, C.; Cai, Q.; Li, D.-K.; Wu, A.-X. *Org. Lett.* **2015**, *17*, 4236. (b) Kim, Y.; Kumar, M. R.; Park, N.; Yeo, Y.; Lee, S. *J. Org. Chem.* **2011**, *76*, 9577. (c) Rai, B.; Kumar, P.; Kumar, A. *RSC Adv.* **2015**, *5*, 85915.
- (21) Markiewicz, J. T.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 4887–4890.
- (22) (a) Tian, X.; Song, L.; Li, E.; Wang, Q.; Yu, W.; Chang, J. *RSC Adv.* **2015**, *5*, 62194. (b) Gawande, S. S.; Warangkar, S. C.; Bandgar, B. P.; Khobragade, C. N. *Bioorg. Med. Chem.* **2013**, *21*, 2772.