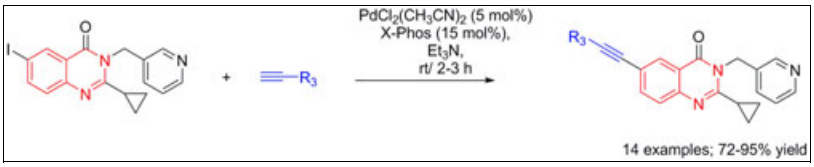
Cu-free Sonogashira Type Cross-Coupling of 6-Halo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) Quinazolin-4(3*H*)-ones as Potential Antimicrobial Agents

Suresh Poudapally,[a,c] Venkateshwarlu Gurram,[a] Ramesh Garlapati,[a] Chiranjeevi Tulluri,[d] Uma Addepally,[d] K. Vidya,[c]* Somesh Sharma,[a] Subhabrata Sen,[b] and Narender Pottabathini[a]*

[a]Medicinal Chemistry Division, GVK Biosciences Pvt. Ltd., Plot 28A, IDA Nacharam, Hyderabad, India
[b]Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Lucknow, Uttar Pradesh 201314, India
[c]College of Engineering, JNTUH, Nachupally, Karimnagar, India
[d]Centre for Innovative Research, CBT, IST, JNTUH, Hyderabad, India
*E-mail: Vidyaorg@yahoo.com; narender.pottabathini@gvkbio.com
Additional Supporting Information may be found in the online version of this article.
Received May 23, 2016
DOI 10.1002/jhet.2815
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).



C(sp)–C(sp2) bond formation via Sonogashira cross-coupling reactions on 6-halo-2-cyclopropyl-3-(pyridyl-3-ylmethyl)quinazolin-4(3*H*)-ones with appropriate alkynes was explored. Optimization of reaction conditions with various catalysts, ligands, bases, and solvents was conducted. The combination of $PdCl_2(MeCN)_2$ with X-Phos proved to be the best metal–ligand system for this conversion in the presence of triethylamine (Et_3N) in tetrahydrofuran at room temperature for iodosubstrates, at 80°C for the bromosubstrates in 8 h, and also for the chlorosubstrates in 16 h. We also demonstrated synthesis of a successful diversity-oriented synthesis library of highly functionalized quinazolinones via Cu-free Sonogashira coupling of diverse aryl halides and azido-alkyne ("click") ligation reactions with substituted azides. The library exhibited significant antimicrobial activity when screened against several microorganisms.

INTRODUCTION

Substituted quinazolinones play a vital role in biology and medicine [1]. Hence, development of chemical methods to modify quinazolinones continues to attract attention [2]. The Sonogashira cross-coupling of aryl halides, triflates, or tosylates with terminal acetylenes in the presence of a Pd(0) catalyst and copper(I) iodide as a cocatalyst provides an efficient route for Csp^2–Csp bond formation to afford arylalkynes and conjugated enynes [3]. Interestingly, at times, the use of Cu(I) iodide leads to the oxidative homocoupling of alkynes to form the Glaser product [4,5]. In recent years, this has prompted interest in the development of Cu-free Sonogashira cross-coupling reactions [6–9]. It has also been reported under Pd-free, amine-free, ligand-free, and solvent-free conditions as well as with tetrabutylammonium salts as additives and in the presence of water as solvent [10]. Despite reports of alkynylation of quinazolinone/quinazolines with terminal acetylenes, very limited information exists in the literature on the Sonogashira cross-coupling of 6-halo-quinazolinones with terminal alkynes to generate 6-alkynylated-substituted quinazolinone derivatives [11–17]. Hence, development of a catalytic system for the alkynylation at the 6-position of iodoquinazolinones, bromoquinazolinones, or chloroquinazolinones is synthetically an interesting potential. Herein, we have reported our efforts towards the synthesis of 6-alkynyl-quinazolinones with 6-halo-quinazolinones and terminal alkynes via Cu-free Sonogashira reactions and demonstrated their utility as a versatile building block for a library of multifunctionalized quinazolinones via diversity-oriented synthesis. The resulting compounds were also evaluated for their antimicrobial activity [18–20].

RESULTS AND DISCUSSION

To begin with, we optimized the reaction condition for Sonogashira cross-coupling between 6-iodoquinazolinone (**1a**) and phenylacetylene. Two palladium catalysts, $PdCl_2(PPh_3)_2$ and $PdCl_2(MeCN)_2$, and three ligands, namely, JohnPhos (**L1**), S-Phos (**L2**), and X-Phos (**L3**), were selected for the optimization study (Fig. 1). We further chose cesium carbonate (Cs_2CO_3), potassium carbonate (K_2CO_3), and triethylamine (Et_3N) as bases with tetrahydrofuran (THF), dimethylformamide (DMF), 1,4-dioxane, and acetonitrile (MeCN) as solvents.

Inspired from earlier reports of the Sonogashira reaction where the combination of palladium and copper catalysts at

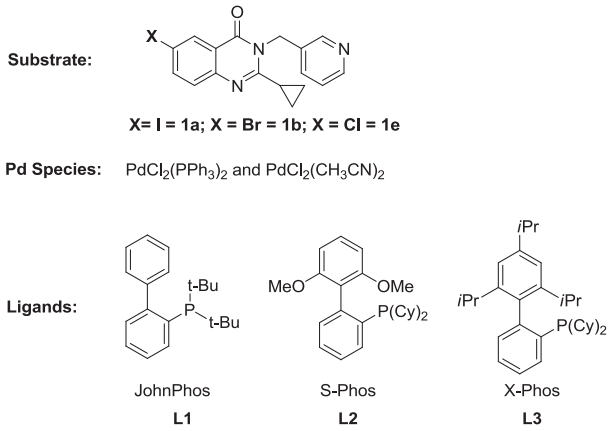


Figure 1. Three ligands and two Pd(II) precatalysts were selected for the initial analysis along with **1a** as the substrate.

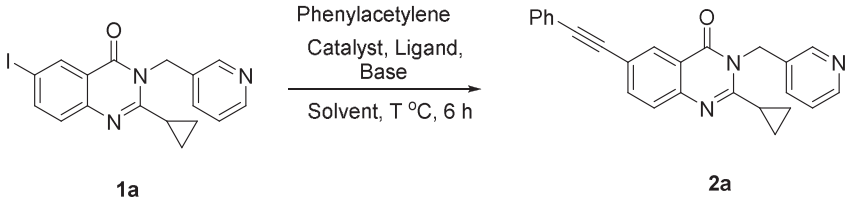
room temperature (RT) resulted in improved yields [21]. We began the reaction optimization with 5 mol% $PdCl_2(PPh_3)_2$/10 mol% Cu(I) and 4.5 eq Et_3N in the presence of THF. It resulted in the formation of 20% of desired **2a** after 16 h at RT (entry 1, Table 1). Altering the solvent to MeCN (entry 2, Table 1) and DMF (entry 3, Table 3) did not improve the yields. Next, we switched to copper-free conditions, with 5 mol% of $PdCl_2(PPh_3)_2$ and 15 mol% of **L1**, **L2**, and **L3** in the presence of Et_3N and THF as solvent at RT to afford **2a** in moderate yields (29, 41, and 50%, respectively) (entries 4, 5, and 6, Table 1).

With ligands **L1** and **L2** constant, we further changed the catalyst to 5 mol% $PdCl_2(MeCN)_2$ (entries 7 and 8, Table 1). It did not make any difference to the yield of the reaction. However, the best condition was, with **L3** as the ligand, the yield of **2a** improved to 95% (entry 9, Table 1). Reaction of **1a** with 5 mol% $PdCl_2(MeCN)_2$ and 15 mol% **L3**, with either Cs_2CO_3 or K_2CO_3 in THF resulted in 77 and 69% yields at RT (entries 10 and 11, Table 1). Altering the base to Et_3N and solvent to DMF or 1,4-dioxane improved the yields marginally (entries 12 and 13). Hence, the optimized Sonogashira reaction between **1a** and phenylacetylene required $PdCl_2(MeCN)_2$ (5 mol%), **L3** (15 mol%), and Et_3N with THF as the solvent at RT. Reactions were also conducted at different catalytic loadings, namely, $PdCl_2(MeCN)_2$ (1 and 2 mol%), **L3** (3 and 6 mol%), and Et_3N, with THF conditions, resulting in moderately reasonable yields (entries 14 and 15, Table 1) when compared to the established conditions.

The optimized protocol could be applied to the Sonogashira reaction of **1b** and **1e** with phenylacetylene; however, the reaction temperature needs to be elevated to 80°C for the best results (yield 85% after 6 h and 70% after 16 h) (Scheme 1). This elevated condition was further applied in the reaction of **1c** and 1**d** with

Table 1

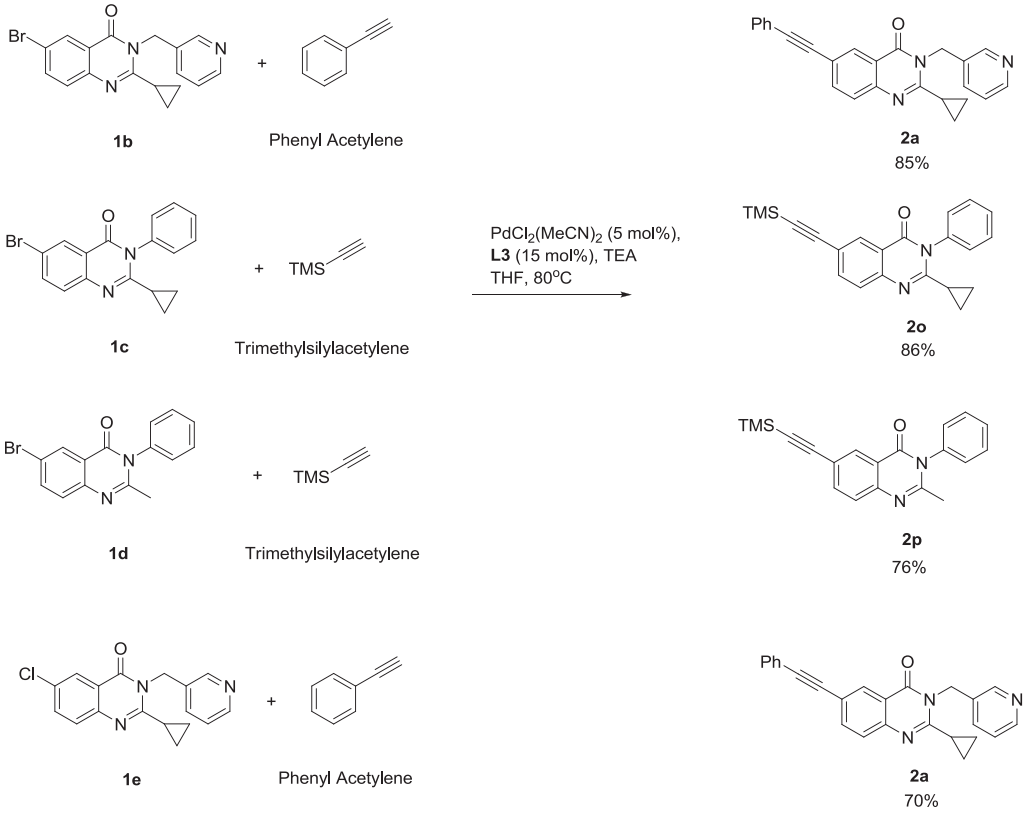
Optimization study for room temperature and Cu-free Sonogashira cross-coupling of phenylacetylene with **1a**.[a,b]



Entry	mol% palladium catalyst/mol% catalytic/base/solvent	**2a** (% yield)[c]
1	5 mol% $PdCl_2(PPh_3)_2$/10 mol% Cu(I), Et_3N, THF	20
2	5 mol% $PdCl_2(PPh_3)_2$/10 mol% Cu(I), Et_3N, MeCN	NR
3	5 mol% $PdCl_2(PPh_3)_2$/10 mol% Cu(I), Et_3N, DMF	NR
4	5 mol% $PdCl_2(PPh_3)_2$/15 mol% **L1**, Et_3N, THF	29
5	5 mol% $PdCl_2(PPh_3)_2$/15 mol% **L2**, Et_3N, THF	41
6	5 mol% $PdCl_2(PPh_3)_2$/15 mol% **L3**, Et_3N, THF	50
7	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L1**, Et_3N, THF	45
8	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L2**, Et_3N, THF	30
9	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L3**, Et_3N, THF	95
10	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L3**, Cs_2CO_3, THF	77
11	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L3**, K_2CO_3, THF	69
12	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L3**, Et_3N, DMF	83
13	5 mol% $PdCl_2(MeCN)_2$/15 mol% **L3**, Et_3N, 1,4-dioxane	67
14	5 mol% $PdCl_2(MeCN)_2$/5 mol% **L3**, Et_3N, THF	30
15	5 mol% $PdCl_2(MeCN)_2$/10 mol% **L3**, Et_3N, THF	54

[a]Reaction conditions (entries 1–15) **1a**, precursor 0.248 m*M* in anhydrous solvent, 1.0 *M* equiv phenylacetylene, 4.5 *M* equiv of base.
[b]Reactions were conducted in closed vial sparged with argon.
[c]Yields refer to isolated and purified products.

Scheme 1. Synthesis of **2a**, **2o**, and **2p** from **1b–1d** at elevated temperature.



trimethylsilyl (TMS) acetylene, to afford **2o** and **2p** in 86 and 76% yields, respectively.

Next, to evaluate the robustness of the optimized procedure, we reacted a number of aliphatic and diversely substituted aryl acetylenes with **1a** (Table 2). The yields ranged from 65 to 95%. With **1a** at RT, we observed a significant difference in the reactivity between 2-methyl- and 4-methyl-substituted aryl acetylenes (entries 2 and 3, Table 2). The reactivity for **1a** at RT, when reacted with 2-methoxy, 3-methoxy, 4-methoxy, and 2-methyl-4-methoxy-substituted aryl acetylenes (entries 4–7, Table 2). Reactions with aryl acetylenes bearing other electron-donating functionalities, namely, *N*,*N*-dimethyl-*p*-acetylene (entry 8, Table 2) and 2-chloroacetylene (entry 9, Table 2) also resulted in good yields.

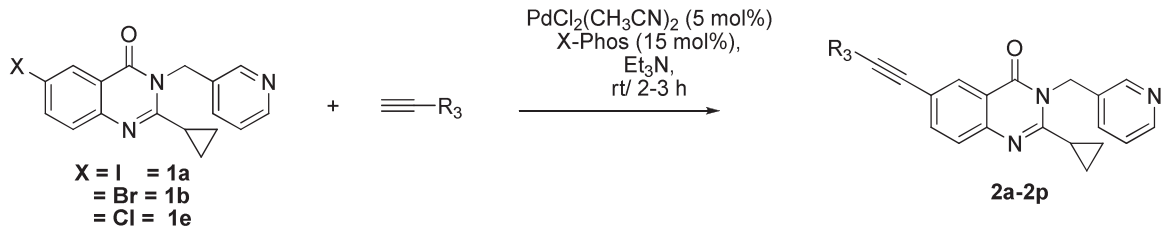
Additionally, the reactions with aryl acetylenes containing electron-withdrawing groups such as 4-(trifluoromethyl), 2-fluoro, 3-fluoro, and 4-nitrophenyl acetylenes with **1a** at RT resulted in 65–88% yields (entries 10–12, Table 2). TMS acetylene also proceeded to afford **2n** in 85% yield with **1a** at RT (entry 14, Table 2).

In order to assess the utility of 6-alkynyl quinazolinones as scaffolds, we subjected **3a** to an array of diverse synthetic transformations, namely, Sonogashira reaction with aryl and heteroaryl halides and "click" chemistry with aryl azides. In a bid to evaluate the synthetic utility of 6-alkynyl quinazolinones as scaffolds, we desilylated **2n** → **2p** in the presence of K_2CO_3 in MeOH at RT, and the resulting compounds **3a** → **3c** were subjected to an array of diversity-imparting reaction. For example, Sonogashira reaction of **3a** with 3-iodopyridine, 2-chloro-5-iodopyridine. and 4-(trifluoromethyl) iodobenzene at RT afforded the desired compounds **4a** → **c** in 76–86% yields. The inactivity of iodophenols/aniline towards the Sonogashira reaction with **3a** prompted us to opt for their corresponding bromoanalogs that afforded the desired compounds **4d–4f** in 43 → 50% yields at 80°C (Scheme 1). "Click" chemistry of **3a** → **3c** with substituted azides (phenyl azide and **11**) in the presence of copper sulfate and sodium-L-ascorbate in *t*-butanol afforded the desired triazoles (**5a–5d)** in 86 → 94% yields at RT for 6 h (Scheme 2).

Antimicrobial activity. All the final products **2a** → **2p**, **5a** → **5d**, and **4a** → **4f** were evaluated for their antimicrobial activity against selected bacterial pathogens such as *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Salmonella typhimurium*, and *Listeria monocytogenes*, by a well diffusion method. The antibiotic amikacin was used as a positive control. From the results, it is evident that **5a**, **5b**, **2c**, and **2k**

Table 2

Sonogashira cross-coupling of various acetylenes with 6-iodo-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one (**2a**).[a,b]



Entry	R^3	Product	Time (h)	Yield (%)[c,d]
1	Phenyl	**2a**	2	95 (90[e]; 70[f])
2	*o*-Tolyl	**2b**	2	90 (70[e])
3	*p*-Tolyl	**2c**	2	70 (72[e]; 68[f])
4	*o*-Anisolyl	**2d**	2	90 (85[e])
5	*m*-Anisolyl	**2e**	2.5	82 (87[e])
6	*p*-Anisolyl	**2f**	2	87 (90[e]; 77[f])
7	*o*-OMe-tolyl	**2g**	2	90 (90[e])
8	*p*-*N*,*N*-diaminophenyl	**2h**	2.5	82 (80[e])
9	*o*-Chlorophenyl	**2i**	2	89 (75[e])
10	*p*-Fluorophenyl	**2j**	2.5	82 (88[e])
11	*o*-Fluorophenyl	**2k**	3	75 (70[e])
12	*m*-Fluorophenyl	**2l**	3	70 (65[e])
13	*p*-Nitrophenyl	**2m**	6	NR (70[e]; 70[f])
14	Trimethylsilyl	**2n**	1	85 (90[e]; 70[f])

[a]Reaction conditions (entries 1–14) iodo, compound (**1a**) 0.248 m*M* in anhydrous.
[b]1 *M* equiv acetylenes, 4.5 equiv Et_3N, 5 mol% of $PdCl_2(MeCN)_2$, 15 mol% X-Phos.
[c]Reactions were conducted in closed vial sparged with argon at room temperature.
[d]Iodo precursor at room temperature; % yields refer to isolated and purified products.
[e]Bromo precursor at 80°C for 8 h.
[f]Chloro precursor at 80°C for 16 h.

demonstrated significant inhibition of bacterial growth (17–25, 18–27, 17–21, 14–18, and 13–18 mm, respectively) (Table 3). From the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), it was observed that **5b** significantly inhibited the growth of tested pathogens, specifically *B. subtilis*, *E. coli*, and *K. pneumoniae* (Table 4) with a potency at par with amikacin. In contrast, the compounds **2b**, **2d**, **2f**, **4b**, **5c**, and **5d** moderately inhibited the growth of these microorganisms.

CONCLUSION

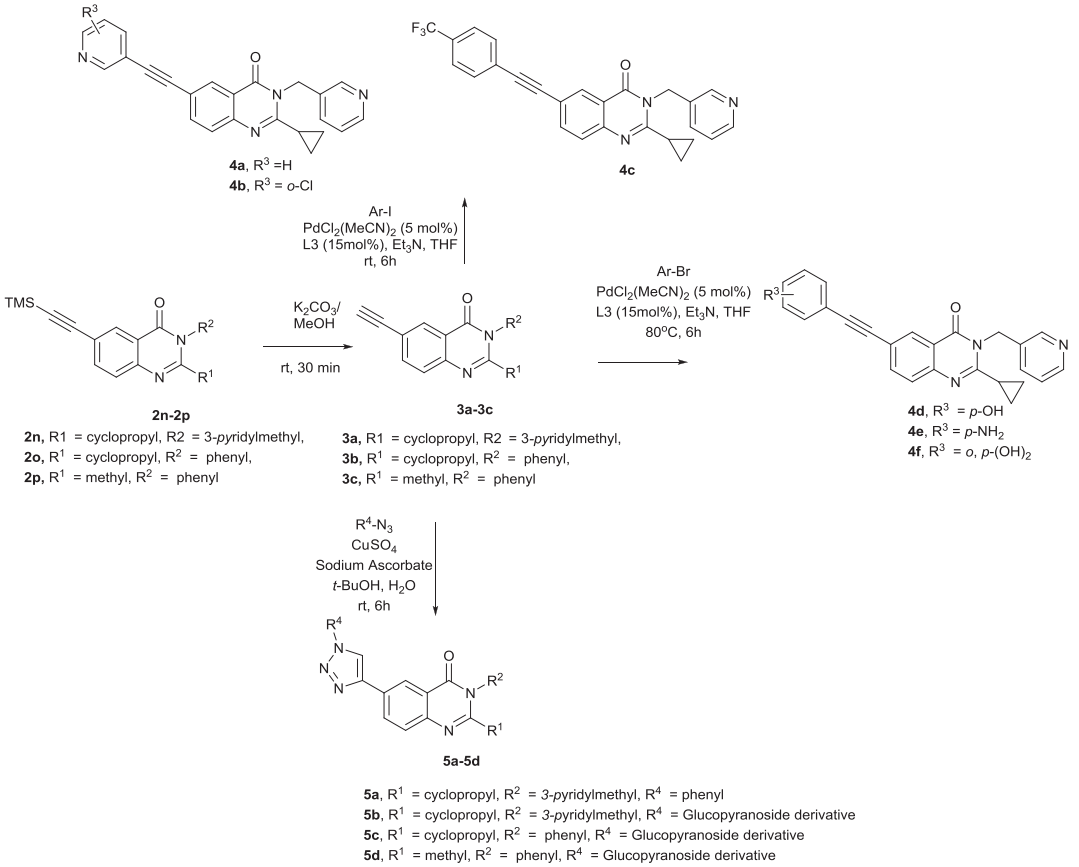
In summary, we have demonstrated a facile Cu-free Sonogashira coupling reaction between substituted 6-halo-quinazolinones with terminal alkynes under mild conditions. Then methodology is tolerant towards various terminal acetylenes, affording the desired compounds in good yields (65–95%). The resulting alkynyl quinazolinone is a versatile scaffold that undergoes diverse transformations to generate highly functionalized quinazolinones exhibiting activity against a variety of microorganisms.

EXPERIMENTAL

General experimental conditions. Thin-layer chromatography was performed on 250-mm silica plates, and column chromatographic purifications were performed on 100- to 200-mesh silica gel. All acetylenes, aromatic halides, ligands **L1**–**L3**, $PdCl_2(PPh_3)_2$, $PdCl_2(CH_3CN)_2$, and all other reagents were obtained from commercial suppliers and were used without further purification. THF was distilled over $NaBH_4$ and then stored over Na. Prior to each reaction, THF was freshly distilled. For syntheses of compounds **1a**, **1b**, and **1c** as well as their precursors, please see the Supporting Information. ^{1}H-NMR spectra were collected at either 400 or 300 MHz, and spectra are referenced to residual protiosolvent. ^{13}C-NMR spectra, collected at either 100 or 75 MHz, are referenced to the carbon resonance of the deuterated solvent. Spectra were obtained either in deacidified $CDCl_3$ (deacidification was performed by percolating the solvent through a bed of solid $NaHCO_3$ and basic alumina) or in hexadeuterated dimethyl sulfoxide (DMSO-d_6) (see specific compound descriptions in the following). High-resolution mass spectrometry (HRMS) was performed at the Mass Spectrometry Laboratory at GVK Biosciences Pvt. Ltd. Liquid chromatography (LC)–mass spectrometry analyses were performed with electrospray ionization (ESI) and operated in the positive ion mode. LC analysis was performed using a diode array detector.

Preparation of 2-cyclopropyl-6-iodo-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (1a). Cyclopropyl carboxylic acid

Scheme 2. Diverse synthesis of functionalized quinazolinones.



(0.41 g, 11.40 mmol) was added to a stirred solution of 2-amino-5-iodobenzoic acid (3 g, 11.40 mmol) and triphenyl phosphite (3.53 g, 11.40 mmol) in pyridine (30 mL); the reaction mixture was heated to reflux for 4 h. After that, pyridin-3-ylmethanamine (1.23 g, 11.40 mmol) was added to the aforementioned refluxed reaction, and heating was continued for 12 h. After completion of the reaction, the reaction mixture was cooled to RT, the mixture was poured into EtOH, and the precipitated solid was filtered. The resulting solid was applied to a silica gel column, packed in 20% EtOAc in *n*-hexane. Sequential elution with 20% EtOAc in *n*-hexane and 50% EtOAc in *n*-hexane gave 1.1 g of 6-bromo-2-cyclopropyl-3-(pyridin-3-ylmethyl)quinazolin-4-(*3H*)-one as a white solid: yield 1.7 g (80%); R_f (70% EtOAc in petroleum ether) = 0.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.57 (s, 1H, pyridyl N attached carbon), 8.50–8.49 (d, J = 4 Hz, 1 H, Ar-H), 8.39–8.39 (d, J = 1.6 Hz, 1H, pyridyl proton), 8.07–8.04 (dd, J = 8.6 Hz, 1H, Ar-H), 7.65–7.63 (d, J = 8.0 Hz, 1H, Ar-H), 7.37–7.32 (m, 1H, Ar-H), 5.58 (s, 2H, NCH_2), 2.18–2.16 (m, 1H, cyclopropyl), 1.08–1.03 (m, 2H, cyclopropyl), 0.96–0.94 (m, 2H, cyclopropyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.3 (amide C=O position), 158.7 (Ar-C), 148.5 (Ar-C), 148.2 (Ar-C), 146.3, 142.7, 134.5, 134.3, 132.2, 128.8, 123.6, 121. 90.6, 43.9 (NCH_2), 13.9 (cyclopropyl), 9.3 (cyclopropyl); mp 142–144°C.

Preparation of 6-bromo-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (1b). Cyclopropylcarboxylic acid (1.67 g, 46.296 mmol) was added to a stirred solution of 2-amino-5-bromobenzoic acid (10 g, 46.296 mmol) and triphenyl phosphite (14.36 g, 46.29 mmol) in pyridine (100 mL); the reaction mixture was heated to reflux for 4 h. Pyridin-3-ylmethanamine (5 g, 46.296 mmol) was added to the aforementioned reaction mixture, and heating was continued for another 12 h. After completion of the reaction [monitored by thin-layer chromatography (TLC)], the reaction mixture was cooled to RT, the mixture was poured into EtOH, and the precipitated solid was filtered. The resulting solid was applied to a silica gel column, compound was eluted with 50% EtOAc in *n*-hexane gave 6-bromo-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (**1b**) as a white solid: yield 13.0 g (78.8%); R_f (70% EtOAc in petroleum ether) = 0.4. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.58 (s, 1H, Ar-H), 8.49 (d, J = 4.8 Hz, 1H, Ar-H), 8.20 (d, J = 1.6 Hz, 1H, Ar-H), 7.93 (dd, J = 2.4, 2.4 Hz, 1H, Ar-H), 7.64 (d, J = 8.0 Hz, 2H, Ar-H), 7.50 (d, J = 8.8 Hz, 1H, Ar-H), 7.39–7.34 (m, 1H, Ar-H), 5.58 (s, 2H, NCH_2), 2.19–2.13 (m, 1H, cyclopropyl), 1.10–1.06 (m, 2H, cyclopropyl), 0.97–0.92 (m, 2H, cyclopropyl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.5 (amide C=O), 158.7 (Ar-C), 148.5 (Ar-C), 148.2 (Ar-C), 146.0 (Ar-C), 137.2 (Ar-C), 134.4 (Ar-C), 132.2 (Ar-C), 129.0 (Ar-C), 128.4 (Ar-C), 123.6 (Ar-C), 121.3 (Ar-C), 118.2 (Ar-C), 44.0 (NCH_2), 13.9 (cyclopropyl), 9.4 (cyclopropyl); mp 158–160°C.

Table 3

Antimicrobial activity (zone of inhibition) of synthesized compounds.

Organisms / Compounds	*Bacillus subtilis*	*Escherichia coli*	*Klebsiella pneumoniae*	*Staphylococcus epidermidis*	*Staphylococcus aureus*	*Staphylococcus typhimurium*	*Listeria monocytogenes*	*Streptococcus faecalis*
1d	13 mm	18 mm	16 mm	12 mm	14 mm	16 mm	13 mm	14 mm
2b	12 mm	10 mm	11 mm	15 mm	13 mm	11 mm	11 mm	10 mm
2c	19 mm	17 mm	20 mm	21 mm	20 mm	19 mm	20 mm	17 mm
2d	14 mm	10 mm	13 mm	15 mm	18 mm	14 mm	16 mm	16 mm
2f	12 mm	15 mm	14 mm	13 mm	16 mm	12 mm	11 mm	14 mm
2g	NZ	NZ	24 mm	NZ	NZ	16 mm	21 mm	18 mm
2k	16 mm	15 mm	17 mm	14 mm	15 m	17 mm	18 mm	15 mm
4b	NZ	11 mm	13 mm	11 mm	10 mm	NZ	13 mm	14 mm
5a	25 mm	22 mm	20 mm	21 mm	20 mm	19 mm	20 mm	17 mm
5b	27 mm	23 mm	25 mm	20 mm	20 mm	24 mm	18 mm	23 mm
5c	14 mm	15 mm	13 mm	16 mm	15 mm	14 mm	15 mm	15 mm
5d	15 mm	14 mm	12 mm	15 mm	14 mm	16 mm	12 mm	11 mm
Amikacin[a]	27 mm	25 mm	25 mm	24 mm	19 mm	21 mm	17 mm	18 mm

NZ = No zone of inhibition.
[a]Standard reference antibiotic (aminoglycosidic antibiotic) and its observed antimicrobial activity in the present investigation.

Table 4

Minimum inhibitory and minimum bactericidal concentrations of active compounds.

Organisms / Compounds	*Bacillus subtilis*	*Escherichia coli*	*Klebsiella pneumoniae*	*Staphylococcus epidermidis*	*Staphylococcus aureus*	*Salmonella typhimurium*	*Listeria monocytogenes*	*Streptococcus faecalis*
Minimum inhibitory concentrations								
1d	0.412	0.412	0.206	0.103	0.103	0.412	0.412	0.206
5a	0.206	0.06	0.06	0.206	0.06	0.103	0.103	0.206
5b	0.206	0.103	0.103	0.206	0.06	0.103	0.103	0.206
5c	0.412	0.412	0.103	0.206	0.206	0.206	0.412	0.412
5d	0.206	0.206	0.412	0.103	0.206	0.103	0.206	0.206
Minimum bactericidal concentrations								
1d	>0.8	>0.8	>0.4	>0.2	>0.2	>0.8	>0.8	>0.4
5a	>0.4	<0.15	<0.15	>0.2	<0.15	>0.2	>0.2	>0.4
5b	>0.4	>0.2	>0.2	>0.4	<0.15	>0.2	>0.2	>0.4
5c	>0.8	>0.8	>0.2	>0.4	>0.4	>0.4	>0.8	>0.8
5d	>0.4	>0.4	>0.8	>0.2	>0.4	>0.2	>0.4	>0.4

Note: The minimum inhibitory and minimum bactericidal concentrations were represented in moles per liter

6-Bromo-2-cyclopropyl-3-phenylquinazolin-4(3H)-one (1c). Cyclopropylcarboxylic acid (1 eq, 9.259 mmol) was added to a stirred solution of 2-amino-5-bromobenzoic acid (2 g, 9.259 mmol) and triphenyl phosphite (1 eq, 9.259 mmol) in pyridine (30 mL); the reaction mixture was heated to reflux for 4 h. Aniline (1 eq, 9.259 mmol) was added to the aforementioned reaction mixture, and heating was continued for another 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to RT, the mixture was poured into EtOH, and the precipitated solid was filtered. The resulting solid was applied to a silica gel column, compound was eluted with 35% EtOAc in n-hexane to gave pure compound **1c** as an off-white solid: yield 3.0 g (95%); R_f (70% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (300 MHz, DMSO-d_6), δ 8.14 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.94 (dd, *J* = 2.7 Hz, 1H, Ar-H), 7.63–7.47 (m, 6H, Ar-H), 1.38–1.32 (m, 1H, cyclopropyl), 1.17 (m, 2H, cyclopropyl), 0.85 (m, 2H, cyclopropyl). ^{13}C-NMR (75 MHz, DMSO-d_6): 160.2 (amide C=O), 158.7 (Ar-C), 146.4 (Ar-C), 137.2 (Ar-C), 137.1 (Ar-C), 129.5 (Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C),121.9 (Ar-C), 118.7 (Ar-C), 118.0 (Ar-C), 115.1 (Ar-C), 14.8 (cyclopropyl), 10.1 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{17}H_{14}ON_2$ Br $[M + H]^+$ 341.0284; found 341.0277.

6-Bromo-2-methyl-3-phenylquinazolin-4(3H)-one (1d). Acetic acid (1 eq, 9.259 mmol) was added to a stirred solution of 2-amino-5-bromobenzoic acid (2 g, 9.259 mmol) and triphenyl phosphite (1 eq, 9.259 mmol) in pyridine (30 mL); the reaction mixture was heated to reflux for 4 h. Aniline (1 eq, 9.259 mmol) was added to the aforementioned reaction mixture, and heating was continued for another 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to RT, the mixture was poured into EtOH, and the precipitated solid was filtered. The resulting solid was applied to a silica gel column, compounds were purified by 38% EtOAc in *n*-Hexane. Sequential elution with 20% EtOAc in *n*-hexane to 50% EtOAc in *n*-hexane. The precipitated compound was triturated by using *n*-hexane and dried to obtain pure compound **1d** as an off-white solid: yield 2.4 g (82%); R_f (70% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.15 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.99 (dd, *J* = 2.4 Hz, 1H, Ar-H), 7.62–7.44 (m, 6H, Ar-H), 2.10 (s, 3H, Me). ^{13}C-NMR (75 MHz, DMSO-d_6): 160.1 (amide C=O), 155.1 (Ar-C), 146.2 (Ar-C), 137.5 (Ar-C), 137.3 (Ar-C), 129.6 (Ar-C), 129.0 (Ar-C), 128.2 (Ar-C), 122.1 (Ar-C), 118.6 (Ar-C), 24.0 (Me). HRMS (ESI): *m/z* Calcd for $C_{15}H_{12}ON_2Br$ $[M + H]^+$ 315.0128; found 315.0122.

Preparation of 6-chloro-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (1e). Cyclopropylcarboxylic acid (0.21 g, 5.828 mmol) was added to a stirred solution of 2-amino-5-chlorobenzoic acid (1.0 g, 5.828 mmol) and triphenyl phosphite (1.8 g, 5.828 mmol) in pyridine (10 mL); the reaction mixture was heated to reflux for 4 h. Pyridin-3-ylmethanamine (0.62 g, 5.828 mmol) was added to the aforementioned refluxed reaction mixture, and heating was continued for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to RT, the mixture was poured into EtOH, and the precipitated solid was filtered. The resulting solid was applied to a silica gel column, compound was eluted with 50% EtOAc in n-hexane to gave compound **1e** as a white solid: yield 1.5 g (82%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.50 (d, *J* = 3.6 Hz, 1 H), 8.06 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.37 (dd, *J* = 7.2, 4.8 Hz, 1H), 5.58 (s, 2H), 2.18–2.16 (m, 1H), 1.08–1.03 (m, 2H), 0.96–0.94 (m, 2H). ^{13}C-NMR (75 MH_Z, $CDCl_3$): δ 160.5, 158.7, 148.5, 148.2, 146.0, 137.2, 134.4, 132.2, 129.0, 128.4, 123.6, 121.3, 118.2, 44.0, 13.9, 9.4; mp 160–162°C. Color of the compound: white solid. R_f: 0.4 (70% EtOAc in petroleum ether).

General procedure for the Sonogashira cross-coupling of 2-cyclopropyl-6-iodo-3-(pyridin-3-ylmethyl) quinazolin-4 (3*H*)-one (1a) to obtain compounds 2a to 2n at RT reactions. In an oven-dried, screw-capped vial equipped with a stirring bar were placed 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), aromatic acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol). These were dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 2–4 h, the reaction mixture was cooled and diluted with EtOAc and filtered on a Celite bed; the filtrate layer was washed with water, and the organic layer was separated and dried over Na_2SO_4. Evaporation under reduced pressure provided the crude product, which was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with petroleum ether, followed by 70% EtOAc in petroleum ether, afforded the requisite compound as a white solid; the obtained yield varied from 70 to 95%. This was finally dried under high vacuum to remove traces of solvent. (See the following specific compound headings for details.)

2-Cyclopropyl-6-(phenylethynyl)-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (2a). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), phenylacetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2a** as an off-white solid: yield 89 mg (95%); R_f (70% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H, Ar-H), 7.82–7.80 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.66–7.64 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.55–7.49 (m, 4H, Ar-H), 7.35–7.25 (m, 4H, Ar-H), 5.63 (s, 2H, NCH_2), 1.89 (m, 1H, cyclopropyl), 1.26 (m, 2H, cyclopropyl), 1.01 (m, 2H, cyclopropyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.9 (amide C=O), 157.9 (Ar-C), 147.05 (Ar-C), 137.07 (Ar-C), 132.1 (Ar-C), 132.0 (Ar-C), 131.8 (Ar-C), 131.6 (Ar-C), 130.3 (Ar-C), 128.8 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 127.2 (Ar-C), 122.9 (Ar-C), 121.4 (Ar-C), 120.1 (Ar-C), 90.6, 88.5, 44.6 (NCH_2), 14.4 (cyclopropyl), 9.3 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{25}H_{20}N_3O$ $[M + H]^+$ 378.1597; found 378.1606; mp 113–116°C.

2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(O-tolylethynyl) quinazolin-4(3H)-one (2b). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *o*-tolyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with

$PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2b**, an off-white solid: yield 88 mg (90%); R_f (70% EtOAc in *n*-hexane) = 0.31. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.62–8.54 (m, 2H, Ar-H), 8.43 (bs, 1H, Ar-H), 7.83–7.80 (m, 1H, Ar-H), 7.60–7.49 (m, 3H, Ar-H), 7.28–7.18 (m, 4H, Ar-H), 5.60 (s, 2H, N-CH_2), 2.53 (m, 3H, Ar-Me), 1.90–1.88 (m, 1H, cyclopropyl), 1.27–1.26 (m, 2H), 1.02–1.00 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.9 (amide C=O), 157.8 (Ar-C), 149.2 (Ar-C), 148.4 (Ar-C), 146.9 (Ar-C), 140.3 (Ar-C), 137 (Ar-C), 134.6 (Ar-C), 132.1 (Ar-C), 131.9 (Ar-C), 130 (Ar-C), 129.5 (Ar-C), 128.5 (Ar-C), 127.2 (Ar-C), 125.6 (Ar-C), 123.7 (Ar-C), 122.6 (Ar-C), 121.6 (Ar-C), 120.1 (Ar-C), 92.4, 89.6, 44.3 (N-CH_2), 20.7 (Ar-Me), 14.4, 9.3 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{25}H_{19}N_4O_3$ $[M + H]^+$ 423.1416; found 423.1457; mp 121–123°C.

2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(p-tolylethynyl) quinazolin-4(3H)-one (2c). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *p*-tolyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2c** as a light-yellow solid: yield 68 mg (70%); R_f (70% EtOAc in *n*-hexane) = 0.4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.61–8.55 (m, 2H, Ar-H), 8.42 (bs, 1H, Ar-H), 7.82 (dd, *J* = 8.7 Hz, 1H, Ar-H), 7.60 (m, 2H, Ar-H), 7.45 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.29–7.26 (m, 1H, Ar-H), 7.17 (d, *J* = 7.8 Hz, 2H, Ar-H), 5.60 (s, 2H, N-CH_2), 2.37 (s, 3H, Ar-Me), 1.91 (m, 1H, cyclopropyl), 1.25 (m, 2H, cyclopropyl), 1.02 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.9 (amide C=O), 157.8 (Ar-C), 149.16 (Ar-C), 148.42 (Ar-C), 146.89 (Ar-C), 138.7 (Ar-C), 137.0 (Ar-C), 134.6 (Ar-C), 132.1 (Ar-C), 131.5 (Ar-C), 130.1 (Ar-C), 129.1 (Ar-C), 127.1 (Ar-C), 123.8 (Ar-C), 121.6 (Ar-C), 120.1 (Ar-C), 119.7 (Ar-C), 87.8, 90.9, 44.3 (N-CH_2) 21.5 (Ar-Me), 14.4, 9.3 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{26}H_{22}N_3O$ $[M + H]^+$ 392.1779; found 392.1763; mp 122–125°C.

2-Cyclopropyl-6-((2-methoxyphenyl)ethynyl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (2d). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *o*-anisolyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2d** as an off-white solid: yield 91 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.35. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H, Ar-H), 8.56 (d, *J* = 4.2 Hz, 1H, Ar-H), 8.47 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.86 (dd, *J* = 8.4 Hz, 1H, Ar-H), 7.60–7.50 (m, 3H, Ar-H), 7.35–7.25 (m, 2H, Ar-H), 6.97–6.90 (m, 2H, Ar-H), 5.60 (s, 2H, N-CH_2), 3.93 (s, 3H, Ar-Me), 1.91 (m, 1H, cyclopropyl), 1.29 (m, 2H, Ar-H), 1.03 (m, 2H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.9 (amide C=O), 160.0 (Ar-C), 157.8 (Ar-C), 149.1 (Ar-C), 148.4 (Ar-C), 146.9 (Ar-C), 137.1 (Ar-C), 134.6 (Ar-C), 133.5 (Ar-C), 132.1 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 127.0 (Ar-C), 123.8 (Ar-C), 121.7 (Ar-C), 120.5 (Ar-C), 120.0 (Ar-C), 112.0 (Ar-C), 110.6, 92.5, 87.1, 55.8 (Ar-OMe), 44.3 (Ar-Me), 14.4, 9.2 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{26}H_{22}N_3O_2$ $[M + H]^+$ 408.1746; found 408.1712; mp 135–138°C.

2-Cyclopropyl-6-((3-methoxyphenyl)ethynyl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (2e). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *m*-anisolyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred for RT at 2.5 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2e** as a white solid: yield 83 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.35. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.62–8.50 (m, 2H, Ar-H), 8.44 (m, 1H, Ar-H), 7.83–7.80 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.60–7.52 (m, 2H, Ar-H), 7.29–7.08 (m, 4H, Ar-H), 6.93 (d, *J* = 7.8 Hz, 1H, Ar-H), 5.60 (s, 2H, N-CH_2), 3.83 (s, 3H, Ar-OMe), 1.89 (m, 1H, cyclopropyl), 1.27 (m, 2H, cyclopropyl), 1.02 (m, 2H, cyclopropyl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.8 9 (amide C=O), 159.3 (Ar-C), 157.9 (Ar-C), 149.1 (Ar-C), 148.4 (Ar-C), 147.0 (Ar-C), 137.0 (Ar-C), 134.5 (Ar-C), 132.1 (Ar-C), 130.3 (Ar-C), 129.4 (Ar-C), 127.1 (Ar-C), 124.1 (Ar-C), 123.8 (Ar-C), 123.7 (Ar-C), 121.2 (Ar-C), 120.1 (Ar-C), 116.3 (Ar-C), 115.2 (Ar-C), 90.5, 88.3, 55.2 (N-CH_2), 44.3 (Ar-OMe), 14.4, 9.3 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{26}H_{22}N_3O_2$ $[M + H]^+$ 408.1759; found 408.1712; mp 155–158°C.

2-Cyclopropyl-6-((4-methoxyphenyl)ethynyl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (2f). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *p*-anisolyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2f** as an off-white solid: yield 88 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 2.5 Hz, 1H, Ar-H), 8.55 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.40 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.80–7.77 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.0, Hz, 1H, Ar-H, Ar-H), 7.53–7.46 (m, 3H, Ar-H), 7.28–7.25 (m, 1H, Ar-H), 6.90–6.87 (d, *J* = 8.8 Hz, 2H, Ar-H), 5.60 (s, 2H, N-CH_2), 3.83 (s, 3H, Ar-OMe), 1.90 (m, 1H), 1.27–1.24 (m, 2H), 1.02 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.9 (amide C=O), 159.8 (Ar-C), 157.7 (Ar-C), 149.1 (Ar-C), 148.4 (Ar-C), 146.8 (Ar-C), 136.9 (Ar-C), 134.5 (Ar-C), 133.1 (Ar-C), 132.1 (Ar-C), 129.9 (Ar-C), 127.1 (Ar-C), 123.7 (Ar-C), 121.7 (Ar-C), 120.1 (Ar-C), 115.0 (Ar-C), 114.0 (Ar-C), 90.7, 87.3, 55.2 (N-CH_2), 44.3 (Ar-OMe), 14.4, 9.2 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{26}H_{22}N_3O_2$ $[M + H]^+$ 408.1661; found 408.1712; mp 138–142°C.

2-Cyclopropyl-6-((4-methoxy-2-methylphenyl)ethynyl)-3-(pyridine-3-ylmethyl)quinazolin-4(3H)-one (2g). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *o*-OMe-tolyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2g** as a pale yellow solid: yield 94.5 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.69–8.49 (m, 2H, Ar-H), 8.40 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.80 (dd, *J* = 8.1, 2.0 Hz, 1H, Ar-H), 7.59 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.53 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.44 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.27 (q, *J* = 4.4, 4.0 Hz, 1H, Ar-H), 6.78 (d, *J* = 2.7 Hz, 1H, Ar-H), 6.73 (dd, *J* = 8.3, 2.7 Hz, 1H, Ar-H), 5.60 (s, 2H, N-CH_2), 3.82 (s, 3H, Ar-OMe), 2.51 (s, 3H, Ar-Me), 1.89 (m, 1H), 1.27 (m, 2H), 1.01 (m, 2H) (cyclopropyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.0 (amide C=O), 159.8 (Ar-C), 157.6 (Ar-C), 149.1 (Ar-C), 148.4 (Ar-C), 146.7 (Ar-C), 142.1 (Ar-C), 136.9 (Ar-C), 134.6 (Ar-C), 133.3 (Ar-C), 132.1 (Ar-C), 129.7 (Ar-C), 127.1 (Ar-C), 123.7 (Ar-C), 122.0 (Ar-C), 120.1 (Ar-C), 115.1 (Ar-C), 114.9 (Ar-C), 111.3 (Ar-C), 91.1, 89.8, 55.2 (N-CH_2), 44.3 (Ar-OMe), 21.0 (Ar-Me), 14.4, 9.2 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{27}H_{24}N_3O_2$ $[M + H]^+$ 422.1886; found 422.1869; mp 143–146°C.

2-Cyclopropyl-6-((4-(dimethylamino)phenyl)ethynyl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (2h). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *p*-*N*,*N*-diaminophenyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2.5 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2h** as a pale yellow solid: yield 85.5 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.2. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.61 (bs, 1H, Ar-H), 8.55 (d, *J* = 4.5 Hz, 1H, Ar-H), 8.38 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.80–7.76 (dd, *J* = 8.5 Hz, 1H, Ar-H), 7.60 (d, *J* = 7.8, Hz, 1H, Ar-H), 7.52 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.43–7.40 (m, 2H, Ar-H), 7.28–7.24 (m, 1H, Ar-H), 6.68–6.65 (m, 2H, Ar-H), 5.60 (s, 2H, N-CH_2), 3.00 (s, 6H, NMe_2), 1.90 (m, 1H), 1.29–1.25 (m, 2H), 1.02–0.98 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.9 (amide C=O), 157.3 (Ar-C), 150.2 (Ar-C), 149.1 (Ar-C), 148.4 (Ar-C), 146.4 (Ar-C), 136.8 (Ar-C), 134.5 (Ar-C), 132.8 (Ar-C), 132.2 (Ar-C), 129.5 (Ar-C), 127 (Ar-C), 123.7 (Ar-C), 122.4 (Ar-C), 120.1 (Ar-C), 111.7 (Ar-C), 109.9 (Ar-C), 109.4 (Ar-C), 92.1, 86.6, 44.3 (N-CH_2), 40.1, 29.6 (NMe_2), 14.4, 9.17 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{27}H_{25}N_4O$ $[M + H]^+$ 421.2065; found 421.2028; mp 214–218°C.

6-((2-Chlorophenyl)ethynyl)-2-cyclopropyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (2i). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *o*-chlorophenyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2i** as a white solid: yield 91 mg (89%); R_f (70% EtOAc in *n*-hexane) = 0.45. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H, Ar-H), 8.56–8.55 (m, 1H, Ar-H), 8.48 (m, 1H, Ar-H), 7.86–7.83 (dd, *J* = 8.2 Hz, 1H, Ar-H), 7.65–7.51 (m, 3H, Ar-H), 7.44–7.40 (m, 1H, Ar-H), 7.35–7.33 (m, 1H, Ar-H), 7.28–7.25 (m, 2H, Ar-H), 5.60 (s, 2H, N-CH_2), 1.90 (m, 1H), 1.28–1.25 (m, 2H), 1.01 (m, 2H) (cyclopropyl). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 161.9 (amide C=O), 157.8 (Ar-C), 149.2 (Ar-C), 148.4 (Ar-C), 146.9 (Ar-C), 140.3 (Ar-C), 137 (Ar-C), 134.6 (Ar-C), 132.1 (Ar-C), 131.9 (Ar-C), 130 (Ar-C), 129.5 (Ar-C), 128.5 (Ar-C), 127.2 (Ar-C), 125.6 (Ar-C), 123.7 (Ar-C), 122.6 (Ar-C), 121.6 (Ar-C), 120.1 (Ar-C), 92.4, 89.6, 44.3(N-CH_2) 14.4, 9.3 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{25}H_{19}N_3OCl$ $[M + H]^+$ 412.1212; found 412.1217; mp 115–118°C.

2-Cyclopropyl-3-(pyridine-3-ylmethyl)-6-(((4-trifluoromethyl)phenyl)ethynyl)quinazolin-4(3H)-one (2j). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *p*-fluorophenyl (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 2.5 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2j** as an off-white solid: yield 91 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.5. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.67–8.51 (m, 2H, Ar-H), 8.46 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.82 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar-H), 7.66–7.54 (m, 6H, Ar-H), 7.29–7.26 (m, 1H, Ar-H), 5.60 (s, 2H, N-CH_2), 1.92–1.88 (m, 1H), 1.28–1.25 (m, 2H), 1.02 (m, 2H) (cyclopropyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.8 (amide C=O), 158.3 (Ar-C), 149.2, 148.4, 147.4, 137.0, 134.6 (Ar-C), 132.0, 131.8, 130.6, 127.3, 126.7, 125.3, 125.3, 123.7, 120.5, 120.2 (Ar-C), 90.8, 89.1, 44.4 (N-CH_2) 14.4, 9.4 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{26}H_{19}N_3OF_3$ $[M + H]^+$ 446.1476; found 446.1480; mp 163–166°C.

2-Cyclopropyl-6-(2-fluorophenyl)ethynyl-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (2k). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *o*-fluorophenyl (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture stirred at RT for 3 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2k** as a brown solid: yield 74 mg (75%); R_f (70% EtOAc in *n*-hexane) = 0.4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.61–8.54 (m, 2H, Ar-H), 8.45 (s, 1H, Ar-H), 7.84 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.59–7.52 (m, 3H, Ar-H),7.33–7.25 (m, 3H, Ar-H), 7.15–7.08 (m, 1H, Ar-H), 5.59 (s, 2H, N-CH_2), 1.88 (m, 1H), 1.26 (m, 2H), 1.01 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.0 (amide C=O), 160.9, 158.1, 149.1, 148.4 (Ar-C), 147.2, 137, 134.6 (Ar-C), 133.4, 132.0 (Ar-C), 130.2, 127.2 (Ar-C), 124.0, 123.9,

123.7, 120.9, 120.1, 115.7 (Ar-C), 93.4, 83.9, 44.3 (N-CH_2), 14.4, 9.3 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{25}H_{19}N_3OF$ $[M + H]^+$ 396.1524; found 396.1512; mp 123–127°C.

2-Cyclopropyl-6-((3-fluorophenyl)ethynyl)-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (2l). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *m*-fluorophenyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 3 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2l** as a brown solid: yield 69 mg (70%); R_f (70% EtOAc in *n*-hexane) = 0.4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.62 (m, 1H, Ar-H), 8.56–8.55 (m, 1H, Ar-H), 8.44 (d, *J* = 1.9 Hz, 1H, Ar-H), 7.82–7.79 (dd, *J* = 8.6 Hz, 1H, Ar-H), 7.61–7.53 (m, 2H, Ar-H), 7.32–7.22 (m, 5H, Ar-H), 5.60 (s, 2H, N-CH_2), 1.92 (m, 1H), 1.30–1.26 (m, 2H), 1.04–0.94 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.8 (amide C=O), 160.7, 158.1 (Ar-C), 149.1 (Ar-C), 148.4, 147.2 (Ar-C), 137.0, 134.6 (Ar-C), 132.0, 130.5, 130.0 (Ar-C), 127.5 (Ar-C), 127.2, 123.8 (Ar-C), 120.7, 120.1 (Ar-C), 118.5, 118.2, 115.7 (Ar-C), 89.3, 83.3, 44.3 (N-CH_2), 14.4, 9.4 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{25}H_{19}N_3OF$ $[M + H]^+$ 396.1515; found 396.1512; mp 105–110°C.

2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-((TMS)ethynyl) quinazolin-4(3H)-one (2n). This was synthesized using 6-iodo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), TMS acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon and added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), and the mixture was stirred at RT for 1 h. The solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2n** as an off-white solid: yield 79 mg (85%); R_f (70% EtOAc in *n*-hexane) = 0.45. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.60–8.54 (m, 2H, Ar-H), 8.37 (m, 1H, Ar-H), 7.75 (dd, *J* = 8.4 Hz, 1H, Ar-H), 7.58 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.50 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.28–7.24 (t, *J* = 6.3 Hz 1H, Ar-H), 5.58 (s, 2H, N-CH_2), 1.90 (m, 1H), 1.28–1.24 (m, 2H), 1.03 (m, 2H) (cyclopropyl), 0.26 (s, 9H) (TMS protons). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.8 (amide C=O), 158.0 (Ar-C), 149.1, 148.4 (Ar-C), 147.1, 137.3, 134.6 (Ar-C), 132.1, 130.8 (Ar-C), 127.0, 123.7 (Ar-C), 121.1, 119.9 (Ar-C), 103.9, 95.7, 44.3 (N-CH_2) 14.4, 9.3 (cyclopropyl), 0.13 (TMS). HRMS (ESI): *m/z* Calcd for $C_{22}H_{24}N_3OSi$ $[M + H]^+$ 374.1663; found 374.1689; mp 127–130°C.

General procedure for the Sonogashira coupling of the bromoanalogs at 80 °C to obtain 1b to **2a**. In an oven-dried, screw-capped vial equipped with a stirring bar, **1b** (150 mg, 1 eq, 0.421 mmol), phenyl acetylene (1 eq, 0.631 mmol), and Et_3N (4.5 eq, 1.894 mmol) were dissolved in anhydrous THF (10 V), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.018 mmol) and X-Phos (**L3**, 0.15 eq, 0.055 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 80°C. The reaction was monitored by TLC. Upon completion, the reaction mixture was cooled and diluted with EtOAc and filtered through a Celite bed; the filtrate layer was washed with water, and the organic layer was separated and dried over Na_2SO_4. Evaporation under reduced pressure provided the crude product, which was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with petroleum ether, followed by 70% EtOAc in petroleum ether, afforded the requisite compound as a white solid in 85% yield. (See **2a** for the characterization details.)

2-Cyclopropyl-6-((4-nitrophenyl)ethynyl)-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (2m). This was synthesized using 6-bromo- and 2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (100 mg, 1 eq, 0.248 mmol), *p*-nitrophenyl acetylene (1 eq, 0.248 mmol), and Et_3N (4.5 eq, 1.12 mmol), in THF (1 mL), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0124 mmol) and X-Phos (**L3**, 0.15 eq, 0.037 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 80°C for 6 h. The reaction was monitored by TLC. Upon completion, the solvent was filtered and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **2m** as a yellow solid: yield 83 mg (70%); R_f (70% EtOAc in *n*-hexane) = 0.5. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.61–8.55 (m, 2H Ar-H), 8.46 (s, 1H, Ar-H), 8.24–8.22 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.85–7.81 (dd, *J* = 8.0, Hz, 1H, Ar-H), 7.70–7.67 (m, 2H, Ar-H), 7.61–7.56 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.30–7.26 (m, 1H, Ar-H), 5.60 (s, 2H, N-CH_2), 1.92 (m, 1H), 1.29–1.28 (m, 2H), 1.04–1.02 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.7 (amide C=O), 158.6 (Ar-C), 149.2, 148.3 (Ar-C), 147.7, 147.1, 137, 134.6, 132.3 (Ar-C), 131.9, 130.9 (Ar-C), 129.8 (Ar-C), 127.4, 123.8 (Ar-C), 123.6, 120.2, 119.9 (Ar-C), 93.6, 88.6, 44.4 (N-CH_2), 14.4, 9.5 (cyclopropyl). HRMS (ESI): *m/z* Calcd for $C_{25}H_{19}N_4O_3$ $[M + H]^+$ 423.1416; found 423.1457; mp 153–156°C.

2-Cyclopropyl-3-phenyl-6-((TMS)ethynyl)quinazolin-4(3H)-one (2o). This was synthesized using **1c** (0.3 g, 1 eq, 0.879 mmol), TMS acetylene (1 eq, 0.879 mmol), and Et_3N (4.5 eq, 3.955 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0439 mmol) and X-Phos (**L3**, 0.15 eq, 0.1318 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 80°C for 6 h. The reaction was monitored by TLC. Upon completion, the solvent was filtered and purified by column chromatography, which was performed using 40% EtOAc in *n*-hexane, and dried to obtain pure compound **2o** as an off-white solid: yield 0.27 g (86%); R_f (40% EtOAc in *n*-hexane) = 0.6. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.33 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.76 (dd, *J* = 1.8 Hz, 1H, Ar-H), 7.58–7.47 (m, 4H, Ar-H), 7.34 (d, *J* = 6.9 Hz, 2H, Ar-H), 1.42 (m, 1H), 1.30 (m, 2H), 0.87 (m, 2H) (cyclopropyl) 0.26 (s, 9H) (TMS). ^{13}C-NMR (75 MHz, $CDCl_3$): 161.1 (amide C=O), 158.8, 147.6 (Ar-C), 137.3 (Ar-C), 137.2, 130.7 (Ar-C), 129.8 (Ar-C), 129.1, 128.4 (Ar-C), 126.8, 120.7 (Ar-C), 120.4 (Ar-C), 104.1, 95.4, 14.8, 10.5, −0.11 (TMS). HRMS (ESI): *m/z* Calcd for $C_{22}H_{23}ON_2$ $[M + H]^+$ 359.1574; found 359.1566.

2-Methyl-3-phenyl-6-((TMS)ethynyl)quinazolin-4(3H)-one (2p). This was synthesized using **1d** (0.3 g, 1 eq, 0.952 mmol), TMS acetylene (1 eq, 0.952 mmol), and Et_3N (4.5 eq, 4.285 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.0476 mmol) and X-Phos (**L3**,

0.15 eq, 0.1428 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 80°C for 6 h. The reaction was monitored by TLC. Upon completion, the solvent was filtered and purified by column chromatography, which was performed using 40% EtOAc in *n*-hexane, and dried to obtain pure compound **2p** as a brown solid: yield 0.25 g (79%); R_f (40% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.35 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.81 (dd, *J* = 2.1 Hz, 1H, Ar-H), 7.60 (m, 4H, Ar-H), 7.27 (m, 2H, Ar-H), 2.23 (s, 3H, Ar-Me), 0.26 (s, 9H) (TMS). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.4 (amide C=O), 154.9, 147.1 (Ar-C), 137.5, 130.7 (Ar-C), 130.0, 129.3, 129.2 (Ar-C), 128.0, 127.9 (Ar-C), 126.8, 126.3 (Ar-C), 121.5, 120.6 (Ar-C), 103.8, 95.9, 24.4 (Ar-Me), −2.09 (TMS). HRMS (ESI): *m*/*z* Calcd for $C_{20}H_{21}ON_2Si$ $[M + H]^+$ 333.1418; found 333.1411.

Synthesis of 3a–3c by desilylation reaction of 2n–2p. To a stirred solution of **2n**, **2o**, or **2p** (1 eq) in anhydrous MeOH (10 volumes) was added K_2CO_3 (2 eq), and the reaction mixture was maintained at 0°C. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc and water (10:2). The organic layer was separated and dried over anhydrous Na_2SO_4, thereby affording the requisite compound as a solid.

2-Cyclopropyl-6-ethynyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (3a). This was synthesized using **2n** (0.5 g, 1 eq, 1.340 mmol), in anhydrous MeOH (10 volumes), was added K_2CO_3 (2 eq) and the reaction mixture was maintained at 0°C. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc and water (10:2). The organic layer was separated and dried over anhydrous Na_2SO_4 and purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **3a** as an off-white solid: yield 0.33 g (81.7%); R_f (70%EtOAc in *n*-hexane) = 0.25. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.60 (s, 1H, Ar-H), 8.51 (d, *J* = 4.2 Hz, 1H, Ar-H), 8.15 (s, 1H, Ar-H), 7.83 (dd, *J* = 8.5 Hz, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.67 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.54 (d, *J* = 8.4, Hz, 1H, Ar-H), 7.39–7.34 (m, 1H, Ar-H), 5.59 (s, 2H, N-CH_2), 4.3 (s, 1H, acetylene), 2.2–2.1 (m, 1H), 1.11–1.09 (m, 2H), 0.97–0.95 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 160.8 (amide C=O), 159.2, 148.5 (Ar-C), 148.3, 147 (Ar-C), 137, 134.3 (Ar-C), 132.3 (Ar-C), 129.7, 127.2, 123.6 (Ar-C), 119.7, 119.1 (Ar-C), 82.5, 81.8, 43.9 (NCH_2), 14, 9.6 (cyclopropyl). HRMS (ESI): *m*/*z* Calcd for $C_{19}H_{16}N_3O$ $[M + H]^+$ 302.1242; found 302.1293; mp 151–154°C.

2-Cyclopropyl-6-ethynyl-3-phenylquinazolin-4(3H)-one (3b). This was synthesized using **2o** (0.2 g, 1 eq, 0558 mmol), in anhydrous MeOH (10 volumes), K_2CO_3 (2 eq) was added, and the reaction mixture was maintained at 0°C. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc and water (10:2). The organic layer was separated and dried over anhydrous Na_2SO_4 and purified by column chromatography, which was performed using 40% EtOAc in *n*-hexane, and dried to obtain pure compound **3b** as an off-white solid: yield 0.15 g (92%); R_f (40%EtOAc in *n*-hexane) = 0.3. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.37 (d, *J* = 1.5 Hz 1H, Ar-H), 7.78 (dd, *J* = 1.2 Hz, 1H, Ar-H), 7.59 (m, 4H, Ar-H), 7.34 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.14 (s, 1H, acetylene), 1.43 (m, 1H), 1.30 (m, 2H), 0.88 (m, 2H). ^{13}C-NMR (75 MHz, DMSO-d_6): 160.8 (amide C=O), 159.2, 148.5 (Ar-C), 148.3 (Ar-C), 147.0, 137.0 (Ar-C), 134.3 (Ar-C), 132.3, 129.7, 128.7(Ar-C), 127.2, 123.6, 119.7, 119.0 (Ar-C), 82.5, 81.8, 14.0, 9.6 (cyclopropyl). HRMS (ESI): *m*/*z* Calcd for $C_{19}H_{15}ON_2$ $[M + H]^+$ 287.1179; found 287.1172.

6-Ethynyl-2-methyl-3-phenylquinazolin-4(3H)-one (3c). This was synthesized using **2p** (0.2 g, 1 eq, 0.602 mmol), in anhydrous MeOH (10 volumes), K_2CO_3 (2 eq) was added, and the reaction mixture was maintained at 0°C. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc and water (10:2). The organic layer was separated and dried over anhydrous Na_2SO_4 and purified by column chromatography, which was performed using 40% EtOAc in *n*-hexane, and dried to get pure compound **3c** as an off-white solid; yield 0.13 g (83%); R_f (40% EtOAc in *n*-hexane) = 0.3. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 2H, Ar-H), 7.90 (d, *J* = 2.4 Hz, 3H, Ar-H), 7.55 (m, 1H, Ar-H), 7.44 (m, 2H, Ar-H), 4.35 (s, 1H, acetylene), 2.13 (s, 3H, Ar-Me). ^{13}C-NMR (75 MHz, DMSO-d_6): 160.5 (amide C=O), 155.6, 147.2 (Ar-C), 138.5, 138.2 (Ar-C), 137.6 (Ar-C), 137.1 (Ar-C), 129.0, 128.5, 128.3 (Ar-C), 127.2 (Ar-C), 120.7, 120.6 (Ar-C), 119.4, 82.5, 81.9, 24.1 (Ar-Me). HRMS (ESI): *m*/*z* Calcd for $C_{17}H_{13}ON_2$ $[M + H]^+$ 261.1022; found 261.1017.

General procedure for the alkynylation 2-cyclopropyl-6-ethynyl-3-(pyridin-3-ylmethyl) quinazolin4(3*H*)-one with aryl/hetaryl iodides to form compounds 4a to 4e. In an oven-dried, screw-capped vial equipped with a stirring bar were placed 2-cyclopropyl-6-ethynyl-3-(pyridin-3-ylmethyl) quinazolin-4(*3H*)-one, **3a** (100 mg, 1 eq, 0.331 mmol), aryl iodides (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol), dissolved in anhydrous THF (10 V), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**, 0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the reaction mixture was cooled and diluted with EtOAc and filtered on a Celite bed; the filtrate layer was washed with water, and the organic layer was separated and dried over Na_2SO_4. Evaporation under reduced pressure provided the crude product, which was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with petroleum ether, followed by 70% EtOAc in petroleum ether, afforded the requisite compound as a white solid. Yields obtained were in the range of 75–82%. This was finally dried under high vacuum to remove traces of the solvent. (See specific compound headings in the following for details.)

2-Cyclopropyl-6-(cyclopropylmethylamino)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (4a). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol), 3-iodopyridine (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**,0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the filtrate layer was purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane and dried to obtain pure compound **4a** as a light brown solid: yield 104 mg (82%); R_f (70% EtOAc in *n*-hexane) = 0.4; ^{1}H-NMR

(300 MHz, DMSO-d_6): δ 8.81 (s, 1H, Ar-H), 8.61–8.52 (m, 3H, Ar-H), 8.27 (s, 1H, Ar-H), 8.04–7.90 (d, J = 8.4, 7.9 Hz, 2H, Ar-H), 7.69–7.36 (m, 4H, Ar-H), 5.61 (s, 2H, N-CH_2), 2.19 (m, 1H), 1.22 (m, 2H), 0.98–0.97 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 160.8 (amide C=O), 159.3 (Ar-C), 151.6, 149.1, 148.5, 148.3, 147.1, 138.6, 136.7, 134.4, 132.3 (Ar-C), 129.6, 127.3, 123.6, 119.9, 119 (Ar-C), 91.4, 87 (acetylene), 43.9 (N-CH2), 14, 9.6 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{24}H_{19}N_4O$ $[M + H]^+$ 379.1529; found 379.1559; mp 140–144°C.

6-((6-Chloropyridin-3-yl)ethynyl)-2-cyclopropyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (4b). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol), 2-chloro-5-iodopyridine (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**, 0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the filtrate layer was purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **4b** as a light brown solid: yield 118 mg (86%); R_f (70% EtOAc in *n*-hexane) = 0.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.66–8.51 (m, 3H, Ar-H), 8.28 (s, 1H, Ar-H), 8.09–7.9 (m, 2H, Ar-H), 7.67–7.57 (m, 3H, Ar-H), 7.38 (m, 1H, Ar-H), 7.28–7.7.23 (m, 1H, Ar-H), 5.60 (s, 2H, N-CH_2), 2.19 (m, 1H),1.2–0.97 (m, 4H) (cyclopropyl). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.8 (amide C=O), 159.5, 152 (Ar-C), 149.8, 148.4, 148.2, 147.3 (Ar-C), 141.8, 136.7, 134.5 (Ar-C), 132.3, 132.2, 129.8 (Ar-C), 12.4, 124.3, 123.7, 119.9 (Ar-C), 118.7, 118.5 (Ar-C), 92.5, 85.9 (acetylene), 43.9 (N-CH_2), 14, 9.7 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{24}H_{18}N_4OCl$ $[M + H]^+$ 413.1179; found 413.1169; mp 199–202°C.

2-Cyclopropyl-3-(pyridine-3-ylmethyl)-6-(((4-trifluoromethyl)phenyl)ethynyl)quinazolin-4(3H)-one (4c). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol), 1-iodo-4-(trifluoromethyl)benzene (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**, 0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the filtrate layer was purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **4c** as an off-white solid: yield 113 mg (76%); R_f (70%EtOAc in *n*-hexane) = 0.5. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.61 (s, 1H, Ar-H), 8.51 (m, 1H, Ar-H), 8.29 (s, 1H, Ar-H), 7.95–7.91 (dd, J = 8.1 Hz, 1H, Ar-H), 7.84 (m, 4H, Ar-H), 7.69 (d, J = 8.1 Hz, 1H, Ar-H), 7.59 (d, J = 9 Hz, 1H, Ar-H), 7.39–7.35 (m, 1H, Ar-H), 5.61 (s, 2H, N-CH_2), 2.2–2.1 (m, 1H), 1.14–1.12 (m, 2H), 0.99–0.96 (m, 2H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 160.8 (amide C=O), 159.4 (Ar-C), 148.5, 148.3, 147.2 (Ar-C), 136.8, 134.4 (Ar-C), 132.3 (Ar-C), 132.1, 129.8 (Ar-C), 128.9, 128.5 (Ar-C), 127.3, 126.3, 125.5 (Ar-C), 123.6, 122.1 (Ar-C), 119.9, 118.9 (Ar-C), 109.5 (Ar-C), 90.9, 88.7, 43.9 (N-CH_2), 14, 9.7 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{26}H_{19}N_3OF_3$ $[M + H]^+$ 446.1504; found 446.1480; mp 164–167°C.

2-Cyclopropyl-6-((4-hydroxyphenyl)ethynyl)-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (4d). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol), 4-iodophenol (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**, 0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the filtrate layer was purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **4d** as a pale yellow solid: yield 66 mg (50%); R_f (70% EtOAc in *n*-hexane) = 0.25. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 9.90 (bs, 1H, Ar-H), 8.6–8.5 (m, 2H, Ar-H, Ar-H, Ar-H), 8.16 (s, 1H, Ar-H), 7.85 (dd, J = 8.7 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H, Ar-H), 7.5 (d, J = 8.4 Hz, 1H, Ar-H), 7.44 (m, 3H, Ar-H), 6.8 (d, J = 8.4 Hz, 2H, Ar-H), 5.75 (s, 1H, Ar-H), 5.6 (s, 2H, N-CH_2), 2.17 (m, 1H), 1.10–1.07 (m, 2H), 0.98–0.95 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 160.9 (amide C=O), 158.7 (Ar-C), 158.2 (Ar-C), 148.5, 148.3, 146.5, 136.5 (Ar-C), 134.4, 133.1 (Ar-C), 132.4, 128.7, 127.2 (Ar-C), 123.6, 120.4 (Ar-C), 119.9, 115.7 (Ar-C), 112.1 (Ar-C), 91.1, 86.6, 43.9 (N-CH_2), 14, 9.5 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{25}H_{20}N_3O_2$ $[M + H]^+$ 394.1540; found 394.1556; mp 212–216°C.

6-((4-Aminophenyl)ethynyl)-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (4e). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol), 4-iodoaniline (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol) and dissolved in anhydrous THF (10 volumes), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**, 0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the filtrate layer was purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **4e** as a brown solid: yield 62.5 mg (48%); R_f (70% EtOAc in *n*-hexane) = 0.3. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.6–8.5 (m, 2H, Ar-H), 8.11 (s, 1H, Ar-H), 7.81 (d, J = 8.1 Hz, 1H, Ar-H), 7.67 (d, J = 7.5 Hz, 1H, Ar-H), 7.53 (d, J = 8.4 Hz, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 7.26 (d, J = 8.4 Hz, 2H, Ar-H), 6.5 (d, J = 8.1 Hz, 2H, Ar-H), 5.62–5.59 (s, 4H N-CH_2 and Ar-NH_2), 2.16 (m, 1H), 1.1 (m, 2H), 0.96–0.94 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 160.9 (amide C=O), 158.5, 149.7 (Ar-C), 148.5 (Ar-C), 148.3, 146.1, 136.4, 134.3 (Ar-C), 132.7 (Ar-C), 132.4, 128.2 (Ar-C), 127.1, 123.6 (Ar-C), 121, 119.8 (Ar-C), 113.5, 107.6 (Ar-C), 92.5, 85.8, 43.9 (N-CH_2), 14, 9.4 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{25}H_{21}N_4O$ $[M + H]^+$ 393.1711; found 393.1715; mp 162–165°C.

2-Cyclopropyl-6-((2,4-dihydroxyphenyl)ethynyl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (4f). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol), 4-iodobenzene-1,3-diol (1 eq, 0.331 mmol), and Et_3N (4.5 eq, 1.493 mmol) and dissolved in anhydrous THF (10 V), and the vial was flushed with argon, added with $PdCl_2(CH_3CN)_2$ (0.05 eq, 0.016 mmol) and X-Phos (**L3**, 0.15 eq, 0.049 mmol), sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at RT. The reaction was monitored by TLC. Upon completion at 6 h, the filtrate layer was purified by column chromatography, which was performed using 100% EtOAc, and dried to obtain pure compound **4f** as a pale yellow solid: yield 58.5 mg (43%); R_f (100% EtOAc) = 0.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.7

(bs, 1H, Ar-H), 8.61 (s, 1H, Ar-H), 8.5–8.4 (m, 2H, Ar-H), 8.24 (dd, J = 8.4 Hz, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 7.62 (d, J = 8.8 Hz, 1H, Ar-H), 7.45 (m, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 7.02 (s, 1H, Ar-H), 6.79 (dd, J = 8.4 Hz, 1H, Ar-H), 5.6 (s, 2H, N-CH_2), 2.19–2.15 (m, 1H), 1.12–1.10 (m, 2H), 0.98–0.94 (m, 2H) (cyclopropyl). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 161.5 (amide C=O), 158.2 (Ar-C), 156.2, 155.7, 152.4, 148.5 (Ar-C), 148.3, 146.6 (Ar-C), 134.4 (Ar-C), 132.5 (Ar-C), 130.2, 127.8 (Ar-C), 127.5, 123.7, 121.4 (Ar-C), 120.7, 120.1 (Ar-C), 112.8, 103 (Ar-C), 97.5, 43.9 (N-CH2), 14, 9.4 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{25}H_{20}N_3O_3$ $[M + H]^+$ 410.1471; found 410.1505; mp 212–216°C.

General procedure for triazole synthesis of substituted quinazolin-4(3*H*)-one. To a stirred solution of 2-cyclopropyl-6-ethynyl-3-(pyridin-3-ylmethyl)quinazolin-4(3*H*)-one (**3a**, **3b**, and **3c**) (1.0 eq, 0.331 mmol), dissolved in *t*-BuOH and water (1:1, in 10 volumes), were added (+)-sodium L-ascorbate (100 mg, 1.0 eq, 0.331 mmol), $CuSO_4$ (0.05 eq, 0.016 mmol), and substituted azides (1 eq, 0.331 mmol). The reaction mixture was stirred at RT. The reaction was monitored by TLC. Upon completion at 6 h, ice-cold water was poured into the reaction mixture and extracted with dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. The crude product was loaded into a silica column packed in CH_2Cl_2. Sequential elution with petroleum ether, followed by 50–100% EtOAc in petroleum ether, afforded the requisite compound as a white solid: yield 120 mg (86%). This was further dried under high vacuum to remove traces of solvent. (See specific compound headings in the following for details.)

2-Cyclopropyl-6-(1-phenyl-1H-1,2,3-triazol-5-yl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one (5a). This was synthesized using **3a** (100 mg, 1 eq, 0.331 mmol) and dissolved in *t*-BuOH and water (1:1, in 10 volumes), and (+)-sodium L-ascorbate (100 mg, 1.0 eq, 0.331 mmol), $CuSO_4$ (0.05 eq, 0.016 mmol), and phenyl azide (1 eq, 0.331 mmol). The reaction mixture was stirred at RT. The reaction was monitored by TLC. Upon completion at 6 h, the crude compound was purified by column chromatography, which was performed using 100% EtOAc, and dried to obtain pure compound **5a** as an off-white solid: yield 120 mg (86%); R_f (100% EtOAc in *n*-hexane) = 0.3. ^{1}H-NMR (400 MHz, D_2O): δ 8.63–8.62 (d, J = 8.8 Hz, 2H, Ar-H), 8.54 (brs, 1H, Ar-H), 8.46–8.45 (d, J = 2.0 Hz, 1 H, Ar-H), 8.33 (s, 1H, Ar-H), 7.80–7.78 (d, J = 6.8 Hz, 2H, Ar-H), 7.69–7.67 (d, J = 8.4 Hz, 1H, Ar-H), 7.61–7.55 (m, 3H, Ar-H), 7.48–7.44 (t, J = 15.2 Hz, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 5.62 (s, 2H, N-CH_2), 1.91–1.87 (m, 1H), 1.29–1.14 (m, 2H), 1.02–0.98 (m, 2H) (cyclopropyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.5 (amide C=O), 157.5 (Ar-C), 149.1(Ar-C), 148.4 (Ar-C), 147.4, 147.3 (Ar-C), 136.9, 134.6 (Ar-C), 132.0, 129.8 (Ar-C), 128.9 (Ar-C), 128.5 (Ar-C), 127.9, 123.6 (Ar-C), 120.5, 120.3 (Ar-C), 118.1, 44.4 (N-CH_2), 14.4, 9.2 (cyclopropyl). LCMS: m/z 301.90 $[M-H]^+$; 97.2% purity; mp 245–257°C.

6-(Acetoxymethyl)-4-(5-(2-cyclopropyl-4-oxo-3-(pyridin-3-ylmethyl)-3,4-dihydroquinazolin-6-yl)-1H-1,2,3-triazol-1-yl) tetrahydro-2H-pyran-2,3,5-triyl triacetate (5b). This was synthesized using **3b** (100 mg, 1 eq, 0.349 mmol) and dissolved in *t*-BuOH and water (1:1 ratio, 10 volumes), and (+)-sodium L-ascorbate (1.0 eq, 0.349 mmol), $CuSO_4$ (0.05 eq, 0.017 mmol), and compound **11** (1 eq, 0.349 mmol) were added. The reaction mixture was stirred at RT. The reaction was monitored by TLC. Upon completion at 6 h, the crude compound was purified by column chromatography, which was performed using 70% EtOAc in *n*-hexane, and dried to obtain pure compound **5b** as a yellow solid: yield 0.2 g (89.2%); R_f (70% EtOAc in *n*-hexane) = 0.4. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.77 (s, 1H, Ar-H), 8.62 (d, J = 1.8 Hz, 3H, Ar-H), 8.35 (dd, J = 1.8 Hz, 1H, Ar-H), 7.68 (dd, J = 3.6 Hz, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.62 (s, 2H, N-CH_2), 5.48 (s, 2H), 5.42 (m, 1H), 4.40–3.99 (m, 3H), 2.2 (s, 3H), 2.06 (s, 6H) (all are sugar H), 2.0 (s, 3H), 1.23 (m, 1H), 1.1 (m, 2H), 0.97 (m, 2H) (cyclopropyl). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 169.9 (amide C=O), 169.5 (Ar-C), 169.3 (Ar-C), 169.2 (Ar-C), 168.1, 161.5 (Ar-C), 158.2, 148.4 (Ar-C), 146.8, 145.4 (Ar-C), 134.2 (Ar-C), 131.4 (Ar-C), 127.9 (Ar-C), 127.5 (Ar-C), 122.6 (Ar-C), 122.2 (Ar-C), 120.1 (Ar-C), 90.5, 70.01, 69.65, 67.9, 61.2, 58.9, 43.9, 20.63, 20.49, 20.36, 20.23 (all are sugar C), 13.97, 9.35 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{33}H_{35}O_{10}N_6$ $[M + H]^+$ 675.2409; found 675.2399.

6-(Acetoxymethyl)-4-(5-(2-cyclopropyl-4-oxo-3-phenyl-3,4-dihydroquinazolin-6-yl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-2,3,5-triyl triacetate (5c). This was synthesized using **3c** (100 mg, 1 eq, 0.384 mmol) and dissolved in *t*-BuOH and water (1:1, in 10 volumes), and (+)-sodium L-ascorbate (1.0 eq, 0.384 mmol), $CuSO_4$ (0.05 eq, 0.019 mmol), and compound **11** (1 eq, 0.349 mmol) were added. The reaction mixture was stirred at RT. The reaction was monitored by TLC. Upon completion at 6 h, the crude compound was purified by column chromatography, which was performed using 60% EtOAc in *n*-hexane, and dried to obtain pure compound **5c** as an off-white solid: yield 0.17 g (92%); R_f (60% EtOAc in *n*-hexane) = 0.6. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.76 (s, 1H, Ar-H), 8.57 (d, J = 1.8 Hz, 1H, Ar-H), 8.36 (dd, J = 1.8 Hz, 1H, Ar-H), 7.70–7.50 (m, 6H, Ar-H), 6.33 (d, J = 1.2 Hz, 1H, Ar-H), 5.53 (s, 1H), 4.34 (s, 3H), 2.14 (s, 3H), 2.05 (m, 6H), 1.92 (m, 3H) (all are sugar protons), 1.38 (m, 1H), 1.19 (m, 2H), 0.85 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 169.9 (amide C=O) 169.4 (Ar-C), 169.2 (Ar-C), 168.1 (Ar-C), 161.2 (Ar-C Ar-C), 158.2 (Ar-C), 147.1 (Ar-C), 145.4 (Ar-C), 137.3 (Ar-C), 131.5 (Ar-C), 129.5 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 127.8 (Ar-C), 127.4 (Ar-C), 122.4 (Ar-C), 122.2 (Ar-C), 120.7 (Ar-C), 90.2, 70.0, 67.9, 64.7, 61.7, 58.9, 20.6, 20.4, 20.36, 20.33 (all are sugar carbons), 14.8, 10.0 (cyclopropyl). HRMS (ESI): m/z Calcd for $C_{33}H_{34}O_{10}N_5$ $[M + H]^+$ 660.2300; found 660.2290.

6-(Acetoxymethyl)-4-(5-(2-methyl-4-oxo-3-phenyl-3,4-dihydroquinazolin-6-yl)-1H-1,2,3triazol-1-yl)tetrahydro-2H-pyran-2,3,5-triyl triacetate (5d). This was synthesized using **3c** (100 mg, 1 eq, 0.384 mmol) and dissolved in *t*-BuOH and water (1:1, in 10 volumes), and (+)-sodium L-ascorbate (1.0 eq, 0.384 mmol), $CuSO_4$ (0.05 eq, 0.019 mmol), and compound **11** (1 eq, 0.384 mmol) were added. The reaction mixture was stirred at RT. The reaction was monitored by TLC. Upon completion at 6 h, the crude compound was purified by column chromatography, which was performed using 60% EtOAc in *n*-hexane, and dried to obtain pure compound **5d** as an off-white solid: yield 0.19 g (94%); R_f (60% EtOAc in *n*-hexane) = 0.6. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.78 (s, 1H, Ar-H), 8.58 (d, J = 1.8 Hz, 1H, Ar-H), 8.40 (dd, J = 1.8 Hz, 1H, Ar-H), 7.78 (d, J = 8.4 Hz, 1H, Ar-H), 7.61 (m, 5H, Ar-H), 6.34 (d, J = 0.9 Hz, 1H, Ar-H), 5.54 (m, 3H), 4.34 (m, 3H), 2.21 (s, 3H) (all are sugar protons), 2.14 (s,

3H, Ar-Me), 2.0 (s, 6H, sugar acetyl), 1.94 (s, 3H), 1.19 (m, 2H), 0.85 (m, 2H) (all are sugar protons). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 170.0 (amide C=O), 169.9 (Ar-C), 169.5 (Ar-C), 169.2 (Ar-C), 168.1 (Ar-C), 167.9 (Ar-C), 161.2 (Ar-C), 154.6 (Ar-C), 147.0 (Ar-C), 145.3 (Ar-C), 137.8 (Ar-C), 131.5 (Ar-C), 129.5 (Ar-C), 128.9, 128.4 (Ar-C), 128.2, 127.4 122.4 (Ar-C), 122.1 (Ar-C), 120.9 (Ar-C), 90.2, 70.84, 67.9, 65.4, 62.7, 58.9, 24.0, 20.64, 20.49, 20.37 (all are sugar carbons), 20.34 (Ar-Me). HRMS (ESI): *m*/*z* Calcd for $C_{31}H_{32}O_{10}N_5$ $[M + H]^+$ 634.2144; found 634.2136.

(4aR, 6S, 7R, 8R, 8aS)-6-Methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (8). To a stirred solution of (2*R*, 3*S*, 4*S*, 5*R*, 6*S*)-2-(hydroxymethyl)-6-methoxytetrahydro-2*H*-pyran-3,4,5-triol (compound **6)** (1.0 g, 5.149 mmol, 1.0 eq) in acetonitrile (50 mL) was added (dimethoxymethyl)benzene (1.54 mL, 10.29 mmol, 2.0 eq) at RT, and then cyanuric chloride (0.28 g, 1.545 mmol, 0.3 eq) was added portion-wise to the aforementioned reaction mixture at RT. Then the reaction mixture was sonicated for 1 h at RT. The reaction was monitored by TLC, and then the reaction mass was poured into ice-cold water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated and dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain (4a*R*,6*S*,7*R*,8*R*,8a*S*)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*] [1,3]dioxine-7,8-diol (**8**) as a white solid: yield 1.1 g (70%); R_f (50% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.3 (m, 5H, Ar-H), 5.56 (s, 1H, Ar-H), 5.12 (bs, 2H, Ar-H), 4.63 (d, *J* = 4 Hz 1H), 4.18 (dd, *J* = 4.4 Hz 1H), 3.68 (t, *J* = 10.4 Hz, 1H), 3.60–3.55 (m, 2H), 3.39–3.31 (m, 3H).

(4aR, 6S, 7R, 8S, 8aS)-8-Hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl trifluoromethane sulfonate (9). To a stirred solution of (4a*R*, 6*S*, 7*R*, 8*R*, 8a*S*)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*] [1,3]dioxine-7,8-diol (compound **8**) (1.0 g, 3.54 mmol, 1.0 eq) was added CH_2Cl_2 (50 mL) and pyridine (10 mL) at −78°C; then triflic anhydride (0.7 mL, 4.24 mmol, 1.2 eq) was added dropwise to the reaction mixture and stirred at the same temperature for 1 h and allowed to warm to RT and stirred for 2 h at RT, and then the reaction mass was concentrated under reduced pressure and purified by column chromatography, being eluted with 20% ethyl acetate in hexanes. (4a*R*, 6*S*, 7*R*, 8*S*, 8a*S*)-8-Hydroxy-6-methoxy-2-phenylhexahydropyrano [3,2-*d*] [1,3]dioxin-7-yl trifluoromethane sulfonate (**9**) was obtained as a yellow-colored oil: yield 1.06 g (70%); R_f (30% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.47–7.37 (m, 5H, Ar-H), 6.20 (d, *J* = 5.7 Hz, 1H, Ar-H), 5.62 (s, 1H OH), 5.03 (d, *J* = 4.2 Hz, 1H), 4.77 (dd, *J* = 3.9 Hz, 1H), 4.26 (dd, *J* = 2.4 Hz, 1H), 3.95–3.63 (m, 4H), 3.41 (s, 3H).

(4aR, 6S, 7S, 8R, 8aS)-7-Azido-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-ol (10). To a stirred solution of (4a *R*, 6*S*, 7*R*, 8*S*, 8a*S*)-8-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-*d*] [1,3]dioxin-7-yl trifluoromethane sulfonate (compound **9**) (1.0 g, 2.41 mmol, 1.0 eq) in DMF (20 mL) was added sodium azide (0.29 g, 4.57 mmol, 1.9 eq) at RT, and then reaction mixture was heated to 80°C for 2 h. The reaction was monitored by TLC after completion of 2 h, and then ice-cold water was poured into the reaction mixture and extracted with ethyl acetate (2 × 50 mL); the organic layer was separated, dried over sodium sulfate, evaporated under reduced pressure, and purified by column chromatography, being eluted with 40% ethyl acetate in hexanes. We obtained (4a*R*, 6*S*, 7*S*, 8*R*, 8a*S*)-7-azido-6-methoxy-2-phenylhexahydropyrano[3,2-d] [1,3]dioxin-8-ol (**10**) as a yellow-colored oil: yield 0.37 g (65%); R_f (30% EtOAc in *n*-hexane) = 0.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.47–7.35 (m, 5H, Ar-H), 5.8 (d, *J* = 4.8 Hz, 1H), 5.66 (s, 1H, br OH), 4.66 (s, 1H), 4.16 (dd, *J* = 4.8 Hz, 1H), 4.03 (m, 2H), 3.82 (t, *J* = 9.2 Hz, 1H), 3.77 (t, *J* = 8 Hz, 1H), 3.59–3.53 (m, 1H).

(2R, 3S, 4R, 5S, 6R)-6-(acetoxymethyl)-3-azidotetrahydro-2H-pyran-2,4,5-triyl triacetate (11). To a stirred solution of (4a*R*, 6*S*, 7*S*, 8*R*, 8a*S*)-7-azido-6-methoxy-2-phenylhexahydropyrano[3,2-D] [1,3]dioxin-8-ol (compound **10**) (0.5 g, 1.62 mmol, 1.0 eq) was added 3% *v*/*v* H_2SO_4 in acetic anhydride at RT, stirred for 2 h at RT. The progress of the reaction was monitored by TLC. After completion in 2 h, the reaction was neutralized with sodium bicarbonate solution and extracted with ethyl acetate; the organic layer was separated and dried over sodium sulfate and evaporated under reduced pressure. A crude compound purified by flash column chromatography and eluted with 40% ethyl acetate in hexanes afforded the required compound (2*R*, 3*S*, 4*R*, 5*S*, 6*R*)-6-(acetoxymethyl)-3-azidotetrahydro-*2H*-pyran-2,4,5-triyl triacetate (**11**) as a white solid: yield 0.5 g (82%); R_f (50% EtOAc in *n*-hexane) = 0.6. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 6.12 (s, 1H, Ar-H), 5.40 (m, 2H), 4.26 (dd, *J* = 4.4 Hz, 1H), 4.10–4.00 (m, 3H), 2.17 (s, 3H, *O*-acetyl), 2.12 (s, 3H, *O*-acetyl), 2.09 (s, 3H, *O*-acetyl), 2.06 (s, 3H, *O*-acetyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 169.7, 169.1, 167.9, 91.1, 70.3, 65.1, 61.5, 60.3, 20.6, 20.4, 20.3, 20.2.

BIOLOGY

Antimicrobial activity assays. ***Zone of inhibition.*** The antimicrobial screening of synthesized alkynyl quinazolinone derivatives was determined using a modified Kirby Bauer method (an agar well diffusion) against different pathogenic bacterial strains such as *B. subtilis*, *E. coli*, *K. pneumoniae*, *S. epidermidis*, *S. aureus*, *S. typhimurium*, and *L. monocytogenes*. All these cultures were obtained as clinical isolates from Chest Hospital, Hyderabad, and stored in glycerol (stock cultures). All these studies were carried out in Muller Hinton culture media which were procured from Hi Media, Mumbai, India. The bacterial strains were reactivated from stock cultures by incubating the inoculated broths at 37 °C for 18 h in an incubator (Cassia). A final inoculum containing 10^6 colony-forming units (1×10^6 CFU/mL) was added aseptically to Muller Hinton Agar medium (2.4%) and poured into sterile Petri dishes. Fifty microliters of each test compound from a stock concentration (4 mg/mL) was added to the wells (8 mm) punched on the agar surface. Plates were incubated in a bacterial incubator (Cassia) overnight at 37°C. The activities were evaluated by measuring the diameter of the inhibition zone (in mm). Amikacin (trade name

Amikin) was employed as a standard reference antibiotic, and this was purchased from Sigma-Aldrich (St. Louis, MO, USA).

MIC and MBC assays. The MIC is defined as the lowest concentration that demonstrates no visible growth by macroscopic assessment, whereas the MBC is the lowest concentration of compound present in the tube that shows no visible growth in drug-free cultivation. MIC and MBC of compounds were determined by broth dilution methods. For culturing the microorganisms, 2.4% MH media (Muller Hinton) was used (National Committee for Clinical Laboratory Standards, 2000). The prepared broths containing microorganisms in test tubes along with testing compounds were incubated at 37°C overnight. MH media of 2.4 g was weighed and dissolved in 100 mL of distilled H_2O and then autoclaved. The media was cooled down to 45°C, and then 0.5 mL sterile medium was poured into sterile fraction test tubes. For each tube, the equal volume of culture was added (0.5 mL), and then the first tube was mixed with the test sample in a concentration of 4 mg/mL. Later, 0.5 mL of pure broth was added, making the final volume of the tube to be 3 mL with broth. The tubes showing no turbidity were diluted to 100-fold with drug-free media and incubated at 37°C for 48 h.

Acknowledgments. Authors are grateful to GVK Biosciences Pvt. Ltd. for the financial support and encouragement. We thank Prof. Mahesh K. Laakshman, Department of Chemistry, The City College and The City University of New York, New York, USA, for his invaluable support and motivation.

REFERENCES AND NOTES

[1] Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Tetrahedron 2005, 61, 10153.

[2] Raymond, E.; Faivre, S.; Armand J. P. Drugs 2000, 60, 15.

[3] Sonogashira, K.; Tohda, Y.; Hagihara, N. Tetrahedron Lett 1975, 16, 4467.

[4] For selected papers on palladium-catalyzed homocoupling reactions of alkynes, see Kotora, M.; Takahashi, T. In Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E.; Meijere, de A., Eds. Wiley-Interscience New York, NY, 2002, p 973.

[5] Liang, Y.; Xie, Y.-X.; Li, J.-H. J Org Chem 2006, 71, 379.

[6] Li, J.-H.; Li, J-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. J Org Chem 2007, 72, 2053.

[7] Díaz-Sánchez, B. R.; Iglesias-Arteaga, M. A.; Melgar-Fernández, R.; Juaristi, E. J Org Chem 2007, 72, 4822.

[8] Mehta, P. V.; Sharma, A.; Van der Eycken, E. Org Lett 2008, 10, 1147.

[9] Silva, S.; Sylla, B.; Suzenet, F.; Tatibouet, A.; Rauter, A. P.; Rollin, P. Org Lett 2008, 10, 853.

[10] Bakherad M.; Ali Keivanloo A.; Mihanparast, S. Synth Commn 2009, 40, 179.

[11] Sardon, T.; Cottin, T.; Xu, J.; Giannis, A.; Vernos, I. Chembiochem 2009, 10, 464.

[12] Ripin, D.H.B.; Bourassa, D.E.; Brandt, T.; Castaldi, M.J.; Frost, H.N.; Hawkins, J.; Johnson, P.J.; Masset, S.S.; Neumann, K.; Phillips, J.; et al. Org Process Res Dev 2005, 9, 440.

[13] Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. J Am Chem Soc 2009, 131, 6632.

[14] Kitano, Y.; Suzuki, T.; Kawahara, E.; Yamazaki, T. Bioorg Med Chem Lett 2007, 17, 5863.

[15] Rambabu, D.; Kumar, S.K.; Sreenivas, B.Y.; Sandra, S.; Kandale, A.; Misra, P.; Rao, M.V.; Pal, M. Tetrahedron Lett 2013, 54, 495.

[16] Charpiot, B.; Brun, J.; Donze, I.; Naef, R.; Stefani, M.; Mueller, T. Bioorg Med Chem Lett 1998, 8, 2891.

[17] Peng, Y.; Huang, P.; Wang, Y.; Zhou, Y.; Yuan, J.; Yang, Q.; Jiang, X.; Deng, Z.; Xu, J. Org Biomol Chem 2014, 12, 5922–5927.

[18] Weinstein, M. J.; Nagman, G. H. Antibiotics (Elsevier Scientific Publishing Company, Amsterdam) 1978, 464.

[19] Barry, A. L.; Thornsbery, C. In susceptibility testing; diffusion tests procedures. In Manual of Clinical Microbiology; J. P. Lennette, Ed.; American Society for Microbiology: 20 Washington, DC, 1981, 561.

[20] O'Shea, R.; Moser, H. E. J Med Chem 2008, 51, 2871.

[21] Hundertmark, T., Littke, A. F.; Buchwald, S. L.; Fu, G. C. Org Lett 2000, 2, 1729.