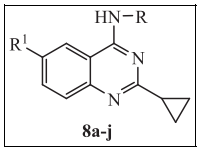
Synthesis, Spectral Characterization, and Antimicrobial Activity of Novel 2,4,6-Trisubstituted Quinazoline Derivatives by Buchwald and Suzuki Coupling Reactions

Kotla Veena Vani, Garlapati Ramesh, and Chunduri Venkata Rao*

Department of Chemistry, Sri Venkateswara University, Tirupati 517502, Andhra Pradesh, India
*E-mail: professorchunduri@gmail.com

Additional Supporting Information may be found in the online version of this article.
Received December 11, 2014
DOI 10.1002/jhet.2459
Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel 2,4,6-trisubstituted quinazoline derivatives were synthesized starting from 2-amino-5-bromobenzoic acid. The structures of the newly synthesized compounds were established by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. All the compounds were tested for antimicrobial activity.

J. Heterocyclic Chem., **00,** 00 (2015).

INTRODUCTION

The quinazoline moiety has proven to be a versatile building block for development of a variety of pharmaceutical entities. Among different heterocyclic compounds, quinazoline and its derivatives have attracted considerable attention because of their synthetic versatility and effective biological activities [1–7]. Various novel classes of structurally different quinazolines have been designed and synthesized, and this nucleus constitutes an integral structural component in a number of drugs currently employed in several clinical therapies.

Palladium-catalyzed amination reactions have become an important type of transformation to construct C—N bonds among a wide range of substrates [8–12]. Buchwald coupling is the direct Pd-catalyzed C—N bond formations [13,14] of aryl halides with amines. It is an effective way to introduce substituted amino groups into aromatic rings.

The Suzuki palladium-catalyzed cross-coupling reaction of aryl boronic acids with aryl halides and related derivatives is a remarkably useful tool in organic synthesis for the construction of C—C bonds. Suzuki coupling also called as Suzuki–Miyaura cross-coupling (SM coupling) has extensively been used in pharmaceutical, agriculture and chemical industries for synthesis of wide range of organic compounds.

The SM reaction has gained prominence in the last few years because the conditions developed for the cross-coupling reaction have many desirable features for large-scale synthesis and are amenable to the industrial synthesis of pharmaceuticals and fine chemicals. The key advantages of the SM coupling are the mild reaction conditions and the commercial availability of the diverse boronic acids that are environmentally safer than the other organometallic reagents. In addition, the handling and removal of boron-containing byproducts are easy when compared to other organometallic reagents, especially in a large-scale synthesis. A number of reviews and reports have been published that enhance the tremendous use of Suzuki coupling in the C—C bond formation [15–24]. Based on the above findings and in continuation of our interest in the synthesis and bioassay of different heterocyclic compounds, we herein report the synthesis, characterization, and antimicrobial activity of novel 2,4,6-trisubstituted quinazoline derivatives.

RESULTS AND DISCUSSION

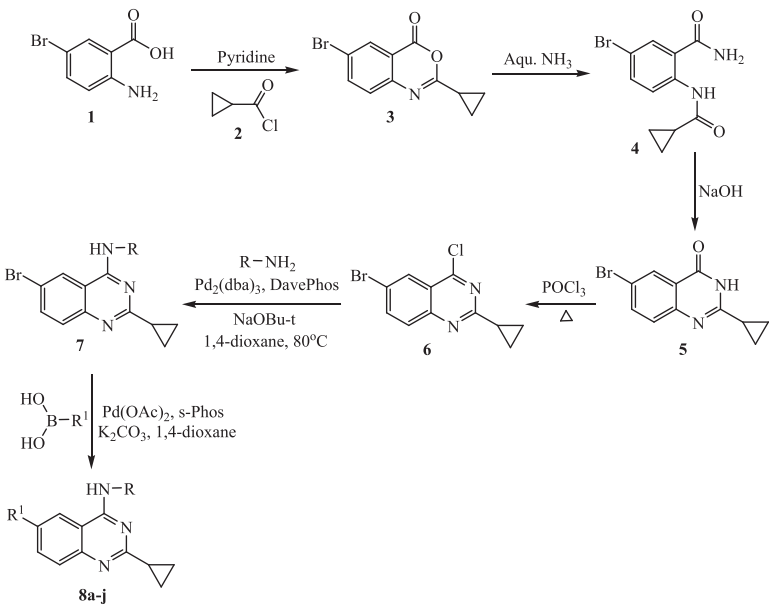
The reaction sequence employed for the synthesis of 2,4,6-trisubstituted quinazoline derivatives (**8a–j**) is depicted in Scheme 1. Reaction of 2-amino-5-bromobenzoic acid (**1**) with cyclopropanoyl chloride (**2**) in dry pyridine at 0°C–RT for 4 h afforded benzoxazinone (**3**) in high yields. Treatment of compound **3** with aqueous ammonia at room temperature produced respective amide derivative (**4**), which on refluxing with aqueous sodium hydroxide gave cyclized product quinazoline-4-one (**5**). Compound **5** was further reacted with $POCl_3$ to afford 6-bromo-4-chloro-2-cyclopropylquinazoline (**6**). Compound **6** on Buchwald reaction with different amines in the presence of catalyst $Pd_2(dba)_3$ and davephos as ligand in NaOBu-t and 1,4-dioxane at 80°C produced 6-bromo-N-substituted-2-cyclopropylquinazolin-4-amine (**7**). Compound **7** on reaction with different aryl boronic acids by Suzuki coupling reaction in the presence of catalyst Pd $(OAc)_2$ and s-phos as ligand in K_2CO_3 and 1,4-dioxane produced 2,4,6-trisubstituted quinazoline derivatives (**8a–j**). The structures of the newly synthesized compounds were established on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the IR spectrum of **8a** showed N—H absorption peak at 3435 cm^{-1}. The ^{1}H NMR spectrum of **8a** showed that a multiplet at δ 0.86–0.95 was assigned to CH_3 and CH_2 protons. Three multiplets at δ 1.03–1.06, 1.35–1.40, and 1.61–1.65 were assigned to three CH_2

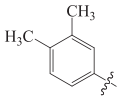
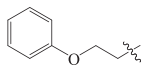
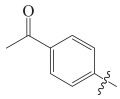
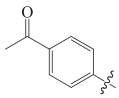
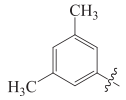
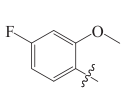
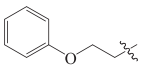
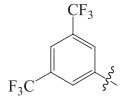
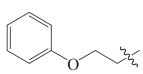
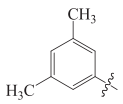
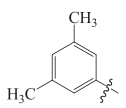
protons. Another multiplet at δ 1.91–2.01 was assigned to CH proton. A singlet at δ 2.27 corresponds to CH_3 protons. Another singlet at δ 2.32 corresponds to CH_3 protons. One more multiplet at δ 3.51–3.52 was assigned to CH_2 protons. A singlet at δ 5.78 was assigned to NH proton. The aromatic region of the spectrum exhibited that multiplets at δ 7.55–7.59 and 7.97–8.42 were assigned to aromatic protons. The ^{13}C NMR spectrum of **8a** showed peaks at δ 8.88, 13.77, 18.01, 19.03, 19.60, 19.73, 24.80, 30.79, 113.69, 119.52, 124.04, 126.92, 127.68, 130.00, 130.75, 135.55, 135.85, 136.69, 136.79, 148.60, 159.42, 166.56. The mass spectrum of **8a** showed $(M+H)^+$ at *m/z* 346.

Biological evaluation. Antimicrobial activity. The antimicrobial activity of newly synthesized compounds **8a–j** was determined using agar well diffusion method. All the compounds were tested *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* (Gram positive bacteria) and *Escherichia coli*, *Pseudomonas aeruginosa* (Gram negative bacteria) using nutrient agar medium (Table 1). Antifungal activity was carried out against *Candida albicans* and *Aspergillus niger* using potato dextrose agar medium (Table 2). Streptomycin was used as standard drug for antibacterial activity, and for antifungal activity Fluconazole was used as standard. The compounds were tested at two different concentrations 100 µg/mL and 200 µg/mL against both bacterial and fungal strains.

Preparation of nutrient agar medium. To prepare 1 L of nutrient agar medium 3 g of beef extract, 3 g of peptone,

Scheme 1. Synthetic route for the compounds **8a–j**.



Compound	R	R¹	Compound	R	R¹
8a			8f		
8b			8g		
8c			8h		
8d			8i		
8e			8j		

and 15 g of agar were used. The ingredients were accurately weighed and dissolved in a liter of distilled water before the addition of agar. The P^H of the medium was adjusted to 7.0 by adding few drops of 0.1 N NaOH/HCl. Later this medium was transferred to conical flasks and plugged with nonabsorbent cotton. Medium was then sterilized by autoclaving at 15 lbs pressure for 15 min, cooled, and used for the study.

Preparation of potato dextrose agar medium. Two hundred grams of potato slices was boiled with distilled water. Dextrose and agar were weighed separately. Twenty grams of dextrose was mixed with potato infusion. Twenty grams of agar was added as a solidifying agent. These constituents were mixed thoroughly, and later this medium was transferred to conical flasks and plugged with nonabsorbent cotton. Medium was then sterilized by autoclaving at 15 lbs pressure for 15 min, cooled, and used for the study.

Method of testing. The sterilized media was poured onto the sterilized petri dishes (20–25 mL, each petri dish) and allowed to solidify. Wells of 6-mm diameter were made in the solidified media with the help of sterile borer, and solutions of the test compounds were added with the help of micropipette. A sterile swab was used to evenly distribute microbial suspension over the surface of solidified media. The plates were incubated at 37°C for 24 h in case of antibacterial activity and 72 h at 25°C for antifungal activity. The zone of inhibition was measured in mm scale.

The results of antibacterial testing of title compounds **8a–j** are presented in Table 1. All the compounds were tested against Gram positive bacteria and Gram negative bacteria, and the results were compared with the standard drug Streptomycin. The results revealed that all the compounds exhibited moderate activity towards all the strains of bacteria. The results of investigation of antifungal screening of title compounds **8a–j** are shown in Table 2. Fluconazole was employed as standard drug. The results revealed that the compounds **8a**, **8g**, and **8j** showed least activity towards both the fungi, and remaining compounds showed moderate activity.

Table 2

Antifungal activity of compounds **8a–j**.

	Zone of inhibition (mm)			
	C. albicans		*A. niger*	
Compound	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL
8a	5	5	5	7
8b	8	11	9	12
8c	8	11	8	13
8d	9	12	10	12
8e	9	13	9	13
8f	10	12	11	11
8g	4	6	4	6
8h	8	12	10	13
8i	9	13	10	13
8j	4	5	4	6
Fluconazole	23	26	24	28

CONCLUSION

In the present study a series of 2,4,6-trisubstituted quinazoline derivatives were synthesized, characterized and evaluated for antimicrobial activity. From the antibacterial screening results, it was found that all the compounds exhibited moderate activity towards all the strains of bacteria. The antifungal screening results revealed that the compounds **8a**, **8g**, and **8j** displayed least activity towards both the fungi and remaining compounds showed moderate activity.

Table 1

Antibacterial activity of compounds **8a–j**.

	Zone of inhibition (mm)							
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*	
Compound	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL
8a	10	13	8	10	9	11	9	11
8b	11	12	8	12	7	10	10	13
8c	7	13	9	11	9	10	8	14
8d	8	11	8	11	7	10	10	12
8e	9	13	9	12	9	11	10	13
8f	10	12	9	12	8	10	10	11
8g	10	10	8	10	7	11	8	13
8h	8	12	8	10	9	11	9	13
8i	9	11	9	13	8	11	10	14
8j	9	13	7	11	8	10	9	12
Streptomycin	22	24	20	23	20	23	21	25

EXPERIMENTAL

All the solvents and reagents were obtained from commercial sources and were used without further purification. Melting points were determined in open capillaries and are uncorrected. TLC was used to monitor the progress of all reactions and to check the purity of compounds. The IR spectra were recorded on JASCO FT/IR-5300 spectrophotometer, Perkin-Elmer spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on Varian spectrometer at 300 MHz with TMS as an internal standard. ^{13}C NMR spectra were recorded on Varian spectrometer at 75 MHz. Mass spectra were recorded on LCMS-2010A, SHIMADZU spectrometer.

Synthesis of 6-bromo-2-cyclopropyl-4*H*-benzo[d][1,3]oxazin-4-one (3). To a stirred solution of 2-amino-5-bromobenzoic acid **1** (4.63 mmol) in pyridine (4 mL) cyclopropanoyl chloride **2** (4.63 mmol) was added at 0°C and maintained for 1 h. Further the reaction mixture was stirred for another 2–3 h at room temperature. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice cold water, and solid obtained was filtered and washed with water. Crude compound was used for next step without any further purification (Yield 69%).

Synthesis of 5-bromo-2-(cyclopropanecarboxamido)benzamide (4). To 6-bromo-2-cyclopropyl-4*H*-benzo[d][1,3]oxazin-4-one **3** (6.66 mmol) taken in a round-bottomed flask, aqueous NH_3 (20 mL) was added and stirred at room temperature for 12 h. After completion of the reaction as checked by TLC, the reaction mixture was poured into ice cold water. The precipitated solid was filtered and dried. Then the solid was given washings with *n*-pentane to remove any impurities (Yield 67%).

Synthesis of 6-bromo-2-cyclopropylquinazolin-4(3*H*)-one (5). To 5-bromo-2-(cyclopropanecarboxamido)benzamide **4** (3.88 mmol) taken in a round-bottomed flask, 2 N NaOH (10–15 mL) was added and refluxed for 4 h. The reaction was monitored by TLC for completion of the starting material. Then the reaction mixture was treated with ice cold water to precipitate the solid. The obtained solid was filtered, dried, and given washings with *n*-pentane to remove any impurities (Yield 71%).

Synthesis of 6-bromo-4-chloro-2-cyclopropylquinazoline (6). To 6-bromo-2-cyclopropylquinazolin-4(3*H*)-one **5** (3.77 mmol), $POCl_3$ (6 mL) was added and refluxed for 2 h. After completion of the reaction, excess $POCl_3$ was removed by distillation under reduced pressure. The resulting residue was poured into ice cold water and extracted with ethyl acetate. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed by distillation to give solid compound which was recrystallized from chloroform (Yield 65%).

Synthesis of 6-bromo-N-substituted-2-cyclopropylquinazolin-4-amine (7). General procedure. In an oven-dried screw-cap vial equipped with a stirring bar, 6-bromo-4-chloro-2-cyclopropylquinazoline **6** (0.28 mmol) dissolved in anhydrous 1,4-dioxane (2 mL), substituted amines (0.85 mmol) and NaOBu-t (0.56 mmol) were placed. The vial was flushed with argon for 10 min, and $Pd_2(dba)_3$ (0.028 mmol) and DavePhos (0.042 mmol) were added. The vial was 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 at 8 h, the mixture was cooled and diluted with CH_2Cl_2. The mixture was washed with water, and the organic layer was separated and dried over anhydrous Na_2SO_4. The mixture was evaporated under reduced pressure. The crude product was purified by column chromatography, and compound was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with pet-ether, followed by 20% EtOAc in pet-ether afforded pure compound (Yield 93%).

Synthesis of 2,4,6-trisubstituted quinazoline derivatives (8a–j)

***N*-Butyl-2-cyclopropyl-6-(3,4-dimethylphenyl)quinazolin-4-amine (8a).** To a mixture of 6-bromo-N-butyl-2-cyclopropylquinazolin-4-amine **7** (1 eq) and 3, 4-dimethylphenylboronic acid (1.5 eq) in dioxane (2 mL), K_2CO_3 (2 eq) was added. Further $Pd(OAc)_2$ (0.01 eq) and s-Phos (0.015 eq) were added while purging argon gas, and reaction mixture was heated to reflux for 16 h. The completion of reaction was monitored by TLC. At the end, the reaction mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. Organic layer was separated and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to obtain crude compound which was purified by column chromatography using hexane:ethyl acetate (7:3) to get pure N-butyl-2-cyclopropyl-6-(3,4-dimethylphenyl)quinazolin-4-amine (**8a**) as white solid. Yield 76%; mp 188–189°C; IR (KBr): 3435, 2923, 2857, 1622, 1453 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.86–0.95 (m, 5H, CH_3 and CH_2), 1.03–1.06 (m, 2H, CH_2), 1.35–1.40 (m, 2H, CH_2), 1.61–1.65 (m, 2H, CH_2), 1.91–2.01 (m, 1H, CH), 2.27 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.51–3.52 (m, 2H, CH_2), 5.78 (s, 1H, NH), 7.55–7.59 (m, 3H, Ar—H), 7.97–8.42 (m, 3H, Ar—H); ^{13}C NMR (DMSO-d_6): δ 8.88, 13.77, 18.01, 19.03, 19.60, 19.73, 24.80, 30.79, 113.69, 119.52, 124.04, 126.92, 127.68, 130.00, 130.75, 135.55, 135.85, 136.69, 136.79, 148.60, 159.42, 166.56; LCMS (*m/z*): 346 $(M+H)^+$. *Anal*. Calcd for $C_{23}H_{27}N_3$: C, 79.96; H, 7.88; N, 12.16. Found: C, 79.94; H, 7.92; N, 12.14.

By employing the same procedure used for **8a**, remaining compounds **8b–j** were synthesized.

***1-(4-(4-(Butylamino)-2-cyclopropylquinazolin-6-yl)phenyl) ethanone (8b).** Yield 83%; mp 170–171°C; ^{1}H NMR (DMSO-d_6): δ 0.92–0.97 (m, 5H, CH_3 and CH_2), 1.03–1.06 (m, 2H, CH_2), 1.38–1.41 (m, 2H, CH_2), 1.62–1.66 (m, 2H, CH_2), 2.03–2.07 (m, 1H, CH), 2.63 (s, 3H, CH_3), 3.54–3.56 (m, 2H, CH_2), 6.97 (s, 1H, NH), 7.64 (d, 1H, Ar—H), 7.97 (d, 2H, Ar—H), 8.11 (d, 2H, Ar—H), 8.43 (d, 1H, Ar—H), 8.61 (s, 1H, Ar—H); ^{13}C NMR (DMSO-d_6):

δ 9.18, 13.74, 17.93, 19.71, 26.76, 30.71, 109.53, 113.64, 120.92, 124.00, 126.76, 128.88, 131.01, 134.41, 135.59, 143.53, 148.88, 159.52, 167.27, 197.44; LCMS (*m/z*): 358 $(M-H)^-$. *Anal*. Calcd for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found: C, 76.83; H, 6.99; N, 11.67.

N-Butyl-2-cyclopropyl-6-(4-fluoro-2-methoxyphenyl)quinazolin-4-amine (8c). Yield 80%; mp 193–194°C; IR (KBr): 3423, 3067, 3026, 2923, 2852, 2229, 1674, 1613, 1583, 1560, 1474, 1444, 1428 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.95–0.99 (m, 5H, CH_3 and CH_2), 1.17–1.21 (m, 2H, CH_2), 1.41–1.46 (m, 2H, CH_2), 1.62–1.68 (m, 2H, CH_2), 2.15–2.19 (m, 1H, CH), 3.59–3.64 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 5.76 (s, 1H, NH), 6.90–6.93 (m, 1H, Ar—H), 6.99–7.04 (m, 1H, Ar—H), 7.05–7.08 (m, 1H, Ar—H), 7.70–7.82 (m, 3H, Ar—H); ^{13}C NMR (DMSO-d_6): δ 9.35, 13.85, 18.42, 20.19, 31.50, 40.76, 56.29, 113.19, 114.53, 114.76, 117.24, 117.47, 120.85, 126.94, 133.64, 133.89, 149.20, 152.68, 158.34, 159.49, 168.10; LCMS (*m/z*): 366 $(M+H)^+$. *Anal*. Calcd for $C_{22}H_{24}FN_3O$: C, 72.31; H, 6.62; N, 11.50. Found: C, 72.34; H, 6.58; N, 11.52.

2-Cyclopropyl-6-(3-(trifluoromethyl)phenyl)-N-(2-phenoxyethyl)quinazolin-4-amine (8d). Yield 71%; mp 209–210°C; IR (KBr): 3435, 3192, 3090, 2923, 2853, 1660, 1616, 1585, 1514, 1481, 1425 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.99–1.05 (m, 2H, CH_2 of cyclopropyl), 1.19–1.25 (m, 2H, CH_2 of cyclopropyl), 2.16–2.23 (m, 1H, CH of cyclopropyl), 4.05–4.10 (m, 2H, CH_2), 4.24–4.27 (m, 2H, CH_2), 6.17 (s, 1H, NH), 6.93–6.99 (m, 3H, Ar—H), 7.26–7.32 (m, 2H, Ar—H), 7.58–7.62 (m, 2H, Ar—H), 7.78–7.92 (m, 5H, Ar—H); ^{13}C NMR (DMSO-d_6): δ 9.58, 18.44, 40.60, 66.20, 113.69, 114.48, 119.18, 121.20, 122.69, 123.85, 123.89, 124.10, 124.14, 125.40, 128.16, 129.38, 129.57, 136.00, 141.08, 149.75, 158.49, 159.59, 168.24; LCMS (*m/z*): 450 $(M+H)^+$. *Anal*. Calcd for $C_{26}H_{22}F_3N_3O$: C, 69.48; H, 4.93; N, 9.35. Found: C, 69.43; H, 4.96; N, 9.36.

2-Cyclopropyl-6-(3,5-dimethylphenyl)-N-(2-phenoxyethyl)quinazolin-4-amine (8e). Yield 84%; mp 162–163°C; IR (KBr): 3434, 3115, 3087, 3020, 2987, 2920, 2851, 1665, 1616, 1584, 1489, 1425, 1406 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91–0.95 (m, 2H, CH_2 of cyclopropyl), 1.04–1.07 (m, 2H, CH_2 of cyclopropyl), 2.06–2.09 (m, 1H, CH of cyclopropyl), 2.36 (s, 6H, $2\times CH_3$), 3.91–3.96 (m, 2H, CH_2), 4.24–4.28 (m, 2H, CH_2), 6.59 (s, 1H, NH), 6.93–7.03 (m, 4H, Ar—H), 7.27–7.29 (m, 2H, Ar—H), 7.41 (s, 2H, Ar—H), 7.63 (d, 1H, Ar—H), 8.02 (d, 1H, Ar—H), 8.48 (s, 1H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 9.77, 18.09, 21.37, 40.66, 66.22, 113.36, 114.55, 118.73, 121.22, 125.08, 126.86, 129.31, 129.58, 132.37, 138.25, 138.52, 140.01, 140.08, 158.49, 159.64, 167.39; LCMS (*m/z*): 410 $(M+H)^+$. *Anal*. Calcd for $C_{27}H_{27}N_3O$: C, 79.19; H, 6.65; N, 10.26. Found: C, 79.23; H, 6.63; N, 10.23.

1-(4-(4-(2-Phenoxyethylamino)-2-cyclopropylquinazolin-6-yl)phenyl)ethanone (8f). Yield 74%; mp 157–158°C; IR (KBr): 3331, 3008, 2944, 2918, 2865, 1664, 1623, 1601, 1574, 1551, 1537, 1497, 1447 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.96–1.01 (m, 2H, CH_2 of cyclopropyl), 1.05–1.09 (m, 2H, CH_2 of cyclopropyl), 2.08–2.11 (m, 1H, CH of cyclopropyl), 2.61 (s, 3H, CH_3), 3.91–3.96 (m, 2H, CH_2), 4.23–4.26 (m, 2H, CH_2), 5.96 (s, 1H, NH), 6.99 (d, 2H, Ar—H), 7.29 (d, 2H, Ar—H), 7.64–7.67 (m, 2H, Ar—H), 7.99–8.10 (m, 5H, Ar—H), 8.64 (s, 1H, Ar—H); ^{13}C NMR (DMSO-d_6): δ 9.16, 18.20, 26.76, 65.42, 110.00, 113.69, 114.42, 120.63, 120.91, 126.75, 127.48, 128.88, 129.51, 131.01, 134.38, 135.59, 143.53, 149.68, 158.38, 159.69, 167.34, 197.44; LCMS (*m/z*): 424 $(M+H)^+$. *Anal*. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.60; H, 5.99; N, 9.94.

N-Butyl-2-cyclopropyl-6-(3,5-dimethylphenyl)quinazolin-4-amine (8g). Yield 76%; mp 175–176°C; IR (KBr): 3414, 2923, 2858, 1620, 1492, 1453 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.93 (t, 3H, CH_3), 1.11–1.13 (m, 2H, CH_2), 1.23–1.25 (m, 2H, CH_2), 1.36–1.41 (m, 2H, CH_2), 1.66–1.74 (m, 2H, CH_2), 2.15–2.18 (m, 1H, CH), 2.31 (s, 6H, $2\times CH_3$), 3.61–3.65 (m, 2H, CH_2), 6.85 (s, 1H, NH), 7.16 (s, 2H, Ar—H), 7.64 (d, 1H, Ar—H), 7.71–7.73 (dd, 1H, Ar—H), 7.95 (d, 1H, Ar—H), 8.26 (s, 1H, Ar—H); LCMS (*m/z*): 346 $(M+H)^+$. *Anal*. Calcd for $C_{23}H_{27}N_3$: C, 79.96; H, 7.88; N, 12.16. Found: C, 79.98; H, 7.84; N, 12.18.

N-Butyl-2-cyclopropyl-6-(3-(trifluoromethyl)phenyl)quinazolin-4-amine (8h). Yield 81%; mp 180–181°C; IR (KBr): 3626, 3436, 3324, 3002, 2949, 2925, 2594, 1625, 1575, 1541, 1511, 1487, 1450 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.98–1.04 (m, 5H, CH_3 and CH_2), 1.21–1.24 (m, 2H, CH_2), 1.44–1.48 (m, 2H, CH_2), 1.69–1.75 (m, 2H, CH_2), 2.17–2.21 (m, 1H, CH), 3.64–3.69 (m, 2H, CH_2), 5.92 (s, 1H, NH), 7.60–7.85 (m, 7H, Ar—H); ^{13}C NMR (DMSO-d_6): δ 9.46, 13.86, 18.50, 20.23, 31.53, 40.88, 110.03, 113.65, 118.89, 123.89, 123.90, 128.29, 129.40, 130.49, 131.47, 131.60, 135.80, 141.27, 149.82, 159.57, 168.51; LCMS (*m/z*): 386 $(M+H)^+$. *Anal*. Calcd for $C_{22}H_{22}F_3N_3$: C, 68.56; H, 5.75; N, 10.90. Found: C, 68.52; H, 5.77; N, 10.93.

6-(3,5-Bis(trifluoromethyl)phenyl)-N-butyl-2-cyclopropylquinazolin-4-amine (8i). Yield 87%; mp 164–165°C; IR (KBr): 3434, 3322, 2915, 2856, 1622, 1581, 1543 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.87 (t, 3H, CH_3), 0.99–1.02 (m, 2H, CH_2), 1.04–1.08 (m, 2H, CH_2), 1.42–1.49 (m, 2H, CH_2), 1.71–1.76 (m, 2H, CH_2), 2.22–2.24 (m, 1H, CH), 3.63–3.68 (m, 2H, CH_2), 6.11 (s, 1H, NH), 7.16 (s, 2H, Ar—H), 7.64 (d, 1H, Ar—H), 7.73–7.75 (dd, 1H, Ar—H), 7.96 (d, 1H, Ar—H), 8.25 (s, 1H, Ar—H); LCMS (*m/z*): 454 $(M+H)^+$. *Anal*. Calcd for $C_{23}H_{21}F_6N_3$: C, 60.92; H, 4.67; N, 9.27. Found: C, 60.95; H, 4.71; N, 9.29.

N,2-Dicyclopropyl-6-(3,5-dimethylphenyl)quinazolin-4-amine (8j). Yield 80%; mp 228–229°C; IR (KBr): 3436, 3158, 3077, 3003, 2923, 2851, 1731, 1671, 1583, 1561, 1513, 1469, 1396 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.60–0.63 (m, 2H, CH_2 of cyclopropyl), 0.73–0.77 (m, 2H, CH_2 of cyclopropyl), 0.87–0.89 (m, 2H, CH_2 of cyclopropyl), 1.05–1.07 (m, 2H, CH_2 of cyclopropyl), 1.99–2.02

(m,1H, CH of cyclopropyl), 2.32 (s, 6H, $2\times CH_3$), 2.96–2.99 (m, 1H, CH of cyclopropyl), 6.15 (s, 1H, NH), 7.34 (s, 2H, Ar—H), 7.56 (d, 1H, Ar—H), 7.91–7.93 (dd, 1H, Ar—H), 8.22 (d, 1H, Ar—H), 8.37 (s, 1H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 7.20, 9.52, 18.33, 21.36, 24.22, 113.39, 118.41, 125.04, 127.59, 129.15, 131.94, 137.77, 138.44, 140.27, 149.00, 160.71, 167.87; LCMS (*m*/*z*): 330 $(M+H)^+$. *Anal*. Calcd for $C_{22}H_{23}N_3$: C, 80.21; H, 7.04; N, 12.76. Found: C, 80.23; H, 7.06; N, 12.79.

Acknowledgments. The authors are thankful to UGC, New Delhi for financial assistance through BSR fellowship.

REFERENCES AND NOTES

[1] Tiwari, R.; Chhabra, G. Asian J Chem 2010, 22, 5981.
[2] Nanda, A. K.; Ganguli, S.; Chakraborty, R. Molecules 2007, 12, 2413.
[3] Shivananda, M. K.; Holla, B. S. J Chem Pharm Res 2011, 3, 83.
[4] Bartroli, J.; Turmo, E.; Algueró, M.; Boncompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; García-Rafanell, J.; Forn, J. J Med Chem 1998, 41, 1869.
[5] Alagarsamy, V.; Solomon, V. R.; Dhanabal, K. Bioorg Med Chem 2007, 15, 235.
[6] Giri, R. S.; Thaker, H. M.; Giordano, T.; Williams, J.; Rogers, D.; Sudersanam, V.; Vasu, K. K. Eur J Med Chem 2009, 44, 2184.
[7] Georgey, H.; Abdel-Gawad, N.; Abbas, S. Molecules 2008, 13, 2557.
[8] Schlummer, B.; Scholz, U. Adv Synth Catal 2004, 346, 1599.
[9] Hartwig, J. F. Acc Chem Res 1998, 31, 852.
[10] Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Acc Chem Res 1998, 31, 805.
[11] Yang, B. H.; Buchwald, S. L. J Organomet Chem 1999, 576, 125.
[12] Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. J Org Chem 1999, 64, 5575.
[13] Abdul Khader, K. K.; Sajith, A. M.; Padusha, M. S. A.; Nagaswarupa, H. P.; Muralidharan, A. Tetrahedron Lett 2014, 55, 1778.
[14] Abdul Khader, K. K.; Sajith, A. M.; Padusha, M. S. A.; Nagaswarupa, H. P.; Muralidharan, A. New J Chem 2014, 38, 1294.
[15] Suzuki, A. Pure Appl Chem 1994, 66, 213.
[16] Miyaura, N.; Suzuki, A. Chem Rev 1995, 95, 2457.
[17] Stanforth, S. P. Tetrahedron 1998, 54, 263.
[18] Suzuki, A. J Organomet Chem 1999, 576, 147.
[19] Kotha, S.; Lahiri, K.; Kashinath, D. Tetrahedron 2002, 58, 9633.
[20] Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. J Org Chem 1994, 59, 8151.
[21] Kuuloja, N.; Kylmälä, T.; Xu, Y.; Franzén, R. Cent Eur J Chem 2008, 6, 390.
[22] Grivas, S.; Lindström, S. J Heterocycl Chem 1995, 32, 467.
[23] Sajith, A. M.; Muralidharan, A. Tetrahedron Lett 2012, 53, 1036.
[24] Sajith, A. M.; Muralidharan, A.; Karuvalam, R. P.; Haridas, K. R. J Korean Chem Soc 2013, 57, 361.