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A COMMON CATALYST FOR C-C AND C-N BOND FORMATION OF 6-BROMO-2-CYCLOPROPYL-3-(PYRIDYL-3-YLMETHYL) QUINAZOLIN-4(*3H*)-ONE AND THEIR ANTI-MICROBIAL ACTIVITY STUDIES

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ABSTRACT
We demonstrate herein a common catalyst for C-C and C-N bond formation reactions of 6-bromo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3H)-one derivative with the aryl, heteroaryl and alkyl boronic acids and amines. Optimization of reaction conditions with different catalysts, ligands, bases, and solvents were conducted. The combination of $Pd_2(dba)_3$ with DavePhos (L3) proved to be best for these conversions in the presence of NaO^tBu in 1,4-dioxane at 100 ^oC. The relative reactivities of p-toluidine and phenyl boronic acid with 6-bromo -2,3-disubstitued quinazolinone was conducted and majority of the product formed was with C-C bond formation reaction compared to C-N bond formation reaction.. We evaluated biological significance of our analogs by screening anti-microbial agents.

KEYWORDS: C-C and C-N, $Pd_2(dba)_{3,,}$ DavePhos,N-Arylation,Anti-Microbial activity

INTRODUCTION

The evolvement of antibacterial agents is one of the utmost successes of 20th century in the medicinal field[I.] Because the serendipitous innovation of penicillin by Alexander Fleming in 1928, an arsenal of antibacterial agents have been developed and found prevalent clinical applications. Bacterial pathogens have evolved numerous defense mechanisms against antimicrobial agents. Because of the lack of fundamental antibiotic research carried out by pharmaceutical companies over recent decades. We are left with a legacy of relatively few efficacious drugs.[II-IV] The phenomenon of antibiotic resistance exhibited by different microbes is different to different antibiotics.[V] The indiscriminate use of numerous antibiotics has led the emergence of multi drug-resistant pathogens. Though, several novel antibiotics are being developed, the efforts become futile once the microbe develops the resistance to the commonly prescribed antibiotic.[VI] The well-established antibiotics are based nearby a limited number of structural classes which impede a small number of biological targets with narrow

array of mechanisms[VII, VIII] and resistance to one antibiotic of a class often leads to resistance to its entire class.[IX]

Therefore, bacterial infection, particularly from multi-drug resistant strains (MRSA), remains a serious intimidation to human lives[X-XII] and there is a clear and critical medical necessity for the discovery of novel chemical entities as potent antimicrobial agents. Smaller organic molecules (compounds) have always been of attention in biochemistry and chemistry due to their capability to exert significant effects on the functions of biological macromolecules.[XIII] There are numerous advantages associated with the employment of small molecules as therapeutic means including synthetic accessibility, improved stability in case of oral administration and further compound bioactivity optimization is substantially at ease in case of smaller molecules rather than complex macro ones. Methods which exploits small molecules as chemical probes to curb the biological systems can be described as 'chemical genetics[XIV] and in general, traditional genetics exploits gene knock-outs or knock–ins on the level of DNA expression but whereas chemical genetics exploits biologically active molecules to mitigate the respective product of biological macromolecule and thus affect the biological response, for example, microbial growth inhibition.[XV,XVI] Small molecules that exhibit biological effects can be discovered by chemical genetics approaches (both forward and reverse) through the screening of collections or libraries of small molecules to identify those with the desired characteristics (so-called 'hits'). In the present article we focus upon the use of diversity-oriented synthesis (DOS) approach for the efficient generation of compound libraries and screening the collections against pathogenic microbial organisms.

Metal mediated catalyzed transformations are now the preferred technique for synthesizing many types of organic molecules. The invention of various ligands and different palladium sources lead to the success in this type of catalysis to form the bonds between carbon and heteroatom's (such as nitrogen, oxygen, sulphur, silicon and boron). In continuation Hartwig and Buchwald introduced many new ligands for effective metal mediated transformations.[XVII] Morris Robins, Michael Hocek and M K Lakshman utilized many suitable Pd-ligand systems for nucleoside modifications.[XVIII] There has been less amount of work carried out for synthesizing modified quinazolinones using palladium mediated C-N and C-C bond formations.[XIX] In our laboratory, we are mainly focused on the modifications of 2-cyclopropyl-3-(pyridyl-3-ylmethyl)quinazolin-4(3*H*)-ones on C-6 position. We have tried to understand the effect of ligand on palladium catalyzed C-N and C-C bond formation. In our recent studies, we have thoroughly screened the Pd catalyst and ligand systems to understand the best conditions for C-N and C-C bond formation reactions separately. For C-N coupling reactions on 6-halo-2-cyclopropyl-3-(pyridyl-3-ylmethyl)quinazolin-4(3*H*)-ones with $Pd_2(dba)_3$, DavePhos in presence of NaO^tBu and 1,4-Dioxane at 100 ^oC given excellent yields. Whereas, $PdCl_2(dcpf)$, K_3PO_4, 1,4-Dioxane (elevated temperature) and THP (at room temperature) resulted with excellent yields for C-C cross coupling reactions with the 6-bromo precursor. Interestingly, we have observed that X-Phos (**L1**), Cy*J*ohnPhos (**L2**), DavePhos (**L3**), XantPhos (**L4**) with Pd source and a ferrocenyl Pd(II) precatalyst (**L5**, Figure 1) undergo both C-N and C-C bond formation reactions with modified quinazolinone substrates. Another highlight of this report is the stability of the cyclopropyl moiety towards the amination and Suzuki-Miyaura cross-coupling reaction conditions.

MATERIALS AND METHODS

Thin-layer chromatography was performed on 250 mm silica plates and column chromatographic purifications were performed on 100–200 mesh silica gel. All boronic acids, $Pd(OAc)_2$, $Pd_2(dba)_3$, ligands L1–L5, $PdCl_2(dppf)$, $PdCl_2(dcpf)$, and $PdCl_2(d^tbpf)$, and all other reagents were obtained from commercial suppliers and were used without

further purification. 1,4-Dioxane was distilled over $NaBH_4$ and then stored over Na. Prior to each reaction 1,4-dioxane was freshly distilled. For syntheses of compounds 1, 3, and 4 as well as their precursors, please see the Supporting Information. ^{1}H NMR spectra were collected either at 400 MHz or at 300 MHz and spectra are referenced to residual portion solvent. ^{13}C NMR spectra, collected either at 100 MHz or at 75 MHz, are referenced to the carbon resonance of the deuterated solvent. Spectra either were obtained in deacidified $CDCl_3$ (deacidification was performed by percolating the solvent through a bed of solid $NaHCO_3$ and basic alumina) or in DMSO-d_6 (see specific compound descriptions below). High-resolution mass spectrometry was performed at the Mass Spectrometry Laboratory LC-MS analyses were performed with electrospray ionization (ESI), and operated in the positive ion mode. LC analysis was performed using a diode array detector

For the present work, 6-bromo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-ones was chosen for study and it was conveniently synthesized by known procedures(See the supporting information for details).[15] With **1** in hand, conditions for Pd-catalyzed amination and C-C cross coupling reactions were evaluated. $Pd(OAc)_2$ and $Pd_2(dba)_3$ served as metal sources, further more ligands **L1-4** (Figure 1) and a ferrocenyl Pd(II) precatalyst (**L5**, Figure 1) was also selected for the investigation.

Synthetic Scheme

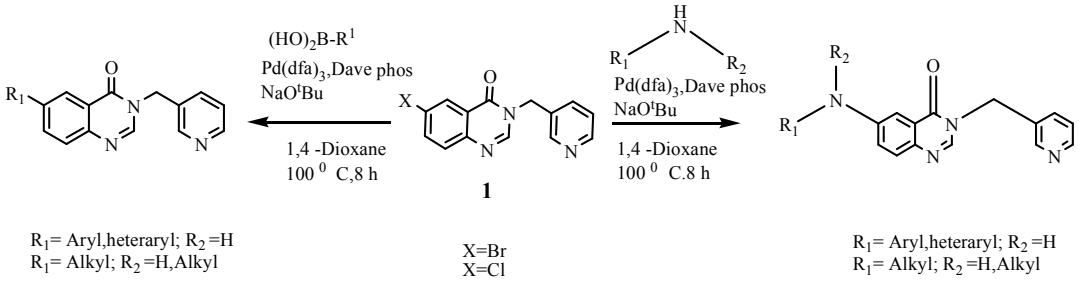
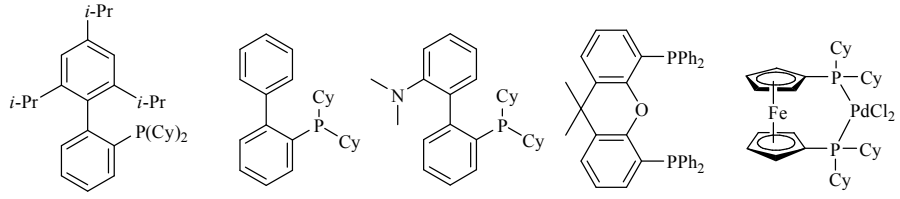


Figure 1. Four ligands and one pre-catalyst selected for the analysis



The optimization experiments were performed with *p*-toluidine for amination and phenyl boronic acid for C-C cross -coupling reactions. Results from our initial investigations are shown in Table 1**.**

The initial attempts with $Pd_2(dba)_3$ (10 mol%), **L1** (15 mol%), resulted amination in good yield (71%) and C-C coupling reaction resulted in low yield (55%, entry 1). Base NaO^{t}Bu, and 1,4-dioxane as solvent kept constant for all the screening reactions. The combination of $Pd(OAc)_2$ (10 mol%)with **L2** (15mol%)resulted C-N coupling reaction in low yield (56%);

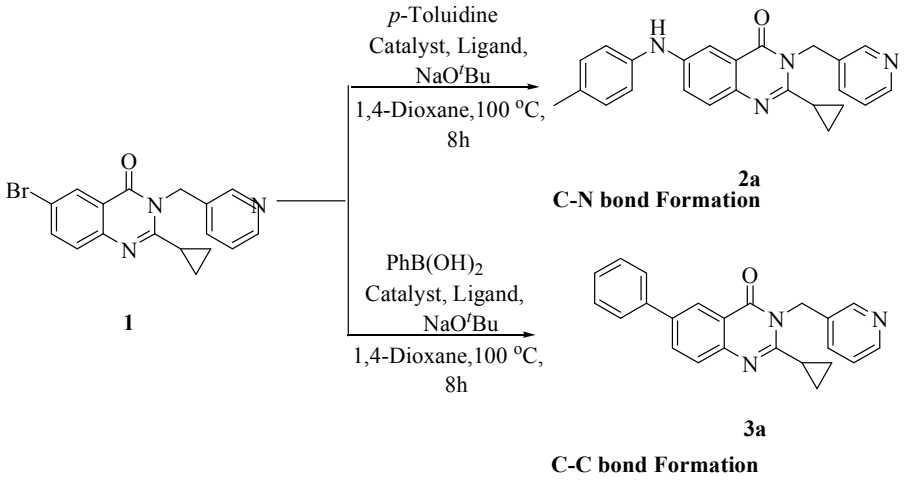
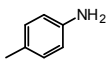
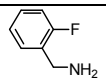
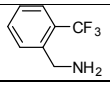
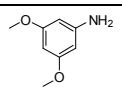
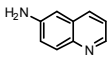
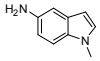
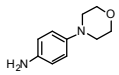


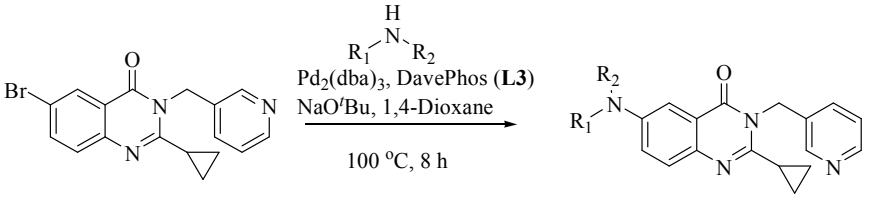
Table 1. Comparison of C-N as well as C-C bond formation using different catalysts[a]

Entry	Catalyst system, conditions, t=8h	C-N bond formation Yield (%)[b]	C-C bond formation Yield (%)[c]
1	10 mol % $Pd_2(dba)_3$/ 15 mol% **L1**	71	55
2	10 mol % $Pd(OAc)_2$/ 15 mol% **L2**	56	81
3	10 mol % $Pd_2(dba)_3$/ 15 mol% **L3**	93	78
4	10 mol % $Pd(OAc)_2$/15 mol % **L4**	64	45
5	10 mol % $PdCl_2(dcpf)$	51	63

Reagents and Conditions (entries 1-5) 6-bromo, **1** precursor 0.0711mM in anhydrous solvent, 3.0 molar equiv *p*-toluidine, 1.5 molar equiv of base. b. Reactions were conducted in closed vial sparged with argon c. % yields refer to isolated and purified products. but, C-C cross coupling resulted in a very good yield(81%, entry 2). $Pd_2(dba)_3$ (10 mol%), **L3** (15 mol%) condition excellent yield (93%) and reasonably good yield for C-C coupling reaction with 78% (entry 3). The combination of $Pd(OAc)_2$ (10 mol%)with **L4** (15mol%)resulted C-N coupling reaction in a good yield (64%); but, C-C cross coupling resulted in a moderate yield(45%, entry 4). Finally**,** ferrocenylpre-catalyst$PdCl_2(dcpf)$ obtained 51% for C-N reaction and 63% yield for C-C coupling reaction. Among these initial screening reactions, 10 mol% $Pd_2(dba)_3$/15 mol% **L3**/1.5molar eq. NaO^{t}Bu in 1,4-dioxane at 100 ^{o}C was proved to be the best (93% for C-N and 65% for C-C coupling reaction, entry 3) catalyst/ligand system for Pd-catalyzed amination and C-C coupling reaction. The total reaction time for all reactions were 8h. Although all these reactions were conducted for 8 h, these yields did not change appreciably when the reactions were conducted beyond this period.

Table 2. Evaluation of the scope of amination reactions of 6-bromo -3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one (**1**)[a, b] using various amines.

Entry	Amine	Product	Yield, %[c]
1		2a	93
2		2b	91
3		2c	88
4		2d	83
5		2e	87
6		2f	92
7		2g	54
8		2h	75
9		2i	88
10		2j	93
11		2kl	68
12		2l	91



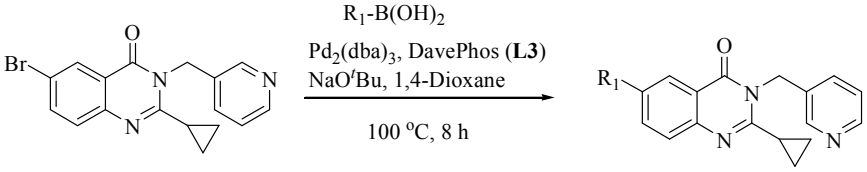
1 **2a - 2l**

Reagents and Reaction Conditions (entries 1-19) 6-bromo,RNH_2, NaOtBu, 10 mol % of $Pd_2(dba)_3$, 15 mol% L3 100 ^oC, b. Reactions were conducted in closed vial sparged with argon c. % yields refer to isolated and purified products...

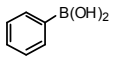
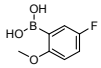
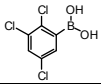
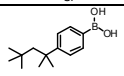
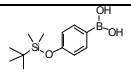
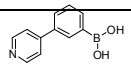
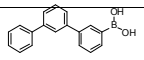
The amines with electron donating groups like *p*-toludine (entry 1), substituted aniline (entry 10), resulted in excellent yields. We were extremely gratified to observe that reactions of

amines with electron-with drawing groups like fluorinated substituent's like 2-fluoro and 2-trifluoromethyl benzyl amines (entries 4 and 5) also resulted in good yields. Reactions with heteroaryl amines resulted in good yields from 54% to 88% (entries 7, 8,9, and 11).
With the optimal conditions ascertained, in the next stage we evaluated the generality of the methodology with variety of amines shown in Table 2. A wide assortment of aryl, and heteroaryl amines participated in the Pd-catalyzed amination reactions.

Table 3. Evaluation of the scope of C-C coupling reactions of 6-bromo -3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one (**1**)[a, b] using various boronic acids.



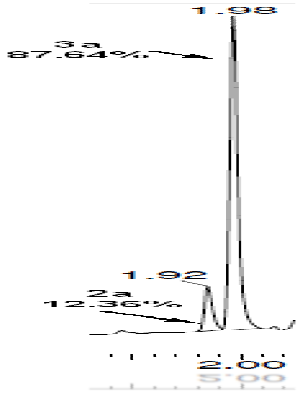
1 **3a - 3g**

Entry	Boronic acid	Product	Yield, %[c]
1		3a	78
2		3b	72
3		3c	82
4		3d	85
5		3e	77
6		3f	81
7		3g	78

Relative reactivity studies of C-N and C-C bond formation with bromo quinazolinone (1)[16]

It is evident that C-N product is superior to **C-C** cross coupling product in terms of product yield with Pd_2 $(dba)_3$ and DavePhos catalyst conditions with NaO^{t}Bu and 1,4-dioxane (Table 1 and 2). We decided to determine the relative reactivities of *p*-toluidine and phenylboronic acid with bromo precursor in a competitive experiment. For this we conducted a reaction of an equimolar amount of *p*-toluidine and phenyl boronic acid (1.0 molar equiv each) with one molar equivalent of bromo precursor, under the optimized conditions. After the complete consumption of bromo precursor the experiment was stopped, products **2a** as well as **3a** were collected together by column chromatography, and subjected to LC/MS analysis. In the mixture, bromo quinazolinone **1** was completely consumed, 87.64% of C-C coupling product **3a** and 12.36% of C-N product **2a** were observed(Figure 3).

Figure 2. LC analysis of the C-N and C-C products mixture from a competitive reaction of *p*-toluidine and phenyl boronic acid with bromo precursor 1 (showing the integrated percentages).



This experiment shows two important factors. First, that phenyl boronic acid is more rapidly reacts with C-6 bromo quinazolinone precursor **1** than *p*-toluidine and second, reductive dehalogenation does not appear to be significant. Figure 2 shows the LC trace of the reaction mixture from the competition experiment. The LC/MS analysis data can be found in the Supporting Information.

Anti-microbial activity

Computational analyses can be performed to determine if a high degree of structural diversity has been achieved in a molecule library or collection. However, it is vital to accentuate that the ultimate success of any small molecule library is determined by the biological relevance of the compounds it contains; if the molecule library does not yield hits in a selected biological screening experiment, it will be considered to beunsuccessful, no matter how structurally diverse it is. The collection of molecules were assayed *in vitro* for their antibacterial activity against a panel of chosen Gram negative and Gram positive pathogens including *Proteus vulgaris* (Gram –ve), *Proteus mirabilis* (Gram –ve), *Escherichia coli* (Gram –ve), *Staphylococcus epidermidis* (Gram +ve), *Klebsiella pneumonia* (Gram –ve) and Methicillin-resistant *Staphylococcus aureus* (Gram +ve) (MRSA), and also the screening was performed on fungal strain, *Aspergillus nigir*. The screening tests were carried out by agar well diffusion and micro dilution methods.[17,18]Mikacin (Amikacin), a powerful aminoglycoside antibiotic was employed as reference standard compound for evaluation, which showed significantly high inhibition in all the screened organisms. The antimicrobial activity was determined by measuring the zone of inhibition resulted against the test organism. A serial 2-fold dilution (ranging from 4.0 - 0.008 mg/ml) was performed for determining the minimum inhibitory concentrations. The minimum inhibitory concentration (MIC) is determined as the lowest concentration that demonstrates no visible growth by macroscopic evaluation, whereas, the lowest concentration of tube that showed no visible growth in drug-free cultivation is considered as minimum bactericidal concentration (MBC).

The diameter of zone of inhibition (DIZ) in 'mm' and the minimum inhibitory and bactericidal (MIC and MBC) concentrations in 'µg' of the screened compounds were tabulated in Tables 4 and 5 respectively. From the antibacterial data through zone of inhibition studies (Table 4), it is evident that in the context of the DOS libraries outlined in schemes 1 (C-N) and 2 (C-C), the former library (C-N) exhibited good antimicrobial activities but unfortunately, where, the whole C-C library had concerned with identifying

with ineffective antimicrobial activity (results shown in Supporting Information). Coming to the C-N library all the molecules exhibited good activities with the exception of compounds **2h** and **1b**, which displayed moderate activity against only *Proteus mirabilis*, *Proteus vulgaris,* respectively. Compounds **2c**, 11**1a**, **2i**, **2*J***, **2k**, **2l** emerged as the most potent antimicrobial agents amongst the screened molecules. Compounds **2k** and **2l** exhibited significant inhibitory activities against *P. vulgaris* (22 mm and 22 mm), *E. coli* (17 mm and 20 mm) and *K. pneumonia* (15 mm and 21 mm). Interestingly, compound **2m** displayed good inhibitory activity against a single pathogen, *P. vulgaris* (20 mm). On the other hand, compounds **2a**, **2b**, **2d**, **2e**, **2g**, and **2i**, demonstrated moderate to potent antimicrobial against all the tested pathogenic microorganisms with the zone of inhibition ranging from 6 mm to 22 mm at the screened concentration of 200 µg/ well. It is worth nothing that, these compounds also moderately inhibited the tested Methicillin Resistant *Staphylococcus aureus* (MRSA) strain at the screened concentration (200 µg/ well), when compared to the reference positive standard, Amikacin, which was also shown moderate activity (14 mm) against employed MRSA.

Figure 3. Antimicrobial activity comparision of potent entities CN library with Amikacin, a potentamynoglycoside antibiotic

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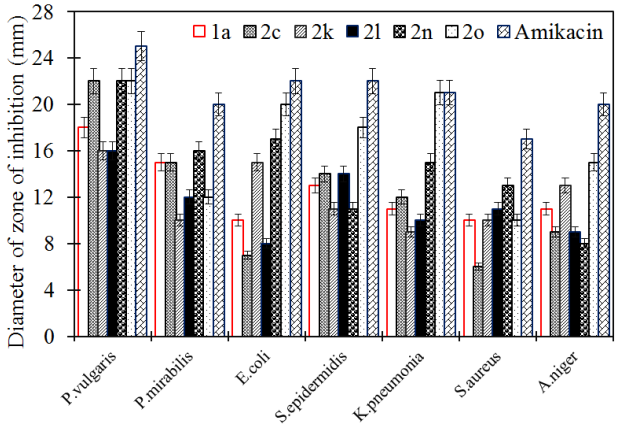

In view of their significant antimicrobial activities evidenced by zone of inhibition experiments against all the examined pathogenic microbes, the most active molecules such as **2c**, **1a**, **2i**, **2*J***, **2k** and **2l** were further evaluated for their corresponding minimum inhibitory and bactericidal (MIC and MBC) concentration values and the determined results were tabulated in terms of µg/mL. All the six compounds demonstrated variable inhibitions against the tested pathogens and the good inhibitory activities (22µg/mL) were found against organisms *P. vulgaris*, *E. coli*, *S. epidermidis* and *K. pneumonia* for compounds **1c**, **1a**, **2k** and **2l** respectively.

RESULTS AND DISCUSSION

Synthesis of Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(phenyl substituted) quinazolin-4(3H)-one, 2a-2l:

In an oven dried, screw-cap vial equipped with a stirring bar were placed 6-bromo-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (**1a**) (100 mg, 0.28 mmol) dissolved in anhydrous 1, 4-dioxane (2 mL), p-toluidine (90 mg, 0.85 mmol) and NaO^tBu (53 mg, 0.56 mmol). The vial was flushed with argon for 10 min, $Pd_2(dba)_3$ (2.5 mg, 0.028 mmol) and DavePhos(**L3**) (1.7 mg, 0.042 mmol) was added. The vial was sealed with a

Teflon-lined cap, and placed in a sand bath that was maintained at 100 ^{o}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 Na_2SO_4. The mixture was evaporated under reduced pressure. The crude product was purified by column chromatography; compound was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with pet-ether, followed by 20% EtOAc in n-hexane afforded compound **2a** (100 mg, 93% yield) as white solid.

Characterization of **2a**: 2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(p-tolylamino) quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 1H), 8.53 (d, J = 3.6 Hz, 1H), 7.84 (d, J = 2.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 8.8, 3.2 Hz, 1H), 7.25-7.24 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.97-6.94 (m, 2H), 6.82 (d, J = 7.2 Hz, 1H), 6.12 (s, 1H), 5.59 (s, 2H), 2.31 (s, 3H), 1.87-1.81 (m, 1H), 1.19-1.17 (m, 2H), 0.96-0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 154.0, 148.8, 148.2, 142.3, 141.9, 141.4, 139.3, 134.6, 129.2, 128.2, 123.7, 122.9, 121.0, 119.5, 115.8, 111.2, 44.2, 21.4, 14.3, 8.4. HRMS (ESI): m/z calcd for $C_{24}H_{23}N_4O$ $[M + H]^+$ 383.1872 found 383.1864. Melting Point: 122-124^{o}C.

Characterization of **2b**:2-Cyclopropyl-6-(phenylamino)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.56 (d, J = 3.2 Hz, 2H), 8.49 (d, J = 4.0 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.46(d, J = 2.4 Hz, 2H), 7.37 (dd, J = 8.0, 4.8 Hz, 1H), 7.32 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H,), 6.94 (t, J =7.2 Hz, 1H), 5.56 (s, 2H), 2.12-2.08 (m, 1H), 1.02-1.00 (m, 2H), 0.91-0.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.3, 154.2, 148.4, 148.2, 142.4, 142.2, 140.4, 134.3, 132.7, 129.2, 127.9, 124.6, 123.6, 120.8, 120.5, 117.7, 108.7, 43.7, 13.7, 8.6. HRMS (ESI): m/z calcd for $C_{23}H_{21}N_4O$ $[M + H]^+$ 369.1715 found 369.1711. Melting point: 172-174^{o}C.

Characterization of **2c:** 2-Cyclopropyl-6-(2-fluorobenzylamino)-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.51 (d, J = 3.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.43-7.33 (m, 3H), 7.25-7.21 (m, 2H), 7.0 -7.02 (m, 3H), 5.56 (s, 2H), 4.52 (s, 1H), 4.46 (s, 2H), 1.85-1.80 (m, 1H), 1.16-1.13 (m, 2H), 0.94-0.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 162.1, 159.6, 152.8, 148.8, 148.2, 146.3, 139.8, 134.5, 132.5, 129.4, 129.3, 129.0, 128.9, 128.1, 126.8, 1262, 125.4, 125.4, 124.1, 123.6, 122.2, 121.1, 115.4, 115.2, 105.3, 44.1, 41.8, 29.5, 14.2, 8.1. HRMS (ESI): m/z calcd for $C_{24}H_{22}FN_4O$ $[M + H]^+$ 401.1778 found 401.1770. Melting Point: 130-132^{o}C.

Characterization of **2d**: 2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(2-(trifluoromethyl) benzyl amino) quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 7.62 (s, 1H), 7.56–7.51 (m, 3H), 7.45–7.42 (m, 2H), 7.35 (d, J = 3.2 Hz, 1H), 7.25-7.22 (m, 1H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H), 5.56 (s, 2H), 4.65 (s,1H), 4.46 (s, 2H), 1.86-1.80 (m, 1H), 1.17-1.40 (m, 2H), 0.95-0.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 153.0, 148.8, 148.2, 146.2, 140.0, 139.7, 134.5, 132.5, 131.1, 130.6, 129.1, 128.2, 124.1, 122.6, 122.2, 121.1, 105.4, 47.6, 44.2, 14.2, 8.1. HRMS (ESI): m/z calcd for $C_{25}H_{22}F_3N_4O$ $[M + H]^+$ 451.1746 found 451.1420. Melting Point: 121-123^{o}C

Characterization of **2e:**. 3.1.5. 2-Cyclopropyl-6-(piperidin-1-yl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 8.61(s,1H), 8.53 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 2.8 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.41 (dd, J = 9.6, 2.8 Hz, 1H), 7.28-7.7.23 (m,1H), 5.60 (s,2H), 3.28-3.25 (m, 4H), 1.86-1.82 (m, 1H), 1.75-1.69 (m, 4H), 1.63-1.57 (m, 2H), 1.19-1.15 (m, 2H), 0.97-0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 153.6, 150.4, 148.3, 140.3, 134.6, 132.5, 127.7, 124.8, 123.6, 120.6, 113.9, 109.8, 50.2, 44.2, 25.6, 24.1, 14.3, 8.2. HRMS (ESI): m/z calcd for $C_{22}H_{25}N_4O$ $[M + H]^+$ 361.2028 found 361.2039. Melting Point: 107-109°C.

Characterization of **2f**.:2-Cyclopropyl-6-(3,5-dimethoxyphenylamino)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in) = 0.5; ^{1}H NMR (400 MHz, DMSO-d: δ = 8.57(s,2H), 8.49 (d, J = 3.2 Hz, 1H), 7.76 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.50-7.44 (m, 2H), 7.37 (t, J = 6.2 Hz,1H), 6.29 (s, 2H), 6.09 (s, 1H), 5.57 (s, 2H), 3.71(s, 6H), 2.11-2.09 (m, 1H), 1.01 (s, 2H), 0.90-0.85 (m, 2H). ^{13}C NMR (100 MHz, CDCl3): δ = 161.4, 161.1, 154.6, 148.4, 148.2, 144.3, 141.6, 140.6, 134.3, 132.7, 127.9, 125.3, 123.7, 120.4, 109.8, 95.6, 92.6, 55.0, 43.7, 13.7, 8.6. HRMS (ESI): m/z calcd for $C_{25}H_{25}N_4O_3$ $[M + H]^+$ 429.1927 found 429.1948. Melting Point: 167-169°C.

Characterization of **2g:**5-chloropyrimidin-4-ylamino)-2-cyclopropyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one,Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65(s, 1H), 8.63(s, 1H), 8.55(s, 1H), 8.51(d, J = 2.4 Hz, 1H), 8.40(s, 1H), 8.10(dd, J = 8.8, 2.4 Hz, 1H), 7.63(t, J = 7.0 Hz, 2H), 7.38(s, 1H), 7.29-7.26(m, 1H), 5.61(s, 2H), 1.92-1.86(m, 1H), 1.28-1.25(m, 2H), 1.02-0.98(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 156.4, 156.1, 155.3, 153.7, 149.0, 148.3, 144.2, 135.9, 134.7, 132.3, 128.1, 128.0, 123.8, 120.6, 117.6, 115.1, 44.4, 14.3, 9.0. HRMS (ESI): m/z calcd for $C_{21}H_{18}ClN_6O$ $[M + H]^+$ 405.1231; found 405.1223. Melting Point: 133-136°C.

Characterization of **2h:**Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(quinolin-3-ylamino)quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73(d, J = 2.0, 1H), 8.61(s, 1H), 8.54(s, 1H), 8.02(s, 2H), 7.99(d, J = 2.4, 1H), 7.81(d, d, J = 7.6, 1H), 7.66(d, J = 7.6, 1H), 7.59(d, J = 9.2, 1H), 7.55-7.51(m, 3H), 7.48(t, J = 7.4, 1H), 7.26-7.23(m, 1H), 5.60(s, 2H), 1.90-1.84(m, 1H), 1.23-1.20(m, 2H), 1.0-0.95(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 155.0, 149.0, 148.4, 145.2, 144.0, 142.5, 140.8, 136.1, 134.5, 132.3, 129.0, 128.6, 127.2, 126.9, 126.6, 125.4, 123.7, 121.2, 118.4, 112.8, 44.3, 14.3, 8.7. HRMS (ESI): m/z calcd for $C_{26}H_{22}N_5O$ $[M + H]^+$ 420.1824; found 420.1877. Melting Point: 173-176°C.

Characterization of **2i:**2-Cyclopropyl-6-(1-methyl-1H-indol-5-ylamino)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60(s, 1H), 8.53(d, J = 3.60, 1H), 7.64(d, J = 2.4, 1H), 7.57(d, J = 2.4, 1H), 7.45(dd, J = 4.8, 3.2, 2H), 7.30(t, J = 4.4, 2H), 7.10(d, J = 8.8, 1H), 7.06(d, J = 2.8, 1H), 6.42(d, J = 2.8, 1H), 5.69(s, 1H), 5.57(s, 2H), 3.79(s, 3H), 1.85-1.81(m, 1H), 1.18-1.14(m, 2H), 0.96-0.91(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 153.2, 148.7, 148.2, 145.5, 140.4, 134.8, 133.5, 132.8, 129.6, 128.1, 123.8, 123.0, 121.2, 118.3, 114.6, 110.0, 108.5, 100.7, 44.2, 32.9, 14.3, 8.25. HRMS (ESI): m/z calcd for $C_{25}H_{23}N_6O$ $[M + H]^+$ 423.1933; found 422.1978. Melting Point: 103-106°C.

Characterization of **2j:**6-(2-Chloro-6-methylphenylamino)-2-cyclopropyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one,Chromatography was performed using 10% MeOH in CH2Cl2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59(s, 1H), 8.52(s, 1H), 7.56(d, J = 8.0, 1H), 7.48(d, J = 8.8, 1H), 7.32(d, J =

8.0, 2H), 7.28-7.21(m, 1H), 7.18(d, J = 7.2, 1H), 7.10-7.06(m, 2H), 5.85(s, 1H), 5.55(s, 2H), 2.21(s, 3H), 1.87-1.82(m, 1H), 1.19-1.16(m, 2H), 0.95-0.92(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 153.7, 148.9, 148.4, 143.7, 141.1, 137.1, 136.3, 134.5, 132.5, 131.4, 129.7, 128.2, 127.6, 126.3, 123.6, 123.1, 121.0, 108.8, 44.2, 18.8, 14.2, 8.3. HRMS (ESI): m/z calcd for $C_{24}H_{22}ClN_4O$ $[M + H]^+$ 417.1482; found 417.1484. Melting Point: 126-129 ^oC.

Characterization of **2k:** 2-Cyclopropyl-6-(4-morpholinophenylamino)-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59(s, 1H), 8.53(d, J = 3.6, 1H), 7.68(d, J = 2.4, 1H), 7.57(d, J = 7.6, 1H), 7.46(d, J = 8.4, 1H), 7.28(d, J = 2.8, 1H), 7.26-7.22(m, 1H), 7.12(d, J = 8.4, 2H), 6.90(d, J = 8.8, 2H), 5.85(s, 1H), 5.57(s, 2H), 3.87(t, J = 4.4, 4H), 3.13(t, J = 4.6, 4H), 1.85-1.81(m, 1H), 1.18-1.17(m, 2H), 0.95-0.94(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 153.5, 148.9, 148.4, 147.6, 144.1, 140.8, 134.5, 134.3, 132.5, 128.2, 123.6, 123.5, 122.5, 121.1, 117.1, 108.9, 66.9, 49.9, 44.2, 14.3, 8.3. HRMS (ESI): m/z calcd for $C_{27}H_{28}N_5O_2$ $[M + H]^+$ 454.2243; found 454.2282. Melting Point: 168-171^oC.

Characterization of **2l:** 2-Cyclopropyl-6-(2-fluorophenylamino)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one, Chromatography was performed using 10% MeOH in CH_2Cl_2 to yield a Pale yellow solid R_f (10% MeOH in CH_2Cl_2) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61(s, 1H), 8.54(s, 1H), 7.91(s, 1H), 7.59(d, J = 6.4, 1H), 7.53(d, J = 8.8, 1H), 7.45-7.37(m, 2H), 7.26(s, 1H), 7.12-7.04(m, 2H), 6.92(d, J = 5.2, 1H), 6.08(s, 1H), 5.59(s, 2H), 1.87-1.86(m, 1H), 1.25-1.21(m, 2H), 0.97-0.96(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 154-.7, 152.3, 148.9, 148.3, 142.2, 141.1, 137.5, 134.6, 132.4, 110.5, 130.4, 129.4, 128.8, 128.4, 125.6, 124.4, 123.7, 121.9, 121.8, 121.4, 118.5, 115.1, 115.6, 112.0, 44.3, 14.3, 8.5. HRMS (ESI): m/z calcd for $C_{23}H_{20}FN_4O$ $[M + H]^+$ 387.1621; found 387.1624. Melting Point: 99-103 ^oC.

Typical experimental procedure for the preparation of compound 3a-3 g: In an oven dried, screw-cap vial equipped with a stirring bar were placed 6-bromo-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3H)-one (**1a**) (100 mg, 0.28 mmol) dissolved in anhydrous 1, 4-dioxane (2 mL), phenyl boronic acid (51mg,0.42 mmol) and NaO^tBu (53 mg, 0.56 mmol). The vial was flushed with argon for 10 min, $Pd_2(dba)_3$ (2.5 mg, 0.028 mmol) and DavePhos(**L3**) (1.7 mg, 0.042 mmol) was added. The vial was sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 100 ^oC. 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 Na_2SO_4. The mixture was evaporated under reduced pressure. The crude product was purified by column chromatography, compound was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with pet-ether, followed by 20% EtOAc in n-hexane afforded compound **3a** (100 mg, 93% yield) as white solid.

Characterization of **3a:**2-Cyclopropyl-6-phenyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one, Chromatography was performed using 70% EtOAc in n-hexane to yield a Pale yellow solid. R_f (70% EtOAc in n-hexane) = 0.55; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.61 (s, 1H), 8.51 (d, J = 3.3 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.13 (dd, J = 9, 2.1 Hz, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.68 (t, J =7.65 Hz, 2H), 7.53 (t, J = 7.65, 2H), 7.43-7.35 (m, 2H), 5.61 (s, 2H), 2.21-2.16 (m, 1H), 1.12 (d, J = 3, 2H), 0.99-0.94 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.6, 157.1, 149.0, 148.4, 146.6, 139.6, 139.2, 134.6, 133.3, 132.3, 128.9, 127.7, 127.5, 127.1, 124.8, 123.7, 120.3, 44.3, 14.4, 9.0. HRMS (ESI): m/z calcd for $C_{23}H_{20}N_3O$ $[M + H]^+$ 354.1606; found 354.1599. Melting Point: 124-128 ^oC.

Characterization of **3b:**2-Cyclopropyl-6-(5-fluoro-2-methoxyphenyl)-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one,Chromatography was performed using 70% EtOAc in n-

hexane to yield a Pale yellow solid R_f (70% EtOAc in n-hexane) = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62(s, 1H), 8.54(s, 1H), 8.41(d, J = 1.6 Hz, 1H), 7.90(dd, J = 8.4, 1.6 Hz, 1H), 7.61(d, J = 8.4 Hz, 2H), 7.28(t, J = 5.8 Hz, 1H), 7.13(dd, J = 9.2, 3.2 Hz, 1H), 7.04(m, 1H), 6.93(m, 1H), 5.61(s, 2H), 3.78(s, 3H), 1.92-1.87(m, 1H), 1.30-1.21(m, 2H), 1.01-0.98(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 158.3, 157.2, 155.9, 152.6, 149.0, 148.9, 148.2, 146.6, 141.2, 135.8, 135.7, 134.7, 132.3, 130.4, 127.3, 126.6, 123.7, 122.9, 120.0, 55.7, 44.2, 14.3, 9.0. HRMS (ESI): m/z calcd for $C_{24}H_{21}FN_3O_2$ $[M + H]^+$ 402.1618; found 402.1656. Melting Point: 123-126 ^oC.

Characterization of **3c**:2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(2,3,5-trichlorophenyl)quinazolin-4(3H)-one,Chromatography was performed using 70% EtOAc in n-hexane to yield a Pale yellow solid R_f (70% EtOAc in n-hexane) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63(s, 1H), 8.56(s, 1H), 8.28(d, J = 2.0, 1H), 7.77(dd, J = 8.4, 2.0 Hz, 1H), 7.65(s, 1H), 7.63-7.60(d, J = 8.4 Hz, 1H), 7.51(d, J = 2.4 Hz, 1H), 7.31(d, J = 2.4 Hz, 2H), 5.62(s, 2H), 1.95-1.88(m, 1H), 1.30-1.25(m, 2H), 1.05-1.0(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 158.2, 149.2, 148.4, 147.4, 142.3, 136.1, 135.3, 134.6, 134.5, 132.7, 129.58, 129.52, 127.5, 127.0, 120.0, 44.4, 14.4, 9.3. HRMS (ESI): m/z calcd for $C_{23}H_{17}Cl_3N_3O$ $[M + H]^+$ 456.0437; found 456.0451. Melting Point: 123-126 ^oC.

Characterization of **3d:**Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(4-(2,4,4-trimethylpentan-2-yl)phenyl)quinazolin-4(3H)-one,Chromatography was performed using 70% EtOAc in n¬-hexane to yield a Pale yellow solid R_f (70% EtOAc in n-hexane) = 0.65; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1H), 8.54(d, J = 4.0 Hz, 1H), 8.51(d, J = 2.0 Hz, 1H), 7.99(dd, J = 8.8, 2.4 Hz, 1H), 7.63(dd, J = 8.4, 1.6 Hz, 1H), 7.59(m, 3H), 7.48(d, J = 8.4Hz, 2H), 7.27-7.24(m, 1H), 5.61(s, 2H), 1.91-1.86(m, 1H), 1.78(s, 2H), 1.41(s, 6H), 1.28-1.23(m, 2H), 1.01-1.96(m, 2H), 0.75(s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 156.8, 149.9, 149.0, 148.4, 146.4, 139.0, 136.3, 134.5, 133.0, 132.3, 132.0, 128.3, 127.4, 126.7, 126.3, 124.4, 123.7, 120.2, 56.8, 44.2, 38.4, 32.3, 31.7, 31.4, 14.4, 8.9. HRMS (ESI): m/z calcd for $C_{31}H_{36}N_3O$ $[M + H]^+$ 466.2858; found 466.2816. Melting Point: 110-113^oC.

Characterization of **3e:**.6-(4-(tert-butyldimethylsilyloxy)phenyl)-2-cyclopropyl-3-(pyridin-3-ylmethyl)quinazolin-4(3H)-one,Chromatography was performed using 70% EtOAc in n-hexane to yield a Pale yellow solid R_f (70% EtOAc in n-hexane) = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65(s, 1H), 8.55(s, 1H), 8.43(s, 1H), 7.92(d, J = 8.0 Hz, 1H), 7.65-7.54(m, 3H), 7.33-7.28(m, 2H), 6.93(d, J = 8.4, 2H), 5.62(s, 2H), 1.88(m, 1H), 1.30-1.19(m, 2H), 1.0 (s, 9H), 0.90-0.86(m, 2H), 0.23(s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =162.5, 156.6, 155.6, 146.0, 138.8, 135.3, 132.5, 129.8, 129.7, 129.5, 128.0, 127.7, 127.3, 125.4, 123.9, 120.1, 120.0, 44.1, 31.7, 25.5, 14.3, 8.9, -4.5. HRMS (ESI): m/z calcd for $C_{29}H_{34}N_3O_2Si$ $[M + H]^+$ 484.2420; found 484.2421

Characterization of **3f:**.2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(4-(pyridin-4-yl) phenyl) quinazolin-4(3H)-oneChromatography was performed using 70% EtOAc in n-hexane to yield a Pale yellow solid R_f (70% EtOAc in n-hexane) = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69(d, J = 3.6 Hz, 2H), 8.64(s, 1H), 8.55(d, J = 1.2 Hz, 2H), 8.02(dd, J = 8.4, 2.0 Hz, 1H), 7.92(s, 1H), 7.75(d, J = 7.6 Hz, 1H), 7.68(d, J = 8.4 Hz, 1H), 7.64(q, 4H), 7.57(d, J = 5.6 Hz, 1H), 7.28(q, 1H), 5.63(s, 2H), 1.95-1.89(m, 1H), 1.30-1.25(m, 2H), 1.04-0.99(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 157.4, 150.2, 149.1, 148.4, 148.0, 146.9, 140.6, 138.9, 138.4, 133.2, 132.1, 129.7, 127.7, 126.2, 125.7, 124.9, 123.7, 121.6, 120.3, 44.3, 29.6, 14.4, 9.1. HRMS (ESI): m/z calcd for $C_{28}H_{23}N_4O$ $[M + H]^+$ 431.1872; found 431.1843. Melting Point: 181-185 ^oC.

Characterization of **3g:.**2-Cyclopropyl-3-(pyridin-3-ylmethyl)-6-(3'-(pyrimidin-5-yl)biphenyl-3-yl)quinazolin-4(3H)- one, Chromatography was performed using 70% EtOAc in n-hexane to yield a Pale yellow solid R_f (70% EtOAc in n-hexane) = 0.5; ^{1}H NMR (400

MHz, $CDCl_3$): δ = ; ^{1}H NMR (400 MHz, $CDCl_3$):δ = 9.23(s, 1H), 9.03(s, 2H), 8.63(s, 1H), 8.58(dd, J = 6.8, 2.4 Hz, 2H), 8.05(dd, J = 8.4, 2.0 Hz, 1H), 7.93(s, 1H), 7.83(s, 1H), 7.76-7.71(m, 2H), 7.69(d, J = 8.0 Hz, 1H), 7.65-7.56(m, 5H), 7.29-7.25(m, 1H), 5.63(s, 2H), 1.94-1.89(m, 1H), 1.30-1.25(m, 2H), 1.04-0.99(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$):δ = 162.6, 157.6, 157.3, 155.0, 149.1, 148.4, 146.9, 142.3, 141.2, 140.4, 138.8, 134.9, 134.6, 134.3, 133.2, 132.2, 129.9, 129.5, 127.9, 127.7, 126.6, 126.5, 126.1, 126.0, 125.9, 124.9, 123.7, 120.4, 44.3, 14.4, 9.1.HRMS (ESI): m/z calcd for $C_{33}H_{26}N_5O$ $[M + H]^+$ 508.2137; found 508.2163. Melting Point: 98-102 ^oC.

APPLICATIONS

All synthesized compounds were screened for antibacterial activity evidenced by zone of inhibition experiments against all the examined pathogenic microbes, the most active molecules such as **2c**, **1a**, **2i**, **2*J***, **2k** and **2l** were further evaluated for their corresponding minimum inhibitory and bactericidal (MIC and MBC) concentration values and the determined results were tabulated in terms of µg/mL. All the six compounds demonstrated variable inhibitions against the tested pathogens and the good inhibitory activities (22µg/mL) were found against organisms *P. vulgaris*, *E. coli*, *S. epidermidis* and *K. pneumonia* for compounds **1c**, **1a**, **2k** and **2l** respectively.

CONCLUSION

In conclusion, a common catalyst system introduced for C–N and C-C bond formation for the introduction of substituted amino and aryl groups at the C-6 position of 2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-ones. The combination of 10 mol% $Pd_2(dba)_3$, 15 mol% DavePhos (**L3**)/NaO^{t}Bu in 1,4-dioxane gave good to excellent yields with 6-bromo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(*3H*)-one using a variety of amines as well as boronic acids. To our knowledge, this is the first report on successful C–N and C-C bond forming reactions at the C-6 position of 2, 3-disubstituted quinazoline-4-ones, particularly with a cyclopropyl substituent that is stable under the amination and Suzuki-Miyaura cross-coupling conditions. We have studied the relative reactivities of p-toluidine and phenyl boronic acid with the bromo quinazolinone precursor towards amination as well as C-C bond forming reaction and it was clear that later is superior.

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