Heterocyclic Letters
Vol. 6| No.3 |413-420|May-July| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

PALLADIUM CATALYZED SUZUKI REACTION FOR SYNTHESIS OF NEW TRISUBSTITUTED QUINAZOLINE DERIVATIVES

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Abstract:A method is presented for the modern derivatization of quinazolinethrough Suzuki cross coupling reaction between 2-chloro-N-alkyl-7-nitroquinolin-4-amine and substituted phenyl boronic acid.The carbon-carbon bond formation has been achieved by this reaction. These products are derivatives of new or very rare heterocycles.The products have been characterized through the usual chemical techniques like, 1HNMR, IR, and mass spectral analyses.

Keywords: Quinazoline derivative, 5, 6 dichloride 7-nitro quinazoline, Suzuki cross-coupling, dichloroquinazoline compound.

Introduction:

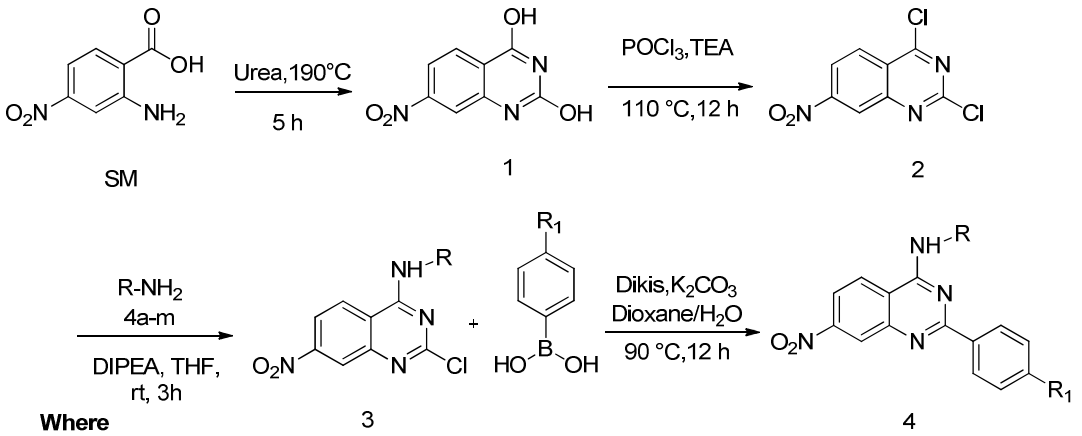
Quinazoline is fused nitrogencontainingheterocyclic compound, most commonly encounter in medicinal chemistry due to its broad range of pharmacological activities. Quinazoline derivatives are a class of chemical compounds have proved tohave activity as anti-inflammatory [I] and the antimicrobial [II-III], anti-allergic[IV], antibacterial and antifungal activity[V-VI]. Some derivatives of quinazolinealsoshowed antitumor [VII] and anticancer activity [VIII]particularlytrisubstitutedquinazoline derivatives showed the cytotoxic activity against THP-1HL-60 A-375 cell lines[IX]. Biologically it has proved some derivatives of 2-chloro -4 anilino-quinazoline played main role in anticancer and antitumor activity as EGFR and VEGFR-2 dual inhibitor [X]. The quinazoline derivatives as 2-trichloromethylquinazolines possessing a variously substituted sulfonamide group at position 4 used to prepare new quinazoline with antiparasitic proprieties and antiplasmodial activity[XI], quinazoline have become a favourite field for many investigation and their effort are quite significant in literature and a couple of themin the past appeared in the literature giving broader perspective of pharmacological activity of quinazoline derivatives [XII].Some authors adopted in theirresearch design synthetic methods of quinazoline derivatives including Suzuki-Miyaurareactionwhich caused universal concerns due to their widely and distinct biopharmaceutical activities[XIII].Some journals have reported synthesis of quinazoline derivatives with different substituent on different position to enhance the biological activity of already reported quinazoline derivative[XIV-XVII]

Materials and Methods:

All melting points are uncorrected and were measured using an electro-thermal apparatus. ^{1}H NMR spectra were recorded on BruckerAvance II 400 NMR spectrometer using DMSO-$d_6$and $CDCl_3$ as solvent and tetramethylsilane as internal standard and chemical shifts being reported in parts per million (δ) relative to TMS. Mass spectra were obtained using waters Micromass Q-Tof Micro instrument at 70 eV. Optical rotations were measured by Equip-Tronics Digital Polarimeter EQ-801. Analytical thin-layer chromatography (TLC) was performed on Silica Gel $60F_{254}$ (Merck, Germany). The spots were visualized by exposure to UV light and I_2vapours.

Synthesis started from 4-nitro anthranilicacid and urea that from SpectrochemIndia Ltd.

General Scheme:



1- cyclopropyl amine , 2- t-Butyl amine , 3- p-Anisidine , 4- 2-amino thizole , 5-amino pyrazine, 6- ethyl amine , 7-Morpholine , 8-Aniline , 9- m-Toludine , 10- Ethyl amine (with 1,1'-biphenyl]-4-ylboronic acid) 11- Imadazole with 2-methoxy phenyl boronic acid), 12-p-Anisidine with 2-methoxy phenyl boronic acid)

Scheme 1: Synthetic route for 4a-n

Table-1: Synthesis of compound-3 (2-chloro-N-alkyl-7-nitroquinolin-4-amine**)**

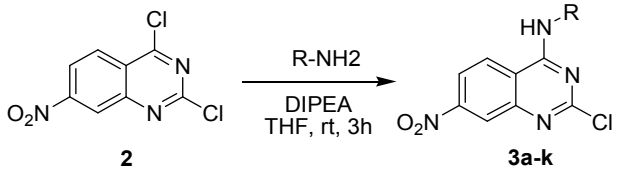


Table-1: Compound -3 (Reaction of dichloride compound with different amines)

Sr.No	Amines Compound	R	Compound-3	Time	Yield (%)
1	Cyclopropyl amine	C3H7N	3a	2h	87
2	tert-Butyl amine	C4H11N	3b	3h	91
3	p-Anisidine	C7H9NO	3c	3h	88
4	Ethyl amine	C2H7N	3f	2h	95
5	Morpholine	C4H9NO	3g	3h	85
6	p-Toludine	C7H9N	3i	3h	87

7	m-Toludine	C7H9N	3k	2.5 h	91
8	1H-Imidazole	C3H4N2	3m	3h	82

Experimental Data:

Synthesized the particular quinazoline derivatives in which amine group on 4th position and electron rich aromatic group on 2nd position with strong electron withdrawing group on 7th position. Synthesis of the 2,4-dichloroquinazoline as per procedure reported in journal synthesis and antimalarial effect of N2-aryl-N4-(dialkylamino) alkyl)- and N4-aryl-N2(dialkyl amino)alkyl)2-4 quinazolinediamine, Journal of Medicinal chemistry, 24(2),127-40,1981.andConvenient Synthetic Approach to 2,4-disubstituted quinazolines Org. Lett. 2007, 9, 69-72.In step-1 Charged 4-nitro anthranilc acid to round bottom flask in nitrogen atmosphere, was mixed with urea by using spatula, mixed material was heated upto 120 °C, reaction mass become dark brown liquid, stirred the reaction mass for 30 min at 120.

Further heated the reaction mass at 180°Cfor 4-5 h, after completion of reaction time reaction mass as brown colored solid was observed, progress of reaction monitored by TLC, it showed complete conversion, charged the methanol into the reaction mass heated the reaction mixture 50-55 °C for 3 h, filtered the reaction mass at 50-55°C, and washed the solid by methanol at room temperature, suck dried the material under vacuum, dry compound used for next step.

In step 2nd step synthesis of 2,4 dichloro 7 nitro quinazoline synthesized from 2, 4 hydroxy 7 nitro quinazoline (5 g 0.02 mol, 1 eq)charged into round bottom flask under nitrogen atm. $POCl_3$(5 eq, 22.99 g 0.121mol) was added to it portion wise. (Some slight exotherm observed if starting compound contain moisture)

Stirred the reaction mixture for 20 min at 30 °C.Cooled the reaction mixture at 0 to 10 °C. Charged triethyl amine via addition funnel drop wise (4.09 mL,1.5eq, 0.03 mol),heated the reaction mixture up to 60°C and after that up to 110°C, maintained the reaction mixture for 7-8 hrs. at 110°C (Oil temp), Progress of reaction monitored by TLC, Reaction mixture becomes dark brown colour turbid solution, TLC showed total consumption starting compound.

Cooled the reaction mass up to room temperature, poured the reaction mixture into wet ice slowly and portion wise sudden exotherm observed (temperature should not be exceed than 30 °C) filtered the reaction mixture under vacuum, unloaded the solid from buckner funnel, transferred the brown solid to next round bottom flask and added ethyl acetate into it.Stirred the turbid material for 30 minute,filtered the solid and again stirred with ethyl acetate until TLC showingdichloro compound present in crude material.Total organic was collected washed with saturated bicarbonate solution, distilled out the organic layer under vacuum at 60-70°C,crude compound purified by column chromatography using 100-200 silica gel and 20 ethyl acetate in petroleum ether as solvent. Pure compound distilled out under vacuum at 60-70°C, afforded light yellow coloured solid material which used for next step.

General procedure for the Synthesis of 2 aryl, 4-amino-7-nitroquinazoline from 2, 4-dichloroquinazoline

7-nitroquinazoline-2, 4-dichloro quinazoline(2..0 g, 1 eq, 8.19mmol)dissolved in THF (20vol) at room temp,stirred the reaction mass for 30 min,dark yellow colour clear solution was observed,cooled the reaction mass at 0-10°C, Charged DIPEA (4,28 mL 3eq, 24.59mmol) into it at 0-10°C, prepared ethylamine solution (2.94 g 0.8eq, 6.55mmol) in THF (5 vol) at room temp, added ethyl amine solution to reaction via addition funnel drop wise, stirred the reaction mass at room temperature for 1-3 h, TLC showed the complete consumption of starting compound, to afforded crude 5a-k,crude,2-chloro-N-alkyl-7-nitroquinolin-4-amines were purified by reprecipitation, trituration and some by recrystallization affordedpure 2-chloro-N-alkyl-7-nitroquinolin-4-amines .

In the final step 5a-j reacted with three different aromatic boronic acids by palladium catalyzed Suzuki reaction to afford 7a-n analysis of the entire compounds7a-n. All the monitored by TLC in Ethyl acetate and petroleum ether system. The entire target compound was confirmed by ^{1}H NMR, LCMS, IR ^{13}CNMR.

To the stirred solution of 2-chloro-7-nitro-4-(amin-1-yl) quinazoline (1 g, 1 eq3.4 mmol) and aryl boronic acid (0.614 g, 1.2eq 4.40mmol) in dioxane (16 ml) and water (4ml) was added potassium carbonate (1.39 g, 3 eq, 10.11 mmol) purged the nitrogen gas for 30 minute at ambient temperature. After degassing (dikis) triphenyl phosphine dichloro palladium (II) (50.0 mg 0.02 eq, 0.0676mmol)stirred it for 12 h at 90°C. The progress of reaction was monitored by TLC. TLC shows the complete conversion of starting material**,** diluted the reaction mixture with ethyl acetate filtered the palladium inorganic part. Water was added to the filtrate and separated the organic layer. The organic layer was dried over the surface of sodium sulfate and evaporated under reduced pressure to afford crude compound**7**. Further crude compound was purified by column chromatography using 100-200 silica and 20% Ethyl acetate in petroleum ether to afford **7**a-m.

The compound was confirmed by IR, ^{1}H NMR, ^{13}C NMR and LCMS.

Experiment No.1:

I. SynthesisN-cyclopropyl-2-(4-methoxyphenyl)-7-nitroquinazolin-4-amine:**(compound 4a)**

Yellow solid, mp 192-194^{o}C.^{1}H NMR δ ppm (DMSO): 8.98 (b, 1H, CH), 8.60-8.49 (m, 1H, Ar-H),8.01 (d, 1H, CH), 8.13-8.10 (dd, 2H, Ar-H), 7.04-7.02 (d, 2H, Ar-H), 3.875 (s, 3H, OCH3), 3.10-3.09 (m, 1H, N-CH). 1.27-1.20 (m, 2H, CH2) 0.96-0.92 (m, 2H, CH2), ^{13} CNMR δ ppm (DMSO):161.9, 160.2, 149.8,130.1, 130.05, 126.3, 125.4, 118, 116.7, 113.5, 55.1, 24.6, 8.44I R (cm^{-1}) : 3414,3196, 3087,2920, 2846, 2343, 2107,1538,1345,1243,1046, 894, 820, 778 MS (m/z), 337.2(M+1,)$^{+}$. Anal.Calcd.forC18H16N4O3: C, 64.28; H, 4.79; N, 16.66; O, 14.27

II. N-(tert-butyl)-2-(4-methoxyphenyl)-7-nitroquinazolin-4-amine:**(compound 4b)**

Brownish solid, mp 138-140^{o}C.^{1}H NMR δ ppm (DMSO): 8.54-8.49 (d, 1H, Ar-CH), 8.16-8.06 (m, 2H, Ar-CH),7.82-7.78 (m, 2H, Ar-CH),7.03-7.01 (d, 1H, Ar-H), 5.78 (s, 1H, NH), 3.89 (s, 3H, OCH), 1.70 (s, 9H, CCH3).^{13} CNMR δ ppm (DMSO):162, 159.5, 158.4, 150.9, 150.08, 130.3, 124.1, 123.5, 122.5, 119.3, 118.5, 117.09, 116.1, 113.8, 54.27, 28.4, I R (cm^{-1}) 3431, 3284, 3122, 2996, 1802, 1542, 1418, 1343, 1030, 899, 820, 799, 734,MS (m/z), 550.9 (M-1)$^{+}$. Anal.Calcd.forC19H20N4O3: C, 64.76; H, 5.72; N, 15.90; O, 13.62 Found: N, 15.78; C, 64.78.H 5.72, O 13.7

III. N,2-bis(4-methoxyphenyl)-7-nitroquinazolin-4-amine :**(compound 4c)**

Dark yellow solid, mp 155-157^{o}C.^{1}H NMR δ ppm (DMSO): 9.996 (s, 1H, Ar-H), 8.76-8.73 (d, 1H, Ar-H),8.1515-8.1513 (d, 1H, Ar-CH), 8.41-8.38 (m, 2H, Ar-H),8.20-8.18 (m, 1H,ArH), 7.83-7.81 (m, 1H, ArH), 7.06-7.00 (m, 4H, ArH) 6.94(s, 1H), 3.86 (s, 3H, OCH3) and 3.83 (s, 3H, OCH3) .^{13} CNMR δ ppm (DMSO): 159.5, 159.3, 158.4, 150.9, 150.4, 130.4, 54.2, 28.7 I R (cm^{-1}): 3424, 3077, 2924, 2842, 2109, 1888,1603,1531, 1341,1244, 1166, 1023, 941, 799, . MS (m/z), 401.0 (M-1)$^{+}$. Anal.Calcd.forC22H18N4O4: C, 65.66; H, 4.51; N, 13.92; O, 15.90. Found: N, 15.78; C, 64.78.H 5.72,O 13.70

IV. 2N-ethyl-2-(4-methoxyphenyl)-7-nitroquinazolin-4-amine: (compound 7f)

Dark yellow solid, mp122-125^{o}C.^{1}H NMR δ ppm (DMSO): 9.16 (s, 1H, ArH), 8.65 (s, 1H, NH), 8.49-8.43 (m, 2H, Ar-H), 8.1881-8.1828 (d, 1H, Ar-H) 7.03-7.01 (m, 2H, Ar-H), 6.96-

6.93 (m, 2H, Ar-CH). 3.86 (s, 3H, OCH3), 3.60-3.58 (quintet, 2H, CCH2), 1.36-1.33(t, 3H, CCH3), I R (cm^{-1}): 3430, 3237, 2975, 2110, 1899, 1584 , 1899, 1584, 1534, 1344, 1242, 1157, 1027, 954, 887, 819, , cm^{-1} , 1724 cm, 1609 MS (m/z), 324.9 $(M+1)^+$. Anal.Calcd for C17H16N4O3: Elemental Analysis: C, 62.95; H, 4.97; N, 17.27; O, 14.80.

V. 4-(2-(4-methoxyphenyl)-7-nitroquinazolin-4-yl)morpholine (compound 4g)

Dark yellow solid, mp120-122^oC.^1H NMR δ ppm (DMSO): 8.45-8.43 (d, 1H,ArH), 8.20-8.18 .(dd, 1H, Ar-H), 7.73.7.71 (m, 2H, Ar-H), 7.04-7.02 (d, 1H, Ar-H),6.84-6.82 (d, 2H, Ar-H) 3.86-3.84 (m, 4H, -CH2),3.72 (s, 3H, OCH3), 3.03-3.03 (m, 4H, -CH2), I R (cm^{-1}): 3343, 2921, 2850, 2342, 2112, 1737, 1678, 1529, 1433, 1340, 1243, 1110, 1021, 951, 818, 736, , cm^{-1} , 1724 cm, 1609 MS (m/z), 367.1 $(M+1)^+$. Anal.C19H18N4O4Calcd.for C, 62.29; H, 4.95; N, 15.29; O, 17.47.

VI. 2-(4-methoxyphenyl)-7-nitro-N-(p-tolyl)quinazolin-4-amine: (compound 4i)

Brown solid, mp 203-205^oC.^1H NMR δ ppm (DMSO): 10.04 (s, 1H,ArH),8.79-8.77 (d, 1H,ArH),8.52-8.51 (d, 1H, Ar-H), 8.42-8.39 (m, 2H, Ar-H), 8.23-8.20 (s, 1H, N-H) 7.82-7.80 (dd, 2H, Ar-H), 7.28-7.26 (dd, 1H, Ar-CH), 7.28-7.26 (dd, 2H, Ar-CH), 7.03-7.01 (m, 2H, Ar-CH), 3.86 (s, 3H, -OCH3), 2.38 (s, 3H), I R (cm^{-1}): 3409, 2921, 2852, 2341, 1898, 1599, 1514, 1404, 1348, 1246, 1163, 1021, 940, 891, 819, 782, MS (m/z), 387.1 $(M+1)^+$.jg/. C22H18N4O3: Elemental Analysis: C, 68.38; H, 4.70; N, 14.50; O, 12.42

VII. 2-(4-methoxyphenyl)-7-nitro-N-(m-tolyl)quinazolin-4-amine: (compound 4k)

Dark yellow solid, mp167-169^oC.^1H NMR δ ppm (DMSO): 10.04 (s, 1H,ArH), 8.79-8.76 (d, 1H,ArH),8.51-8.50 (,s 1H, NH), 8.39-8.37 (m, 2H, Ar-H), 8.21-8.18 (dd, 1H, Ar-H) 7.79-7.78(d, 1H, Ar-H), 7.75.7.73(dd, 1H, Ar-H), 7.36-7.32 (m, 1H, Ar-CH), 7.02-6.99 (m, 1H, Ar-CH), 7.69-6.67(m, 1H, Ar-CH), 3.81 (s, 3H, -OCH3), 2.43 (s, 3H, ArCH3), I R (cm^{-1}) : 3402, 2913, 2869, 2333, 1900, 1583, 1511, 1398, 1340, 1251, 1170, 1016, 942, 893, 812, MS (m/z), 387.1 $(M+1)^+$. Anal.Calcd.forC22H18N4O3: Elemental Analysis: C, 68.38; H, 4.70; N, 14.50; O, 12.42

VIII. 2-([1,1'-biphenyl]-4-yl)-N-ethyl-7-nitroquinazolin-4-amine : (compound 4l)

yellow solid, mp135-137^oC.^1H NMR δ ppm (DMSO): 8.83 (s, 1H,ArH),8.8346-8.8603 (d, 1H, Ar-H), 8.18-8.17 (d, 2H, Ar-H),7.75-7.72 (m, 2H, Ar-H) 7.79-7.78 (d, 1H, Ar-H), 7.60.757(dd, 2H, Ar-H), 7.49-7.47 (m, 2H, Ar-CH), 7.38-7.36 (m, 2H, Ar-CH), 5.07 (s, 1H, NH), 3.92-3.68 (quintet, 2H, CCH2), 1.47-1.43 (t, 3H, CCH3), I R (cm^{-1}) I R: 3363, 3033, 2976, 2343, 1547, 1469, 1421, 1341, 1165, 1079, 1045, 954, 827, 737, cm, MS (m/z), 370.9 $(M+1)^+$. Anal.Calcd.forC22H18N4O2: Elemental Analysis: C, 71.34; H, 4.90; N, 15.13; O, 8.64

IX. 2-([1,1'-biphenyl]-4-yl)-N-ethyl-7-nitroquinazolin-4-amine : (compound 4m)

Yellow solid, mp 135-137^oC.^1H confirmed on the basis of IR and mass only: I R (cm^{-1}): 3423, 3197, 2920, 2342,1732, 1531, 1487, 1453,1174, 1130, 1018, 8263cm,MS (m/z), 385.1$(M-1)^+$. Anal.Calcd.forC18H13N5O3: Elemental Analysis: C, 62.24; H, 3.77; N, 20.16; O, 13.82

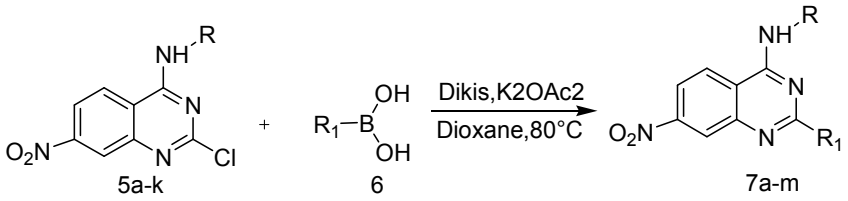
X. 2-(2-methoxyphenyl)-N-(4-methoxyphenyl)-7-nitroquinazolin-4-amine: (compound 4n)

brown solid, mp 203°C.^{1}H NMR δ ppm (DMSO): 10.09 (s, 1H,ArH),8.59-8.58 (dd, 1H,ArH),8.46-8.44 (dd, 1H, Ar-H),8.42-8.40 (d, 1H, NH), 8.23-8.20 (dd, 1H, Ar-H) 8.12-7.10 (m, 1H, Ar-H), 7.82-7.79 (m, 1H, Ar-CH), 7.66-7.65 (dd, 1H, Ar-CH), 7.56-7.54 (m, 1H, Ar-CH), 7.16-7.14 (m, 1H, Ar-CH), 6.99-6.97 (m, 2H, Ar-CH), 3.85 (s, 3H, -OCH3), 3.77 (s, 3H, -OCH3), I R (cm^{-1}) I R: I R: 3407, 3281, 2925, 1639, 1589, 1502, 1456,1231, 1170, 1126, 1028, 826 cm, MS (m/z), 403 $(M+1)^+$. Anal.Calcd.forC22H18N4O4: Elemental Analysis: C, 65.66; H, 4.51; N, 13.92; O, 15.90

Results and Discussions:

We synthesized the target compound as per above procedure by Suzuki reactions in between phenyl boronic acids and substituted quinazolines as below

Table-2: Synthesis of compound 4 (N-(alkyl)-2-(4-methoxyphenyl)-7-nitroquinazolin-4-amine)



Sr. No.	Compound 3a- m	Catalyst	R (boroniccaid)	Product a-n	Time	Yield	Melting Point
1	3a	$Pd(PPh_3)_4$	R1	4a	9 h	70%	194°C
2	3b	$Pd(PPh_3)_2Cl_2$	R1	4b	12h	88%	138°C
3	3c	$Pd(PPh_3)_4$	R1	4c	12h	80%	155°C
4	3f	$Pd(PPh_3)_2Cl_2$	R1	4f	12h	46%	148°C
5	3g	$Pd(PPh_3)_2Cl_2$	R1	4g	11h	78%	203°C
6	3i	$Pd(PPh_3)_2Cl_2$	R1	4i	12h	91%	186°C
7	3k	$Pd(PPh_3)_4$	R2	4k	12h	90%	156°C
8	3f	$Pd(PPh_3)_2Cl_2$	R3	4l	10h	74%	135°C
9	3m	$Pd(PPh_3)_2Cl_2$	R1	4m	12h	70%	162°C
10	3c	$Pd(PPh_3)_2Cl_2$	R2	4n	12h	58%	193°C

Note: **R1**-(4-methoxyphenyl) boronic acid, **R2**-(2-methoxyphenyl) boronic acid and **R3**-[1,1'-biphenyl]-4-ylboronic acid

Conclusion:

Hence we synthesized the quinazolinederivatives by Suzuki reactions after four steps, synthesis on basis of wield range biological activityof quinazoline derivatives in Pharmaceutical sciences, our library synthesis provided suitable route for synthesis of biological active quinazolinederivativesand it could help the design the new quinazoline drug in drug discovery**.**

I would like to emphasize that the most of compound synthesized by using dikis ($Pd(PPh_3)_2Cl_2$) catalyst but for the compound 7a and 7 k we synthesized it by using tetrakis$Pd(PPh_3)_4$ for better yield, consumed all the starting material with dikis but taken 20-24 hrs. formation of extra impurity in the crude reaction mixture it could hard to isolated pure

compound and with tetrakis reaction proceed smoothly with little formation of other impurity,out them 4i, 4k, 4b, 4f compound isolated in very good yield compare to other.
In summary synthesis of 2N-alkyl-2-(4-phenyl)-7-nitroquinazolin-4-amine derivatives were synthesized it will help to add in biological active chromphore.
All the reaction with 4-methoxy boronic acid excepts 4l - [1, 1'-biphenyl]-4-ylboronic acid and 4n R2-(2-methoxyphenyl) boronic acid, but reaction with some of amine derivatives we got very poor yield of difficult to isolate.
All the reactions are monitored by TLC in process to optimized good yield.Some compound like 4d, 4e,4 h 4j, all these compounds not isolated from crude , critically isolated but analytical data did not matched and for some compound reaction did not work well number of impurity formed with starting compound remained as it is even after number of trial with different reaction condition.

Acknowledgement:
The authors are thankfulto Post graduate Teaching Department of Chemistry of Shri Shivaji Science College Amravati to provideneedful laboratory facility, also thanks to Saif analytical PanjabUniversity, Chandigarh to provided analytical support, the work has been carried out without any financial support.

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Received on 1 May 2016.