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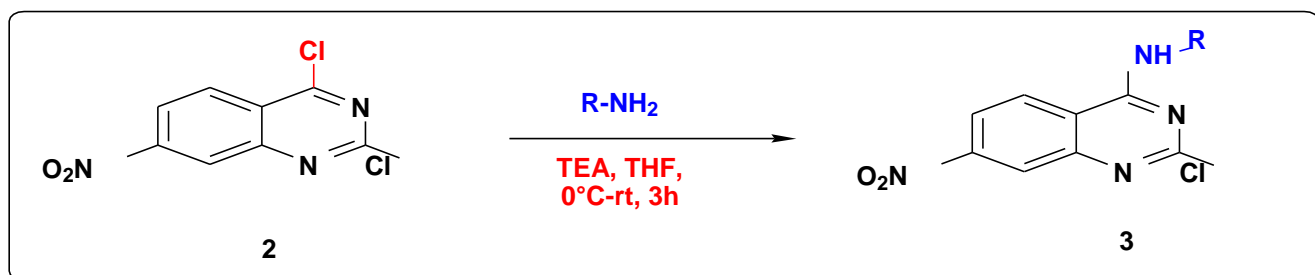
Research Article

### SELECTIVE SYNTHESIS OF 2-CHLORO-N-ALKYL-7-NITROQUINAZOLIN-4-AMINES DERIVATIVES FROM 2, 4 DICHLORO 7 NITRO QUINAZOLINE BY CONTROL REACTION CONDITIONS

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#### Graphical abstract:



#### Abstract:

A method is presented for the synthesis of selective derivatization of quinazoline by controlling the temperature and solvent concentration, 2,4-dichloro-7-nitroquinazoline reacted with different amines to form the selective 2-chloro-N-alkyl-7-nitroquinazolin-4-amines by chloro amine reaction, The products have been characterized through the usual chemical transformations, IR, NMR and mass spectral analyses.

**Keywords:** Quinazoline derivative, 5, 6 dichloride 7-nitro quinazoline, chloro amine coupling, dihydroxy compound.

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**INTRODUCTION:**

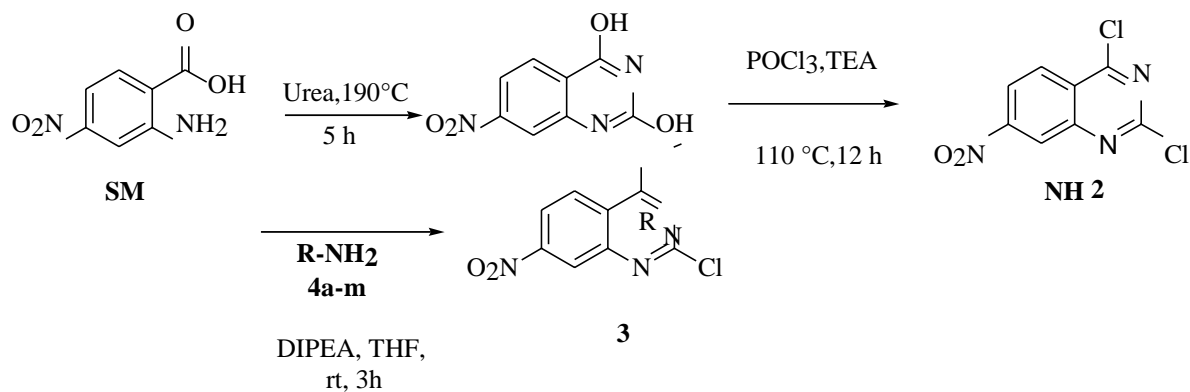
Quinazoline represent a fundamental and abundant class of nitrogen containing heterocyclic, quinazoline derivatives are of special importance because of their versatile biological and pharmacological activities and the researcher have all ready determined many therapeutic activity of quinazoline including antitumor, antiplasmodial [1-5], anti microbial [6-7], anti cancer [8-9], antitubercular activity [10]. In recent journal have reported the quinazoline has anti-inflammatory [11] activity and many compounds that contain the quinazoline motif possess a wide range of remarkable biological and medicinal activities as anti hypertensive [12], some article has reported quinazoline has anti hypertension and anti-oxidation activity [13], recently in journal has reported ant malarial activity of quinazoline derivatives [16] and in next journal has reported the quinazoline showed anti fungal and anti diabetes activity [14-15]. Quinazoline derivatives showed the different biological activity and also potential application in field of biology, pesticide and medicine quinazoline is a heterocyclic compound with unique place in field of medicinal chemistry [16-18]. Medicinal chemistry is concerned with discovery, development synthesis in laboratory and identifies action of physical and chemical methods. Here most of activity of directed to new natural or synthetic organic compounds. Inorganic

compounds continue to be important in therapy that is trace element in nutritional therapy, antacids and radiopharmaceutical.

Quinazoline (1, 3-diazanaphthalene) was prepared by garbrial in 1903 although the first derivative was synthesized by griess. The name was proposed by widdege, other names such as phenmiazine, benzo-1, 3-diazine and 5,6- benzopyrimidine has occasionally been used.

**MATERIALS AND METHODS:**

4-nitro anthranilic acid ordered from the Spectrochem Pvt. Ltd, POCl<sub>3</sub> also from spectrochem inda.pvt ltd., all amine purchased from different companies, spectrochem, Avra chemical pvt. ltd. chemical pvt.Ltd. SD fine chemicals, all melting points are uncorrected and were measured using an electro- thermal apparatus. <sup>1</sup>H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer using DMSO-d<sub>6</sub> and CDCl<sub>3</sub> 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. Analytical thin-layer chromatography (TLC) was performed on Silica Gel 60F254 (Merck, Germany). The spots were visualized by exposure to UV light and I<sub>2</sub>vapors.

**Scheme:****Where,****3a** : Cyclopropyl amine**3b** : t-Butyl amine**3c** : p-Anisidine**3d** : 2-Amino thizole**3e** : 2-Amino pyrazine,**3f** : Ethyl amine**3g** : Morpholine**3h** : Piperidine **3i**: p-Toludine **3j** :

Aniline

**3k** : m-Toludine**3l** : Imidazole**3m** : Methyl amine **3n**: n Propyl amine **3o** :

4 Nitro aniline

**3p** : 4-Amino pyridine

### Part A: Synthesis of scaffold up to Dichloro quinazoline

First two steps we consider as scaffold synthesis, in the first step as scheme started from 4 nitro anthranilic acid and urea to form 7-nitroquinazoline-2,4-diol in the in the second step 2,4 7 dichloro-7 nitro-quinazoline has synthesized by using POCl<sub>3</sub>, scaffold synthesis played important role for synthesis of whole scheme. We have synthesized the 2,4-dichloroquinazoline as per procedure reported in some journals[20-23]

#### Step-1: Synthesis of 7-nitroquinazoline-2,4-diol

4-nitro anthranilic acid (10 g, 1 eq, 54.94 mmol) was mixed with urea (9.89 g, 3 eq, 164.8 mmol) in nitrogen atmosphere, mixed material was heated at 120 °C, reaction mass become dark brown liquid, stirred the reaction mass for 30 min at 120. Further heated the reaction mass at 180°C for 4-5 hrs, reaction mass became brown colored solid, Progress of reaction monitored by TLC, it showed complete conversion. Cooled the reaction mixture up to room temperature, the methanol was added into the reaction mixture and heated the reaction mixture 50-55 °C, maintained the reaction mixture 3 hrs at 50-55°C, cooled it to 30-35°C, filtered the reaction mass at 30-35°C, washed the solid by methanol. Suck dried the solid under vacuum to afforded light yellow colored solid (10.2 g) yield .90.26 %, same material used for next step.

Properties of compound -1: Melting Point: 214 °C  
Mass: (M-1): 206

#### Step-2: synthesis of 2, 4-dichloro-7-nitroquinazoline

Synthesis of 2,4 dichloro 7 nitro quinazoline synthesized from 2, 4 hydroxy 7 nitro quinazoline (5 g, 1 eq, 24.15 mmol ) charged into RBF under nitrogen atm. TEA (10.16 mL, 3 eq, 72.45 mmol ) was added into it at room temperature POCl<sub>3</sub> ( 22.95 g , 5 eq, 120.77 mmol) added to it portion wise. (Some slight exotherm observed if starting compound contains 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. 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 complete conversion of starting compound. Cooled the reaction mass up to rt. Pored 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 RBF added the ethyl acetate into it. Stirred the turbid material for 30 min. filtered the solid and again stirred with ethyl acetate until TLC showing dichloro compound. Total organic was collected washed with saturated bicarbonate solution, distilled out the organic layer. Crude compound was purified by column chromatography by using 100-200 mesh size silica and 01 ethyl acetate in petroleum ether. Afforded 7 g of pure material same material used for next step.

Properties of compound -2: Light yellow colour.  
Melting Point: 131°C  
Mass (M+1): 244.02

#### Step-3: synthesis of 2-chloro-N-alkyl-7-nitroquinazolin-4-amine

7- nitroquinazoline-2, 4-dichloro quinazoline (3 g, 1 eq, 12.29 mmol) dissolved in THF (15 vol), stirred the reaction mass for 30 min at 25 to 30°C, TEA ( 5.17 mL, 3eq, 36.68 mmol ) was added into it at room temperature, Prepared cyclopropyl amine solution (0.56 mL,0.8 eq, 9.83 mmol ) in THF (10 Vol) at 0°C, stirred the reaction mass at room temperature for 1-3 hrs, Reaction of some derivatives completed with 2 hrs, but with others reaction completed within 3 hrs. TLC showed the complete consumption of starting compound, charged ethyl acetate (5 vol) to reaction mass prepared 1 M HCL (5 vol), solution to reaction mass, confirmed the pH, if required pH should be acidic, washed the reaction mass by 1 M HCL (2 vol), total aqueous layer was collected washed the by ethyl acetate layer, combined organic layers and washed with brine solution. distilled out the organic layer under vacuum and finally poured the crude compound was purified by column chromatography using 100-200 silica and 20 ethyl acetate in petroleum ether used as mobile phase to afforded pure product, but few compounds have purified by triturating with organic solvent and remaining by recrystallization afforded pure 2-chloro-N-alkyl-7-nitroquinolin-4-amines . The entire target compound was confirmed by <sup>1</sup>H NMR, LCMS, IR. TLC: (TLC solvent system 20% ethyl acetate in petroleum ether) TLC Stain: Ninhydrin

#### RESULT AND DISCUSSION:

In the result and discussion, while synthesizing 16 derivatives it is observed that experiment in the higher temperature the formation of disubstituted derivatives in more percentage and reaction in minimum dilution of solvent also helped to form disubstituted product. Compound 3a to 3c scheme went smoothly but the reaction on compound 3d and 3e was critical, reaction taken longer time and product were polar compared to other. Reaction with Aliphatic primary amines was preceded fast

compared to aromatic amines which has taken longer time. All the compounds have representative colour.

Compound 3p has unique quality of material and

very polar in nature. Compound 3h and 3m afford less yield and critical to isolate the pure material, colour of compound little dark than other derivatives.

#### List of Compounds:

Sr. No	Amines	R	Comp 3	Time	Yield (%)	Colour
1	Cyclopropyl amine	C3H7N	3a	2h	87	Light yellow
2	tert-Butyl amine	C4H11N	3b	3h	91	Light yellow
3	p-Anisidine	C7H9NO	3c	3h	88	Light brown
4	2 Amino thiozole	C3H4N2S	3d	3h	90	Dark brown
5	2 Amino pyrazine	C4H5N3	3e	2h	91	Dark brown
6	Ethyl amine	C2H7N	3f	2h	95	Yellow
7	Morpholine	C4H9NO	3g	3h	85	Dark yellow
8	Piperidine	C4H10N2	3h	2.h	98	Light brown
9	p-Toludine	C7H9N	3i	3h	87	Yellow
10	Aniline	C6H7N	3j	3h	91	Light yellow
11	m- Toludine	C7H9N	3k	2.5 h	91	Yellow
12	1H-Imidazole	C3H4N2	3l	3h	82	Light brown
13	methyl amine	CH5N	3m	2.5 h	85	Yellow
14	n-propyl amine	C3H9N	3n	3 h	84	Yellow
15	4-niroaniline	C6H6N2O2	3o	3 h	90	Dark yellow
16	4-amino pyridine	C5H6N2	3p	2 h	85	Light brown

#### 1. N-tert-butyl-2-chloro-7-nitroquinazolin-4-amine: (compound 3a)

Yellow solid, mp 155-158 °C.  $^1\text{H NMR } \delta$  ppm (DMSO): 8.91 (s, 1H) 8.54-8.50 (dd, 1H), 8.06- 8.08 (d, 1H), 4.10 (exchangeable, 1H), 1.10 (s, 9H), IR ( $\text{cm}^{-1}$ ): 3414, 3196, 3087, 1538, 1345, 1243, 1046, 894, 820, 778 MS (m/z), 281.06 (M+1), 283.06(M+3) Anal.Calcd.for C<sub>12</sub>H<sub>13</sub>CIN<sub>4</sub>O<sub>2</sub>: C 64.28, H 4.79 N, 16.66; O, 14.27

#### 2. 2-chloro-7-nitro-N-p-tolylquinazolin-4-amine :(compound 3i)

Dark yellow solid, mp 163-166 °C.  $^1\text{H NMR } \delta$  (DMSO): 8.95 (s, 1H) 8.57-8.54 (dd, 1H), 8.10-8.08 (d, 1H) 6.78-6.76 (d,1H, Ar-H), 6.34-6.36 (d,1H, Ar-H), 4.10 (exchangeable, 1H), 2.20 (s, 3H), IR ( $\text{cm}^{-1}$ ): 3410, 3194, 3080, 1542, 1348, 3840, 1310, 1048, 896, 824, 782 MS (m/z), 281.06 (M+1), 283.06(M+3)

#### 3. 2-chloro-7-nitro-N-phenylquinazolin-4-amine : (compound 3j)

Dark yellow solid, mp 168-171 °C.  $^1\text{H NMR } \delta$  ppm (DMSO):  $\delta$  8.97 (s, 1H) 8.62-8.58 (dd, 1H), 8.14-8.12 (d, 1H) 7.02-6.98 (d, 1H, Ar-H), 6.62-6.58 (m,1H), 6.44-6.42 (d,1H), 4.10(exchangeable, 1H), IR ( $\text{cm}^{-1}$ ): 3422, 3200, 3060,3038, 1532, 1346, 1310, 1220, 1042, 824, 782 MS (m/z), 301.04 (M+1), 303.04 (M+3),

**CONCLUSION:**

In conclusion, we would like to emphasize that synthesized 16 quinazoline derivatives selectively by control reaction condition, up to 1 to 5% disubstituted compounds also formed with desired product, it is concluded that disubstituted compound formed in high reaction temperature and low dilution, on the basis of bond dissociation energy and reactivity of pyrimidine desired target compounds synthesized after three steps, synthesis on basis of wide range biological activities of quinazoline derivatives in pharmaceutical sciences, our library synthesis of above sixteen derivatives could be helpful to synthesis biologically active quinazoline derivatives and upcoming research on quinazoline, all the above derivatives afforded in good percentage of yield. Compound 3d and 3e were tough to synthesize and afforded low yield, then compound 3c, 3f, 3k formed in clean on TLC with better yield compared to other and our quinazoline derivatives synthesis could help the design of the new quinazoline drug in drug discovery.

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