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Authors: Raghuram Gujjarappa, Nagaraju Vodnala, Velma Ganga Reddy, and Chandi C Malakar

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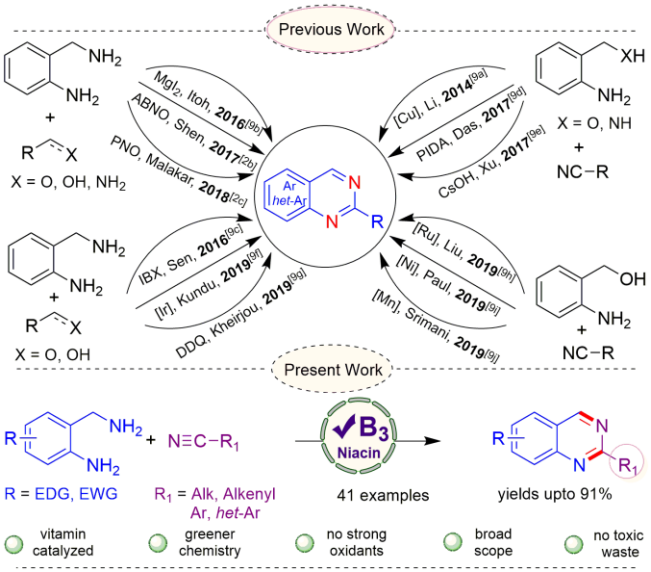
Niacin as a Potent Organocatalyst towards the Synthesis of Quinazolines using Nitriles as C-N Source

Raghuram Gujjarappa,[a] Nagaraju Vodnala,[a] Velma Ganga Reddy,[b] and Chandi C. Malakar*[a]

Abstract: An efficient and cost-effective Vitamin-B_3-catalyzed protocol towards the synthesis of diversely substituted quinazolines is illustrated using 2-aminobenzylamines and nitriles as substrates. An organocatalytic transformation has been investigated where nitrile plays a role of C-N bond donor. The developed approach is applicable on a wide range of 2-aminobenzylamines and nitriles for the synthesis substituted quinazolines in high yields with a broad functional group tolerance.

Introduction

The role of an organocatalyst in the field of synthetic organic chemistry is impeccable and irreplaceable because of its unique way of actions in chemical transformations.[1-2] The contribution of these organocatalysts for synthesizing wide variety of *N*-heterocycles is noticeable.[1i, 2] Owing to their biological importance, immense research work has been performed for the betterment of available protocols towards the synthesis of diverse range of *N*-heterocycles.[2-3] Among these distinctive class of *N*-heterocycles, quinazoline scaffolds have marked their presence because of their biological and medicinal importance such as anticancer, antibacterial, antitubercular and antiviral activities.[4] The quinazoline scaffolds found their recognition as FDA-approved marketed drugs to treat lung cancer (afatinib, erlotinib and gefitinib),[5] breast cancer (lapatinib)[6] and other life threatening diseases.[7] Quinazolines have also been well-known for their medicinal activities possessed by naturally occurring quinazoline alkaloids.[8] On realizing the significance of these *N*-heterocyclic moieties, a large number of reports have appeared over the past decades by addressing the issues of previous reports and for their betterment (Scheme 1).[2b-c, 9] These chemical transformations were realized using metal catalysts such as Mn, Ni, Cu, Ru, Rh, Ir and Pt utilizing varieties of starting materials.[9a, f, h-j, 10] In recent times, chemists have also came across the synthesis of quinazolines by utilizing non-catalytic methods such as DDQ, IBX, PIDA and CsOH mediated reactions.[9c-e, g] More interestingly, few reports towards the synthesis of substituted quinazolines are known using the concept of organocatalysis.[2a-c] It is noteworthy that, 2-aminobenzylamines or 2-aminobenzyl alcohols are largely explored for synthesis of these structurally unique molecules by employing aldehydes, alkyl alcohols and alkyl amines as C1 synthon under metal-catalyzed, non-metal-catalyzed and organocatalyzed reaction conditions.[2a-c, 9-10] The previously reported methods have their significance in obtaining broad range of quinazolines along with certain limitations such as restricted applicability of protocol, harsh reaction conditions and harmful by-products.



Scheme 1. Approaches towards the synthesis of 2-substituted quinazolines.

However, there have been limited numbers of reports on using nitrile as a source of C-N bond.[9e, h-j, 10k, p] In most of the cases, nitrile has been used as a C-N bond donor along with 2-aminobenzyl alcohol under metal-catalyzed reaction conditions or with 2-aminobenzylamines as C1 synthon under non-metal-catalyzed reaction conditions. There are no reports available pertaining the use of nitrile as a C-N bond donor along with 2-aminobenzylamines under organocatalyzed reaction conditions. In continuation of our research work in developing efficient protocol towards the synthesis of wide range of *N*-heterocycles using organocatalysis,[2c, i-j] we have described an efficient and cost-effective Vitamin-B_3-catalyzed protocol towards the synthesis of substituted quinazolines by employing 2-aminobenzylamines and nitriles as a C-N bond donor.

[a] R. Gujjarappa, N. Vodnala, Dr. C. C. Malakar
Department of Chemistry
National Institute of Technology Manipur
Langol, Imphal - 795004, Manipur, India
E-mail: chdeepm@gmail.com, cmalakar@nitmanipur.ac.in
Homepage: https://chdeepm.wixsite.com/mysite
[b] Dr. V. G. Reddy
Centre for Advanced Materials & Industrial Chemistry (CAMIC),
School of Science
RMIT University
GPO Box 2476, Melbourne, 3001, Australia

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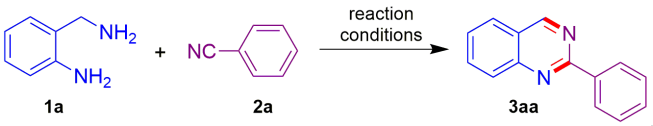
Results and Discussion

With the objective of designing an efficient organocatalytic platform towards the synthesis of quinazolines, we began our experimental studies by taking 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) as our model substrates. We intended to start our proceedings by screening the previously known organocatalysts[2c, i-j] for the successful conversion of 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) into 2-phenylquinazoline (**3aa**). Initially, the reaction of 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) was carried out using 30 mol% thiourea as an organocatalyst in DMSO as solvent at 110 °C for 24 h (Table 1, Entry 1). Under thiourea-catalyzed reaction condition, 28% of reaction yield was observed. Next, we focused on using pyridine based organocatalysts for this chemical transformation. In this process, we have screened organocatalysts like 3-nitropyridine, 2-picolinic acid, isonicotinic acid and vitamin-B_3 (Entries 2-5). Gratifyingly, all the organocatalysts were performed well to deliver the desired product **3aa** in the range of 66-86%. The maximum yield of **3aa** was observed when 30 mol% of vitamin-B_3 was used as an organocatalyst in DMSO at 110 °C for 24 h (Entry 5). After obtaining the highest yield using vitamin-B_3, we were fascinated in carrying out the reaction under UV-light (Entry 6). To our disappointment, we did not observe any product formation under UV-light, rather starting materials were recovered. Further, the reaction of 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) were performed using 30 mol% of vitamin-B_3 in different solvents such as DMF, DMA, dioxane, THF and H_2O at 110 °C for 24 h (Entries 7-11). The reaction yields were not further improved by using solvents other than DMSO. Next, we carried out the reaction of **1a** and **2a** under different amounts of organocatalysts (Entries 12-13). It was observed that decreasing the catalysts loading to 20 mol% will affect the yield by 18% and increasing the catalysts load to 40 mol% did not alter the reaction yield. It is to be noted that, 30 mol% catalysts is optimum to realize this chemical transformation. In continuation, we also carried out the reaction of **1a** and **2a** under different reaction temperature (Entries 14-15). It was observed that the decrease in temperature had affected the reaction yield and increase in temperature gave similar yield of the product. Moreover, the reaction of **1a** and **2a** for different time period delivered unsatisfactory results (Entries 16-18). Having performed an extensive optimization of the reaction conditions, it was observed that the highest yield of 2-phenylquinazoline (**3aa**) was acquired when the reaction of 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) was carried out using 30 mol% vitamin-B_3 in DMSO at 110 °C for 24 h (Entry 5).

After realizing the best optimized reaction conditions towards the synthesis of quinazoline, we performed reactions of wide range of aryl nitriles **2a**-**p** bearing electron rich as well as electron poor functional groups with 2-aminobenzylamine **1a** to access diversified quinazoline derivatives. The reaction conditions showed superior tolerance over electron donating OH, Me, OMe as well as electron withdrawing F, Cl, Br, NO_2, CF_3, CO_2Me functional groups by delivering desired quinazolines in up to 98% isolated yield (Scheme 2).

Table 1. Optimization of organocatalytic conditions for the reaction of **1a** with **2a**.[a]



1a **2a** **3aa**

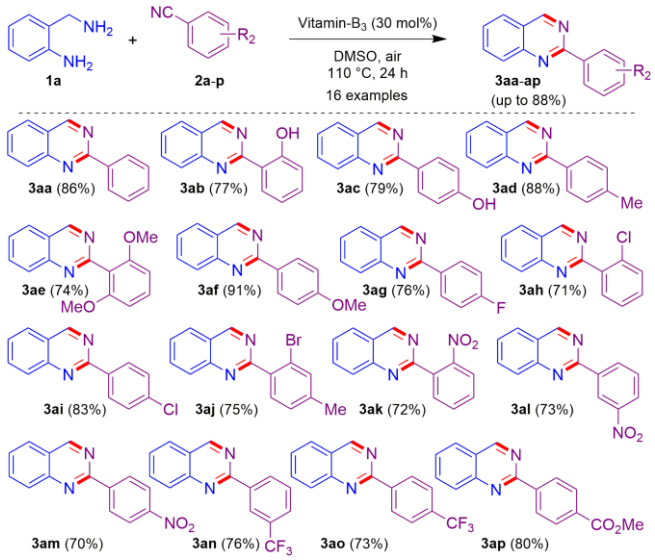
Entry	Catalyst (mol %)	Conditions	**3aa** % Yield[b]
1	Thiourea (30)	DMSO, air, 110 °C, 24 h	28
2	3-nitropyridine (30)	DMSO, air, 110 °C, 24 h	74
3	2-picolinic acid (30)	DMSO, air, 110 °C, 24 h	66
4	Isonicotinic acid (30)	DMSO, air, 110 °C, 24 h	79
5	**Vitamin-B_3 (30)**	**DMSO, air, 110 °C, 24 h**	**86**
6	Vitamin-B_3 (30)	DMSO, air, UV, 24 h	0[c]
7	Vitamin-B_3 (30)	DMF, air, 110 °C, 24 h	73
8	Vitamin-B_3 (30)	DMA, air, 110 °C, 24 h	63
9	Vitamin-B_3 (30)	dioxane, air, 110 °C, 24 h	60
10	Vitamin-B_3 (30)	THF, air, 110 °C, 24 h	42
11	Vitamin-B_3 (30)	H_2O, air, 110 °C, 24 h	15
12	Vitamin-B_3 (20)	DMSO, air, 110 °C, 24 h	68
13	Vitamin-B_3 (40)	DMSO, air, 110 °C, 24 h	85
14	Vitamin-B_3 (30)	DMSO, air, 120 °C, 24 h	86
15	Vitamin-B_3 (30)	DMSO, air, 100 °C, 24 h	78
16	Vitamin-B_3 (30)	DMSO, air, 110 °C, 16 h	64
17	Vitamin-B_3 (30)	DMSO, air, 110 °C, 20 h	75
18	Vitamin-B_3 (30)	DMSO, air, 110 °C, 30 h	80

[a] Unless otherwise indicated: All reactions were performed using 1.0 mmol **1a** and 1.0 mmol **2a** in 2 mL solvent. [b] Isolated yields. [c] Starting materials were recovered.

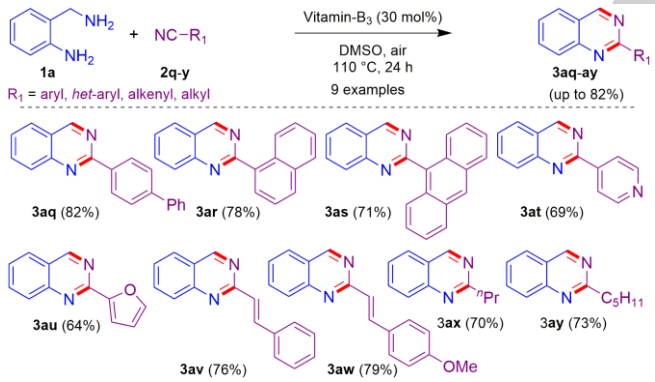
Further, the scope of the reaction conditions were extended by utilizing polycyclic aromatic nitriles **2q**-**s**, *hetero*-aromatic nitriles **2t**-**u**, alkenyl nitriles **2v**-**w** and aliphatic nitriles **2x**-**y** to access broad range of 2-substituted quinazolines **3aq**-**ay** in 64-82% isolated yield (Scheme 3).

After developing an organocatalytic protocol towards the efficient conversion of various aryl and alkyl nitriles into quinazolines, we intended to screen varieties of substituted 2-aminobenzylamines under the developed reaction conditions. To implement this objective, 2-aminobenzylamines **1b**-**f** with electron donating and electron withdrawing functional groups

were examined to obtain a wide range of substituted quinazolines **3** in high isolated yields (Scheme 4).

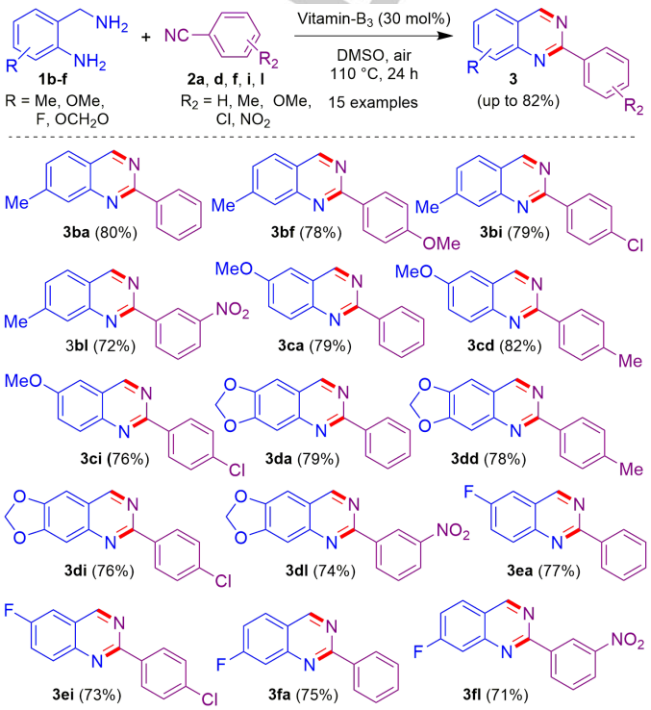


Scheme 2. Scope of aryl nitriles towards the synthesis of 2-substituted quinazolines.

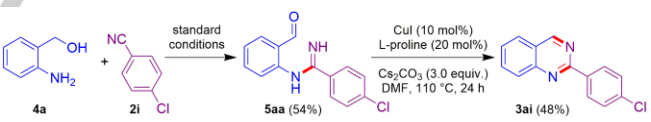


Scheme 3. Further scope of aryl nitriles towards the synthesis of 2-substituted quinazolines.

Having realized an organocatalytic pathway to access diverse range of substituted quinazolines by utilizing substituted 2-aminobenzylamines and nitrile derivatives, we were determined to extend scope of the reaction to 2-aminobenzyl alcohols. In this process, we carried out the reaction of 2-aminobenzyl alcohol (**4a**) with 4-chlorobenzonitrile (**2i**) under the standard conditions. To our disappointment, the reaction did not undergo completion to deliver 2-substituted quinazoline **3ai**, rather it stopped at an intermediate stage **5aa** which was confirmed by NMR data. Intermediate **5aa** on treatment with copper-catalyzed reaction conditions,[10a] delivered the desired product **3ai** in 48% isolated yield (Scheme 5). The probable reason can be asserted to the electronic nature of aldehyde group which is stopping the intermediate to undergo intramolecular cyclization under organocatalyzed reaction conditions. We assume, in case of 2-aminobenzylamines, the imine intermediate may facilitates intramolecular cyclization to obtain 2-substituted quinazolines.



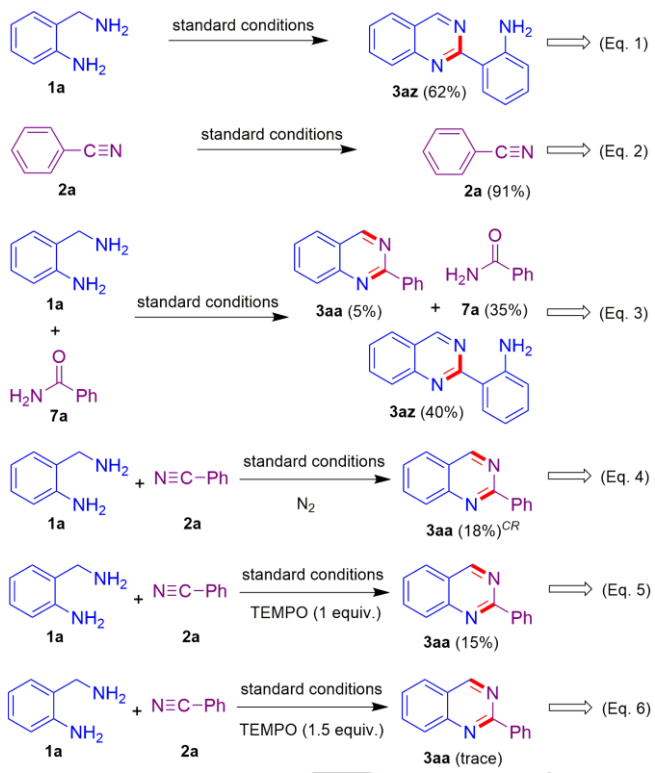
Scheme 4. Scope of 2-aminobenzylamines towards the synthesis of 2-substituted quinazolines.



Scheme 5. Reaction of 2-aminobenzyl alcohol **4a** to access 2-substituted quinazolines.

Next, we focused on establishing a plausible reaction mechanism for this organocatalytic process by considering the difference in reactivity of 2-aminobenzylamines and 2-aminobenzyl alcohols. To gain further insight of the reaction mechanism, we carried out control experiments by varying different reaction parameters. Firstly, we carried out the reaction of 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) separately under the developed reaction conditions. Surprisingly, the reaction of 2-aminobenzylamine (**1a**) gave 2-(quinazolin-2-yl)aniline (**3az**) in 62% isolated yield, which is the self-cyclized product (Scheme 6, Eq. 1). It is believed that, 2-aminobenzylamine (**1a**) getting *in situ* oxidized to 2-aminobenzaldehyde (**6a**) followed by condensation with another molecule of 2-aminobenzylamine (**1a**) and subsequent oxidation

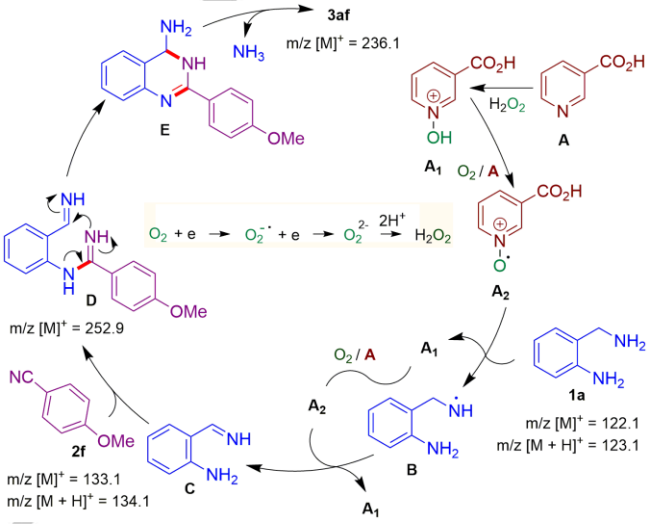
delivered the 2-(quinazolin-2-yl)aniline (**3az**). In another experiment, the reaction of benzonitrile (**2a**) under standard conditions yielded only starting material (Scheme 6, Eq. 2). We suspected that, 2-aminobenzylamine (**1a**) and benzonitrile (**2a**) could lead to the formation of 2-aminobenzaldehyde (**6a**) and benzamide (**7a**) respectively and subsequent condensation followed by oxidation to furnish 2-phenylquinazoline (**3aa**). As the above reaction did not have sufficient proofs on reaction mechanism, we decided to carry out the reaction of 2-aminobenzylamine (**1a**) and benzamide (**7a**) under standard conditions (Scheme 6, Eq. 3). Again, it was observed that, 2-aminobenzylamine (**1a**) is getting self-cyclized to 2-(quinazolin-2-yl)aniline **3az** in higher proportion with only 5% of the desired **3aa**. The starting material benzamide (**7a**) was inactive which was isolated in 35% yield. The possibility of the reaction pathway *via* 2-aminobenzaldehyde (**6a**) and benzamide (**7a**) intermediates was ruled out due to above negative results.[9f]



Scheme 6. Control experiments to establish plausible reaction mechanism.

Next, we carried out the reaction of **1a** and **2a** using standard reaction conditions under nitrogen atmosphere (Scheme 6, Eq. 4). The reaction conditions furnished a complex reaction mixture with only 18% of desired product **3aa**. Hence, it was cleared that the reaction conditions requires a sufficient amount of oxygen to accomplish the desired chemical transformations. Additionally, we also carried out the reaction of **1a** and **2a** under standard reaction conditions with added radical scavenger TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl) to check the probability of reaction pathway (Scheme 6, Eq. 5 and 6). The isolated yields of the reaction were drastically reduced under the influence of radical scavenger, which confirms the radical pathway of the reaction.

Then to understand the plausible reaction mechanism, we were inspired to carry out the reaction of 2-aminobenzylamine (**1a**) ([M]$^+$ = 122.1, [M + H]$^+$ = 123.1) and 4-methoxybenzonitrile (**2f**) ([M]$^+$ = 133.1, [M + H]$^+$ = 134.1) under standard reaction conditions. The course of the reaction was investigated and examined by liquid chromatography-mass spectrometry (LC-MS) after an interval of 5 h, 10 h and 15 h. The mass-spectroscopic data revealed that the mechanism proceeds *via* the formation of intermediate **D** ([M]$^+$ = 252.9) to obtain the desired product **3af** ([M]$^+$ = 236.1) (details of mass spectra are given in Figure S1, SI).



Scheme 7. Proposed organocatalytic reaction pathway.

With this much information, we proposed a plausible reaction mechanism based on the experimental and literature evidences (Scheme 7).[2c, j] According to the proposed reaction mechanism, catalytic amounts of hydrogen peroxide is generated by aerial oxidation.[2c] Next, catalytic amounts of **A$_1$** and **A$_2$** were also generated by the successive oxidation of vitamin-B$_3$ by H_2O_2 and air. The *in situ* generated **A$_2$** abstract a proton for **1a** *via* radical pathway leading to the formation of amine radical **B**. Subsequently, amine radical **B** undergo oxidation in presence of **A$_2$** to give imine intermediate **C**, followed by nucleophilic addition on 4-methoxybenzonitrile (**2f**) resulting in an amidine embedded imine intermediate **D** ([M]$^+$ = 252.9). Finally, nucleophilic attack of amidine nitrogen on to imine carbon leads to the intermediate **E**, which on dehydroamination afforded the desired 2-(4-methoxyphenyl)quinazoline (**3af**) ([M]$^+$ = 236.1) (Scheme 7).

Conclusions

In conclusion, we have presented an organocatalytic protocol to obtain quinazolines from 2-aminobenzylamines and benzonitriles as substrates. The reaction conditions were perceived using catalytic amounts of Vitamin-B_3 as an organocatalyst in presence DMSO as solvent under aerial oxygen. The reaction conditions were implemented on a wide range of 2-aminobenzylamines and benzonitriles to obtain quinazolines in moderate to good yields. Additionally, we have also carried out a series of control experiments to know insight into the reaction mechanism. A probable reaction mechanism was depicted based on the evidences obtained from control experiments and mass-spectroscopy.

Experimental Section

General Method: The starting material 2-amino-4-methylbenzylamine (**1b**) was prepared using previously reported method[11] and all other starting materials were purchased from commercial suppliers (Sigma-Aldrich, Alfa-Aesar, SD fine chemicals, Merck, HI Media, Ambinter) and were used without further purification unless otherwise indicated. All reactions were performed in a 10 mL reaction vial with magnetic stirring. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on TLC plates purchase from Merck. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in $KMnO_4$ staining solution followed by heating. Products were purified by column chromatography on silica gel, 100 - 200 mesh. Melting points were determined in open capillary tubes on EZ-Melt automated melting point apparatus and are uncorrected. IR spectra were measured on Perkin-Elmer Spectrum One (FT-IR spectrometer) using potassium bromide pellets. All the compounds were fully characterized by ^1H and ^{13}C NMR and further confirmed by EI-HRMS analysis. All HRMS are recoreded in EI-QTOF method and LC-MS are recorded in APCI method in acetonitrile solvent. ^1H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Brucker spectrometer using $CDCl_3$ and DMSO-d_6 as a solvent. The ^1H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26/77.28 ($CDCl_3$) and $\delta_{H/C}$ 2.51 /39.50 (DMSO-d_6) relative to TMS as internal standards. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), overlapped and br (broad).

General Experimental Procedure for the Synthesis of Quinazolines 3aa-az and 3ba-fl Using Nitriles 2a-y.

A 10 mL reaction vial was charged with a mixture of 2-aminobenzylamines **1a-f** (1.0 mmol), nitriles **2a-y** (1.0 mmol), DMSO (2 mL) and Vitamin-B_3 (0.3 mmol, 37 mg). The reaction vial was then heated at 110 °C for 24 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 4:1), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent were removed under reduced pressure and the crude products were purified by column chromatography using silica gel (100-200 mesh) with hexane/EtOAc (4:1) as the eluent to obtain the desired products **3aa**-**az** or **3ba**-**fl** in high isolated yields.

General Experimental Procedure for the Synthesis of 2-(4-Chlorophenyl)quinazoline (3ai) Using 2-Aminobenzyl Alcohol (4a).

A 10 mL reaction vial was charged with a mixture of 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 4-chlorobenzonitrile (**2i**) (1.0 mmol, 137.6 mg), DMSO (2 mL) and Vitamin-B_3 (0.3 mmol, 37 mg). The reaction vial was then heated at 110 °C for 24 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 4:1), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent were removed under reduced pressure and the crude products were purified by column chromatography using silica gel (100-200 mesh) with hexane/EtOAc (4:1) as the eluent to obtain the intermediate **5aa** in 54% yield (140 mg).

Further, the intermediate **5aa** (0.5 mmol, 130 mg), L-proline (0.2 mmol, 23 mg), Cs_2CO_3 (1.5 mmol, 489 mg) and DMF (5 mL) were charged in a reaction flask, the mixture was stirred for 30 min under nitrogen atmosphere at room temperature, and then CuI (0.1 mmol, 19 mg) was added. After a 30 min-stirring under the same condition, reaction temperature was raised to 110 °C for 24 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 4:1), the resulting solution was cooled to room temperature and filtered, and the inorganic salts were removed. The filtrate was concentrated with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel to provide the desired product **3ai** in 48% yield (58 mg).

Experimental Procedures and Analytical Data of Synthesized Compounds 3aa-az and 3ba-fl.

Preparation of 2-Phenylquinazoline (3aa)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and benzonitrile (**2a**) (1.0 mmol, 103 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-phenylquinazoline (**3aa**) in 86% (177 mg) yield as yellow solid (Scheme 2).

2-Phenylquinazoline (3aa)[2c] (Scheme 2): **Yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 101-102 °C (Lit[2c] 100-102 °C); **^1H NMR** (400 MHz, $CDCl_3$): δ = 9.48 (s, 1H; 4-H), 8.63 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.11 (d, ^3J = 8.2 Hz, 1H; 8-H), 7.94-7.88 (m, 2H; 5-H and 7-H), 7.62 (t, ^3J = 7.8 Hz, 1H; 6-H), 7.58-7.48 (m, 3H; 13-H, and 14-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.07 (C-2), 160.54 (C-4), 150.8 (C-9), 138.0 (C-11), 134.20 (C-7), 130.7 (C-14), 128.7 (C-8), 128.67 (C-13), 128.63 (C-12), 127.33 (C-6), 127.17 (C-5), 123.64 (C-10) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{11}N_2$: 207.0922; found: 207.0919.

Preparation of 2-(Quinazolin-2-yl)phenol (3ab)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 2-hydroxybenzonitrile (**2b**) (1.0 mmol, 119 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(quinazolin-2-yl)phenol (**3ab**) in 77% (171 mg) yield as pale yellow solid (Scheme 2).

2-(Quinazolin-2-yl)phenol (3ab)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 135-136 °C (Lit[2c] 136-137 °C); **^1H NMR** (400 MHz, $CDCl_3$): δ = 13.31 (s, 1H; 17-H), 9.48 (s, 1H; 4-H), 8.66 (d, ^3J = 8.0 Hz, 1H; 8-H), 8.02-7.91 (m, 3H; 5-H, 7-H and 16-H), 7.64 (t, ^3J = 8.0 Hz, 1H; 6-H), 7.41 (t, ^3J = 8.0 Hz, 1H; 14-H), 7.08 (d, ^3J = 8.0 Hz, 1H; 13-H), 7.01 (t, ^3J = 8.0 Hz, 1H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.80 (C-2), 160.91 (C-4), 160.55 (C-12), 148.17 (C-9), 135.08 (C-16), 133.31 (C-7), 129.74 (C-14), 127.63 (C-8), 127.50 (C-5),

127.12 (C-6), 123.06 (C-10), 119.16 (C-15), 119.14 (C-11) 117.92 (C-13) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0868.

Preparation of 4-(Quinazolin-2-yl)phenol (3ac)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-hydroxybenzonitrile (**2c**) (1.0 mmol, 119 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 4-(quinazolin-2-yl)phenol (**3ac**) in 79% (175 mg) yield as white solid (Scheme 2).

4-(Quinazolin-2-yl)phenol (3ac)[9d] (Scheme 2): **White solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 131-133 °C (Lit[9d] 130-132 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.42 (s, 1H; 15-H), 9.31 (s, 1H; 4-H), 8.50 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.03 (d, ^3J = 8.2 Hz, 1H; 8-H), 7.92-7.88 (m, 2H; 5-H and 7-H), 7.59 (d, ^3J = 8.0 Hz, 1H; 6-H), 6.98 (d, ^3J = 8.0 Hz, 2H; 13-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.0 (C-2), 160.5 (C-4), 160.34 (C-14), 150.0 (C-9), 134.5 (C-11), 130.51 (C-7), 128.31 (C-12), 128.31 (C-8), 127.32 (C-6), 126.9 (C-5), 123.30 (C-10), 115.65 (C-13) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0868.

Preparation of 2-(4-Methylphenyl)quinazoline (3ad)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-methylbenzonitrile (**2d**) (1.0 mmol, 117 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-methylphenyl)quinazoline (**3ad**) in 88% (193 mg) yield as pale yellow solid (Scheme 2).

2-(4-Methylphenyl)quinazoline (3ad)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 105-106 °C (Lit[2c] 105-107 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.45 (s, 1H; 4-H), 8.50 (td, ^3J = 8.0 Hz, 2H; 12-H), 8.07 (d, ^3J = 8.6 Hz, 1H; 8-H), 7.94-7.87 (m, 2H; 5-H and 7-H), 7.59 (dt, ^3J = 8.0 Hz, 1H; 6-H), 7.34 (d, ^3J = 8.0 Hz, 2H; 13-H), 2.45 (s, 3H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.26 (C-2), 160.56 (C-4), 150.9 (C-9), 141.0 (C-11), 135.4 (C-7), 134.2 (C-14), 129.5 (C-8), 128.68 (C-13), 128.66 (C-12), 127.25 (C-6), 127.17 (C-5), 123.65 (C-10), 21.65 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{13}N_2$: 221.1079; found: 221.1076.

Preparation of 2-(2,6-Dimethoxyphenyl)quinazoline (3ae)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 2,6-dimethoxybenzonitrile (**2e**) (1.0 mmol, 163 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(2,6-dimethoxyphenyl)quinazoline (**3ae**) in 74% (197 mg) yield as pale yellow solid (Scheme 2).

2-(2,6-Dimethoxyphenyl)quinazoline (3ae)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 59-60 °C (Lit[2c] 58-59 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.46 (s, 1H; 4-H), 8.11 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.94-7.88 (m, 2H; 5-H and 7-H), 7.83 (d, ^3J = 6.8 Hz, 2H; 13-H), 7.62 (dt, ^3J = 8.0 Hz, 1H; 6-H), 6.64 (dt, ^3J = 8.0 Hz, 1H; 14-H), 3.94 (s, 6H; 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.12 (C-2), 160.64 (C-4), 160.42 (C-12), 150.66 (C-9), 140.0 (C-7), 134.22 (C-14), 128.7 (C-8), 127.44 (C-6), 127.16 (C-5), 123.73 (C-10), 106.27 (C-13), 103.93 (C-11), 55.65 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{16}H_{15}N_2O_2$: 267.1134; found: 267.1132.

Preparation of 2-(4-Methoxyphenyl)quinazoline (3af)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-methoxybenzonitrile (**2f**) (1.0 mmol, 133 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-methoxyphenyl)quinazoline (**3af**) in 91% (215 mg) yield as pale yellow solid (Scheme 2).

2-(4-Methoxyphenyl)quinazoline (3af)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.63 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 88-89 °C (Lit[2c] 89-91 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.42 (s, 1H; 4-H), 8.58 (dt, ^3J = 8.0 Hz, 2H; 12-H), 8.04 (d, ^3J = 8.6 Hz, 1H; 8-H), 7.91-7.85 (m, 2H; 5-H and 7-H), 7.57 (t, ^3J = 8.0 Hz, 1H; 6-H), 7.03 (d, ^3J = 8.0 Hz, 2H; 13-H), 3.90 (s, 3H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.81 (C-2), 160.84 (C-4), 160.36 (C-14), 150.80 (C-9), 134.0 (C-11), 130.7 (C-7), 130.2 (C-12), 128.4 (C-8), 127.10 (C-6), 126.8 (C-5), 123.30 (C-10), 113.95 (C-13), 55.37 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{13}N_2O$: 237.1027; found: 237.1024.

Preparation of 2-(4-Fluorophenyl)quinazoline (3ag)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-fluorobenzonitrile (**2g**) (1.0 mmol, 121 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-fluorophenyl)quinazoline **(3ag**) in 76% (170 mg) yield as white solid (Scheme 2).

2-(4-Fluorophenyl)quinazoline (3ag)[2c] (Scheme 2): **White solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 131-132 °C (Lit[2c] 130-131 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.46 (s, 1H; 4-H), 8.62 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.07 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.95-7.90 (m, 1H, 5-H and 7-H), 7.62 (t, ^3J = 8.0 Hz, 1H; 6-H), 7.20 (d, ^3J = 8.0 Hz, 2H; 13-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.93 (C-2), 164.4 (C-4), 160.36 (d, J = 32 Hz, C-14), 150.74 (C-9), 134.26 (C-11), 130.7 (C-7), 130.63 (C-12), 128.56 (J = 262 Hz), 127.25 (d, J = 12 Hz, C-12), 123.5 (C-10), 115.6 (d, J = 21 Hz, C-13) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0825.

Preparation of 2-(2-Chlorophenyl)quinazoline (3ah)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 2-chlorobenzonitrile (**2h**) (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(2-chlorophenyl)quinazoline (**3ah**) in 71% (171 mg) yield as yellow solid (Scheme 2).

2-(2-Chlorophenyl)quinazoline (3ah)[2c] (Scheme 2): **Yellow solid**, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 66-67 °C (Lit[2c] 67-68 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H; 4-H), 8.14 (d, ^3J = 8 Hz, 1H; 8-H), 8.02-7.94 (m, 2H; 5-H and 7-H), 7.86-7.80 (m, 1H; 13-H), 7.71 (t, ^3J = 7.8 Hz, 1H; 6-H), 7.57-7.52 (m, 1H; 16-H), 7.45-7.37 (m, 2H; 14-H and 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.92 (C-2), 160.27 (C-4), 150.36 (C-9), 138.19 (C-11), 134.52 (C-7), 132.96 (C-12), 131.84 (C-14), 130.6 (C-13), 130.4 (C-16), 128.66 (C-8), 128.16 (C-6), 127.22 (C-5), 126.94 (C-15), 123.31 (C-10) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}ClN_2$: 241.0532; found: 241.0530.

Preparation of 2-(4-Chlorophenyl)quinazoline (3ai)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-chlorobenzonitrile (**2i**) (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-chlorophenyl)quinazoline (**3ai**) in 83% (200 mg) yield as pale yellow solid (Scheme 2).

2-(4-Chlorophenyl)quinazoline (3ai)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 131-133 °C (Lit[2c] 130-132 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.46 (s, 1H; 4-H), 8.58 (dt, ^3J = 8.0 Hz, 2H; 12-H), 8.07 (d, ^3J = 8.2 Hz, 1H; 8-H), 7.95-7.90 (m, 2H; 5-H and 7-H), 7.63 (dt, ^3J = 8.0 Hz, 1H; 6-H), 7.50 (dt, ^3J = 8.0 Hz, 2H; 13-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.56 (C-2), 160.06 (C-4), 150.71 (C-9), 136.85 (C-14), 136.53 (C-11), 134.29 (C-7), 129.91 (C-13), 128.85 (C-12), 128.62 (C-8), 127.5 (C-6), 127.2 (C-5), 123.64 (C-10) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}ClN_2$: 241.0532; found: 241.0530.

Preparation of 2-(2-Bromo-4-methylphenyl)quinazoline (3aj)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 2-bromo-4-methylbenzonitrile (**2j**) (1.0 mmol, 196 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(2-bromo-4-methylphenyl)quinazoline (**3aj**) in 75% (224 mg) yield as yellow solid (Scheme 2).

2-(2-Bromo-4-methylphenyl)quinazoline (3aj)[2c] (Scheme 2): **Yellow solid**, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 50-51 °C (Lit[2c] 49-50 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H; 4-H), 8.12 (d, ^3J = 7.2 Hz, 1H; 8-H), 8.00-7.93 (m, 2H; 5-H and 7-H), 7.71-7.66 (m, 2H; 6-H and 16-H), 7.57 (s, 1H; 13-H), 7.25 (d, ^3J = 7.9 Hz, 1H; 15-H), 2.41 (s, 3H; 17-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.8 (C-2), 160.15 (C-4), 150.3 (C-9), 140.86 (C-11), 137.26 (C-14), 134.32 (C-13), 134.2 (C-7), 131.6 (C-16), 128.62 (C-15), 128.3 (C-8), 127.92 (C-6), 127.14 (C-5), 123.23 (C-10), 121.7 (C-12), 20.97 (C-17) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{12}BrN_2$: 299.0183; found: 299.0180.

Preparation of 2-(2-Nitrophenyl)quinazoline (3ak)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 2-nitrobenzonitrile (**2k**) (1.0 mmol, 148 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(2-nitrophenyl)quinazoline (**3ak**) in 72% (181 mg) yield as yellow solid (Scheme 2).

2-(2-Nitrophenyl)quinazoline (3ak)[2c] (Scheme 2): **Yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 94-95 °C (Lit[2c] 95-96 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.44 (s, 1H; 4-H), 8.13 (dd, ^3J = 7.8 Hz, 1H; 8-H), 8.08 (d, ^3J = 8.6 Hz, 1H; 16-H), 7.99-7.93 (m, 2H; 13-H and 15-H), 7.90 (d, ^3J = 8.0 Hz, 1H; 14-H), 7.75-7.67 (m, 2H; 5-H and 7-H), 7.60 (td, ^3J = 8.2 Hz, 1H; 6-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.55 (C-2), 159.7 (C-4), 150.4 (C-12), 150.0 (C-9), 134.66 (C-15), 133.63 (C-16), 132.3 (C-7), 131.9 (C-14), 130.2 (C-8), 128.65 (C-6), 128.4 (C-5), 127.3 (C-11), 124.2 (C-10), 123.5 (C-13) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}N_3O_2$: 252.0773; found: 252.0770.

Preparation of 2-(3-Nitrophenyl)quinazoline (3al)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 3-nitrobenzonitrile (**2l**) (1.0 mmol, 148 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(3-nitrophenyl)quinazoline (**3al**) in 73% (183 mg) yield as pale yellow solid (Scheme 2).

2-(3-Nitrophenyl)quinazoline (3al)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 101-103 °C (Lit[2c] 101-102 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.52-9.50 (m, 2H; 4-H and 12-H), 8.99 (dt, J = 8.0 Hz, 1H; 16-H), 8.36 (ddd, ^3J = 8.0, 2.4, 1.2 Hz, 1H; 14-H), 8.14 (d, ^3J = 8.0 Hz, 1H; 8-H), 8.00-7.95 (m, 2H; 5-H and 15-H), 7.74-7.67 (m, 2H; 6-H and 7-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.74 (C-2), 158.7 (C-4), 150.60 (C-9), 148.86 (C-13), 139.9 (C-16), 134.56 (C-7), 134.2 (C-11), 129.52 (C-15), 128.77 (C-8), 128.07 (C-6), 127.2 (C-5), 125.01 (C-10), 123.96 (C-14), 123.6 (C-12) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}N_3O_2$: 252.0773; found: 252.0770.

Preparation of 2-(4-Nitrophenyl)quinazoline (3am)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-nitrobenzonitrile (**2m**) (1.0 mmol, 148 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-nitrophenyl)quinazoline (**3am**) in 70% (176 mg) yield as yellow solid (Scheme 2).

2-(4-Nitrophenyl)quinazoline (3am)[9d] (Scheme 2): **Yellow solid**, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 214-216 °C (Lit[9d] 215-217 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.50 (s, 1H; 4-H), 8.80 (d, J = 8.0 Hz, 1H; 13-H), 8.36 (d, ^3J = 8.0 Hz, 1H; 12-H), 8.12 (d, ^3J = 8.0 Hz, 1H; 8-H), 8.03-7.97 (m, 2H; 5-H and 7-H), 7.69 (t, ^3J = 8.0 Hz, 1H; 6-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.71 (C-2), 159.75 (C-4), 150.60 (C-9), 149.17 (C-14), 143.83 (C-11), 134.62 (C-7), 129.38 (C-12), 128.85 (C-8), 128.33 (C-6), 127.2 (C-5), 123.87 (C-13), 123.76 (C-10) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}N_3O_2$: 252.0773; found: 252.0770.

Preparation of 2-(3-(Trifluoromethyl)phenyl)quinazoline (3an)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 3-(trifluoromethyl)benzonitrile (**2n**) (1.0 mmol, 171 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(3-(trifluoromethyl)phenyl)quinazoline (**3an**) in 76% (208 mg) yield as white solid (Scheme 2).

2-(3-(Trifluoromethyl)phenyl)quinazoline (3an) (Scheme 2): **White solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 108-110 °C; IR (KBr) v = 2925, 1541, 1459, 1260, 752 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.49 (s, 1H; 4-H), 8.93 (d, J = 3.6 Hz, 1H; 12-H), 8.83 (dt, J = 8.0 Hz, 1H; 16-H), 8.12 (ddd, ^3J = 8.2, 2.2, 1.2 Hz, 1H; 14-H), 7.98-7.93 (m, 2H; 5-H and 15-H), 7.76 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.68-7.64 (m, 2H; 6-H and 7-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.66 (C-2), 159.57 (C-4), 150.68 (C-9), 138.82 (C-11), 134.41 (C-16), 131.68 (C-7), 131.27 (q, J = 32 Hz, C-11), 130.95 (C-15), 129.1 (C-8), 128.73 (C-6), 127.79 (C-5), 127.20 (C-10), 127.07 (q, J = 11 Hz, C-12), 125.50 (q, J = 16 Hz, C-14), 123.84 (C-17) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{10}F_3N_2$: 275.0796; found: 275.0792.

Preparation of 2-(4-(Trifluoromethyl)phenyl)quinazoline (3ao)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-(trifluoromethyl)benzonitrile (**2o**) (1.0 mmol, 171 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-(trifluoromethyl)phenyl)quinazoline (**3ao**) in 73% (200 mg) yield as pale yellow solid (Scheme 2).

2-(4-(Trifluoromethyl)phenyl)quinazoline (3ao)[2c] (Scheme 2): **Pale yellow solid**, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 135-136 °C (Lit[2c] 136-137 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.36 (s, 1H; 4-H), 8.75 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.50 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.83 (d, ^3J = 8.0 Hz, 2H; 13-H), 7.74 (m, 2H; 5-H and 7-H), 7.62 (d, ^3J = 8.0 Hz, 1H; 6-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.61 (C-2), 159.60 (C-4), 150.65 (C-9), 141.31 (C-11), 134.37 (C-7), 132.11 (q, J = 32 Hz, C-14), 128.82 (C-8), 128.77 (C-6), 127.86 (C-5), 127.16 (C-12), 125.57 (C-10),

125.52 (q, *J* = 3.2 Hz, C-13), 123.84 (C-15) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{15}H_{10}F_3N_2$: 275.0796; found: 275.0792.

Preparation of Methyl 4-(quinazolin-2-yl)benzoate (3ap)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and methyl 4-cyanobenzoate (**2p**) (1.0 mmol, 161 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired methyl 4-(quinazolin-2-yl)benzoate (**3ap**) in 80% (211 mg) yield as brown solid (Scheme 2).

Methyl 4-(quinazolin-2-yl)benzoate (3ap)[2c] (Scheme 2): **Brown solid**, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 120-122 °C (Lit[2c] 120-121 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.50 (s, 1H; 4-H), 8.70 (d, ^3J = 8.1 Hz, 2H; 13-H), 8.21 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.12 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.98-7.93 (m; 2H, 5-H and 7-H), 7.67 (t, ^3J = 8.0 Hz, 1H; 6-H), 3.97 (s, 3H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.95 (C-15), 160.56 (C-2), 160.0 (C-4), 150.67 (C-9), 142.12 (C-11), 134.33 (C-7), 131.7 (C-14), 129.84 (C-12), 128.76 (C-8), 128.5 (C-13), 127.8 (C-6), 127.15 (C-5), 123.75 (C-10) 52.22 (C-16) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0975.

Preparation of 2-([1,1'-Biphenyl]-4-yl)quinazoline (3aq)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-cyanobiphenyl (**2q**) (1.0 mmol, 179 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-([1,1'-biphenyl]-4-yl)quinazoline (**3aq**) in 82% (231 mg) yield as white solid (Scheme 3).

2-([1,1'-Biphenyl]-4-yl)quinazoline (3aq)[2c] (Scheme 3): **White solid**, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 117-118 °C (Lit[2c] 116-117 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.49 (s, 1H; 4-H), 8.69 (d, ^3J = 7.8 Hz, 2H; 12-H), 8.11 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.96-7.91 (m, 2H; 5-H and 7-H), 7.79 (d, ^3J = 8.2 Hz, 2H; 16-H), 7.71 (d, ^3J = 7.8 Hz, 2H; 13-H), 7.63 (t, ^3J = 8.2 Hz, 1H; 6-H), 7.49 (t, ^3J = 8.2 Hz, 2H; 17-H), 7.39 (t, ^3J = 8.0 Hz, 1H; 18-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.87 (C-2), 160.52 (C-4), 150.87 (C-9), 143.3 (C-14), 140.66 (C-15), 137.0 (C-11), 134.16 (C-7), 129.06 (C-17), 128.85 (C-12), 128.7 (C-8), 127.7 (C-6), 127.4 (C-16), 127.3 (C-18), 127.2 (C-13), 127.2 (C-5), 123.65 (C-10) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{20}H_{15}N_2$: 283.1235; found: 283.1233.

Preparation of 2-(Naphthalen-1-yl)quinazoline (3ar)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 1-cyanonaphthalene (**2r**) (1.0 mmol, 153 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(naphthalen-1-yl)quinazoline (**3ar**) in 78% (200 mg) yield as pale yellow solid (Scheme 3).

2-(Naphthalen-1-yl)quinazoline (3ar)[2c] (Scheme 3): **Pale yellow solid**, R_f = 0.66 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 122-123 °C (Lit[2c] 123-124 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.61 (s, 1H; 4-H), 8.70 (d, ^3J = 8.2 Hz, 1H; 18-H), 8.21-8.17 (m, 2H; 14-H and 15-H), 8.04-7.91 (m, 4H; 5-H, 8-H, 12-H and 13-H), 7.71 (t, ^3J = 7.8 Hz, 1H; 7-H), 7.64 (t, ^3J = 8.2 Hz, 1H; 17-H), 7.61-7.50 (m, 2H; 6-H and 16-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 163.45 (C-2), 160.45 (C-4), 150.6 (C-9), 136.22 (C-11), 134.4 (C-20), 134.2 (C-19), 131.2 (C-7), 130.5 (C-8), 129.7 (C-15), 128.7 (C-14), 128.54 (C-5), 127.84 (C-6), 127.2 (C-16), 126.93 (C-17), 125.95 (C-18), 125.92 (C-13) 125.35 (C-10), 123.17 (C-12) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{18}H_{13}N_2$: 257.1078; found: 257.1075.

Preparation of 2-(Anthracen-9-yl)quinazoline (3as)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 9-athracenecarbonitrile (**2s**) (1.0 mmol, 153 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(anthracen-9-yl)quinazoline (**3as**) in 71% (217 mg) yield as yellow solid (Scheme 3).

2-(Anthracen-9-yl)quinazoline (3as)[2c] (Scheme 3): **Yellow solid**, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 111-112 °C (Lit[2c] 112-114 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.71 (s, 1H), 9.00 (d, ^3J = 8.0 Hz, 1H; 8-H), 8.60 (s, 1H; 18-H), 8.21 (d, ^3J = 8.0 Hz, 1H; 5-H), 8.12 (d, ^3J = 7.2 Hz, 1H; 7-H), 8.08 (d, ^3J = 8.6 Hz, 2H; 13-H), 7.81 (t, ^3J = 7.2 Hz, 1H; 6-H), 7.60 (d, ^3J = 7.0 Hz, 2H; 16-H), 7.46 (t, ^3J = 7.6 Hz, 2H; 15-H), 7.37 (t, ^3J = 7.6 Hz, 2H; 14-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 163.63 (C-2), 160.84 (C-4), 150.65 (C-9), 134.79 (C-11), 133.59 (C-17), 131.55 (C-7), 130.07 (C-12), 128.84 (C-18), 128.72 (C-6), 128.48 (C-16), 128.43 (C-5), 127.42 (C-8), 126.43 (C-15), 125.69 (C-10), 125.26 (C-14), 125.39 (C-13) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{22}H_{15}N_2$: 307.1235; found: 307.1230.

Preparation of 2-(Pyridin-4-yl)quinazoline (3at)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-pyridinecarbonitrile (**2t**) (1.0 mmol, 104 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(pyridin-4-yl)quinazoline (**3at**) in 69% (143 mg) yield as pale yellow solid (Scheme 3).

2-(Pyridin-4-yl)quinazoline (3at)[2c] (Scheme 3): **Pale yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 124-126 °C (Lit[2c] 125-127 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H; 4-H), 8.80 (d, *J* = 4 Hz, 2H; 13-H), 8.46 (d, *J* = 4 Hz, 2H; 12-H), 8.14 (d, ^3J = 8 Hz, 1H; 8-H), 8.00-7.95 (m, 2H; 5-H and 7-H), 7.71 (d, *J* = 8 Hz, 1H; 6-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.75 (C-2), 158.90 (C-4), 150.9 (C-13), 150.4 (C-9), 145.40 (C-11), 134.53 (C-7), 128.9 (C-8), 128.3 (C-6), 127.2 (C-5), 124.2 (C-10), 122.4 (C-12) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{13}H_{10}N_3$: 208.0874; found: 208.0870.

Preparation of 2-(Furan-2-yl)quinazoline (3au)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 2-furonitrile (**2u**) (1.0 mmol, 93 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(furan-2-yl)quinazoline (**3au**) in 64% (125 mg) yield as yellow solid (Scheme 3).

2-(Furan-2-yl)quinazoline (3au)[2c] (Scheme 3): **Yellow solid**, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 126-128 °C (Lit[2c] 126-127 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.40 (s, 1H; 4-H), 8.11 (d, ^3J = 7.9 Hz, 1H; 8-H), 7.93-7.90 (m, 2H; 5-H and 7-H), 7.77 (d, ^3J = 12 Hz, 1H; 13-H), 7.61 (t, ^3J = 8 Hz, 1H; 6-H), 7.51 (d, ^3J = 7.8 Hz, 1H; 15-H), 6.63 (s, 1H; 14-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.72 (C-2), 154.1 (C-4), 152.50 (C-11), 150.42 (C-9), 145.34 (C-13), 134.5 (C-7), 128.36 (C-8), 127.3 (C-6), 127.3 (C-5), 123.26 (C-10), 114.1 (C-14), 112.2 (C-15) ppm; **HRMS** (EI-QTOF, [M + H]$^+$): calculated for $C_{12}H_9N_2O$: 197.0714; found: 197.0710.

Preparation of (*E*)-2-Styrylquinazoline (3av)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and cinnamonitrile (**2v**) (1.0 mmol, 129 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to

obtain the desired (*E*)-2-styrylquinazoline (**3av**) in 76% (176 mg) yield as white solid (Scheme 3).

(*E*)-2-Styrylquinazoline (3av)[2c] (Scheme 3): **White solid**, R_f = 0.59 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 120-122 °C (Lit[2c] 122-123 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.38 (s, 1H 4-H), 8.17 (d, ^3J = 20 Hz, 1H; 11-H), 8.01 (d, ^3J = 9.0 Hz, 1H; 8-H), 7.92-7.86 (m, 2H; 5-H and 7-H), 7.68 (d, ^3J = 7.6 Hz, 2H; 14-H), 7.60 (t, ^3J = 7.5, ^4J = 1.3 Hz, 1H; 6-H), 7.46-7.32 (m, 4H; 12-H, 15-H and 16-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.26 (C-2), 160.38 (C-4), 150.42 (C-9), 138.84 (C-13), 136.2 (C-12), 134.37 (C-7), 129.17 (C-15), 128.86 (C-14), 128.0 (C-8), 127.77 (C-16), 127.73 (C-6), 127.29 (C-5), 127.27 (C-10), 123.4 (C-11) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{16}H_{13}N_2$: 233.1078; found: 233.1075.

Preparation of (*E*)-2-(4-Methoxystyryl)quinazoline (3aw)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and 4-methoxycinnamonitrile (**2w**) (1.0 mmol, 159 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired (*E*)-2-(4-methoxystyryl)quinazoline (**3aw**) in 79% (207 mg) yield as white solid (Scheme 3).

(*E*)-2-(4-Methoxystyryl)quinazoline (3aw)[2c] (Scheme 3): **White solid**, R_f = 0.61 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 101-102 °C (Lit[2c] 103-103 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H; 4-H), 8.12 (d, ^3J = 24.0 Hz, 1H; 11-H), 7.98 (d, J = 10.0 Hz, 1H; 8-H), 7.87 (d, ^3J = 7.7 Hz, 2H; 6-H and 7-H), 7.62 (d, J = 8.6 Hz, 2H; 14-H), 7.56 (t, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H; 5-H), 7.29 (d, ^3J = 20.0 Hz, 1H; 12-H), 6.94 (d, ^3J = 8.0 Hz, 2H; 15-H), 3.85 (s, 3H; 17-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.6 (C-2), 160.56 (C-16), 160.3 (C-4), 150.52 (C-9), 1385.45 (C-12), 134.3 (C-7), 129.23 (C-14), 129.0 (C-13), 127.95 (C-8), 127.3 (C-6), 127.0 (C-5), 125.54 (C-10), 123.28 (C-11), 114.34 (C-15), 55.4 (C-17) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{17}H_{15}N_2O$: 263.1184; found: 263.1180.

Preparation of 2-Propylquinazoline (3ax)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and butyronitrile (**2x**) (1.0 mmol, 69 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-propylquinazoline (**3ax**) in 70% (120 mg) yield as pale brown solid (Scheme 3).

2-Propylquinazoline (3ax)[2c] (Scheme 3): **Pale brown solid**, R_f = 0.61 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 121-123 °C (Lit[2c] 120-122 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.36 (s, 1H; 4-H), 8.00 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.91-7.90 (m, 2H; 5-H and 7-H), 7.61 (t, ^3J = 7.8 Hz, 1H; 6-H), 3.11 (t, ^3J = 7.7 Hz, 2H; 11-H), 1.99-1.93 (m, 2H; 12-H), 1.05 (t, ^3J = 7.2 Hz, 3H; 13-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.56 (C-2), 160.33 (C-4), 150.1 (C-9), 134.0 (C-7), 127.72 (C-8), 127.0 (C-6), 126.9 (C-5), 122.97 (C-10), 41.7 (C-11), 22.2 (C-12), 13.9 (C-13) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{11}H_{13}N_2$: 173.1078; found: 173.1076.

Preparation of 2-Pentylquinazoline (3ay)

According to the general procedure, reaction between 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) and hexanenitrile (**2y**) (1.0 mmol, 97 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-pentylquinazoline (**3ay**) in 73% (146 mg) yield as pale brown solid (Scheme 3).

2-Pentylquinazoline (3ay) (Scheme 3): **Pale brown solid**, R_f = 0.50 (SiO_2, Hexane/EtOAc = 4:1); **IR** (KBr) ν = 2960, 2851, 1651, 1577, 1484, 1378, 1230, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.36 (s, 1H; 4-H), 7.98 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.91-7.87 (m, 2H; 5-H and 7-H), 7.60 (t, ^3J = 8.0 Hz, 1H; 6-H), 3.12 (t, ^3J = 7.5 Hz, 2H; 11-H), 1.94-1.90 (m, 2H; 12-H), 1.42-1.38 (m, 4H; 13-H and 14-H), 0.92 (t, ^3J = 7.2 Hz, 3H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.96 (C-2), 160.43 (C-4), 150.37 (C-9), 134.0 (C-7), 127.9 (C-8), 127.1 (C-6), 126.94 (C-5), 123.07 (C-10), 40.06 (C-11), 31.8 (C-12), 28.8 (C-13), 22.6 (C-14), 14.1 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{13}H_{17}N_2$: 201.1391; found: 201.1388.

Preparation of 2-(Quinazolin-2-yl)aniline (3az)

According to the general procedure, reaction of 2-aminobenzylamine (**1a**) (1.0 mmol, 122 mg) was performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(quinazolin-2-yl)aniline (**3az**) in 62% (69 mg) yield as pale yellow solid (Scheme 6).

2-(Quinazolin-2-yl)aniline (3az)[12] (Scheme 6): **Pale yellow solid**, R_f = 0.50 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 86-88 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.44 (d, ^3J = 0.3 Hz, 1H; 4-H), 8.63 (dd, ^3J = 8.1 Hz, 1H; 8-H), 8.00-7.98 (m, 1H; 5-H), 7.91-7.86 (m, 2H; 7-H and 16-H), 7.59 (td, ^3J = 8.0 Hz, 1H; 6-H), 7.27 (td, ^3J = 8.0 Hz, 1H; 14-H), 6.86-6.78 (m, 2H; 13-H and 15-H), 6.57 (s, br, 2H; 17-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.47 (C-2), 159.8 (C-4), 149.6 (C-12), 148.91 (C-9), 134.08 (C-7), 131.77 (C-14), 131.4 (C-16), 127.9 (C-8), 127.17 (C-5), 126.9 (C-6), 122.5 (C-10), 119.0 (C-11), 117.13 (C-15) 116.97 (C-13) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{12}N_3$: 222.1031; found: 222.1028.

Preparation of 7-Methyl-2-phenylquinazoline (3ba)

According to the general procedure, reaction between 2-amino-4-methylbenzylamine (**1b**) (1.0 mmol, 136 mg) and benzonitrile (**2a**) (1.0 mmol, 103 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 7-methyl-2-phenylquinazoline (**3ba**) in 80% (176 mg) yield as colorless solid (Scheme 4).

7-Methyl-2-phenylquinazoline (3ba)[13] (Scheme 4): **Colorless solid**, R_f = 0.40 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 106-108 °C (Lit[13] 107-109 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.42 (s, 1H; 4-H), 8.61 (br, dd, ^3J = 8.0 Hz, 2H; 12-H), 7.92 (s, 1H; 8-H), 7.83 (d, ^3J = 8.0 Hz, 1H; 5-H), 7.56-7.50 (m, 3H; 13-H and 14-H), 7.46 (dd, ^3J = 9.0 Hz, 1H; 6-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.9 (C-2), 159.9 (C-4), 150.9 (C-9), 145.6 (C-7), 137.8 (C-11), 130.7 (C-14), 129.76 (C-6), 128.68 (C-13), 128.64 (C-12), 127.46 (C-8), 126.9 (C-5), 121.85 (C-10), 22.44 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{13}N_2$: 221.1079; found: 221.1076.

Preparation of 7-Methyl-2-(4-methoxyphenyl)quinazoline (3bf)

According to the general procedure, reaction between 2-amino-4-methylbenzylamine (**1b**) (1.0 mmol, 136 mg) and 4-methoxybenzonitrile (**2f**) (1.0 mmol, 133 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 7-methyl-2-(4-methoxyphenyl)quinazoline (**3bf**) in 78% (195 mg) yield as brown gummy solid (Scheme 4).

7-Methyl-2-(4-methoxyphenyl)quinazoline (3bf) (Scheme 4): **Brown gummy solid**, R_f = 0.40 (SiO_2, Hexane/EtOAc = 4:1); IR (KBr) ν = 2921, 2834, 1611, 1586, 1556, 1490, 1369, 1231, 1163, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (s, 1H; 4-H), 7.49 (d, ^3J = 8.0 Hz, 1H; 5-H), 7.46 (s, 1H; 8-H), 7.23 (d, ^3J = 8.0 Hz, 2H; 12-H), 6.91 (d, ^3J = 8.0 Hz, 1H; 6-H), 6.85 (d, ^3J = 8.0 Hz, 1H; 13-H), 3.78 (s, 1H; 16-H), 2.44 (s, 1H;

15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.19 (C-2), 159.67 (C-14), 158.95 (C-4), 149.51 (C-9), 145.33 (C-7), 135.84 (C-11), 129.6 (C-12), 127.9 (C-6), 124.63, 122.5, 119.8, 114.3 (C-13), 55.34 (C-16), 22.22 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{16}H_{15}N_2O$: 251.1184; found: 251.1180.

Preparation of 7-Methyl-2-(4-chlorophenyl)quinazoline (3bi)

According to the general procedure, reaction between 2-amino-4-methylbenzylamine (**1b**) (1.0 mmol, 136 mg) and 4-chlorobenzonitrile (**2i**) (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 7-methyl-2-(4-chlorophenyl)quinazoline (**3bi**) in 79% (201 mg) yield as pale yellow solid (Scheme 4).

5-Methyl-2-(4-chlorophenyl)quinazoline (3bi)[13] (Scheme 4): **Pale yellow solid**, R_f = 0.40 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 160-161 °C (Lit[13] 159-160 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.48 (s, 1H; 4-H), 8.65 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.10 (s, 1H; 8-H), 7.90 (d, ^3J = 8.0 Hz, 1H; 5-H), 7.55-7.51 (overlapped, 3H; 6-H and 13-H), 2.65 (s, 1H; 15-H) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{12}ClN_2$: 255.0689; found: 255.0684.

Preparation of 7-Methyl-2-(3-nitrophenyl)quinazoline (3bl)

According to the general procedure, reaction between 2-amino-4-methylbenzylamine (**1b**) (1.0 mmol, 136 mg) and 3-nitrobenzonitrile (**2l**) (1.0 mmol, 148 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 7-methyl-2-(3-nitrophenyl)quinazoline (**3bl**) in 72% (191 mg) yield as yellow solid (Scheme 4).

7-Methyl-2-(3-nitrophenyl)quinazoline (3bl) (Scheme 4): **Yellow solid**, R_f = 0.40 (SiO_2, Hexane/EtOAc = 4:1); IR (KBr) ν = 2926, 1640, 1524, 1352, 765 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 9.56 (s, 1H; 4-H), 9.32 (d, J = 3.6 Hz, 1H; 12-H), 8.94 (dt, ^3J = 8.0 Hz, 1H; 16-H), 8.32 (ddd, ^3J = 8.0, 2.4, 1.2 Hz, 1H; 14-H), 8.02 (s, 1H; 8-H), 7.93-7.87 (m, 2H; 5-H and 15-H), 7.54 (dd, ^3J = 9.0 Hz, 1H; 6-H), 2.59 (s, 3H; 17-H) ppm; **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 161.8 (C-2), 160.2 (C-4), 150.15 (C-9), 145.08 (C-13), 143.68 (C-7), 138.12 (C-16), 133.04 (C-11), 131.09 (C-15), 129.94 (C-6), 128.53 (C-8), 127.32 (C-12), 126.75 (C-5), 125.8 (C-10), 122.9 (C-14), 21.78 (C-17) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{12}N_3O_2$: 266.0929; found: 266.0924.

Preparation of 6-Methoxy-2-phenylquinazoline (3ca)

According to the general procedure, reaction between 2-amino-5-methoxybenzylamine (**1c**) (1.0 mmol, 152 mg) and benzonitrile (**2a**) (1.0 mmol, 103 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6-methoxy-2-phenylquinazoline (**3ca**) in 79% (186 mg) yield as colorless solid (Scheme 4).

6-Methoxy-2-phenylquinazoline (3ca)[2c] (Scheme 4): **Colorless solid**, R_f = 0.63 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 119-121 °C (Lit[2c] 118-119 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.38 (s, 1H; 4-H), 8.57 (d, ^3J = 8 Hz, 2H; 12-H), 8.01 (d, ^3J = 8.2 Hz, 1H; 8-H), 7.58-7.48 (m, 4H; 7-H, 13-H and 14-H), 7.16 (d, J = 2.8 Hz, 1H; 5-H), 3.98 (s, 3H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.42 (C-2), 158.83 (C-4), 158.3 (C-6), 147.0 (C-9), 138.116 (C-11), 130.21 (C-14), 130.16 (C-8), 128.6 (C-13), 128.2 (C-12), 127.24 (C-7), 124.5 (C-10), 103.93 (C-5), 55.77 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1025.

Preparation of 6-Methoxy-2-(*p*-tolyl)quinazoline (3cd)

According to the general procedure, reaction between 2-amino-5-methoxybenzylamine (**1c**) (1.0 mmol, 152 mg) and 4-methylbenzonitrile (**2d**) (1.0 mmol, 117 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6-methoxy-2-(*p*-tolyl)quinazoline (**3cd**) in 82% (201 mg) yield as colorless solid (Scheme 4).

6-Methoxy-2-(*p*-tolyl)quinazoline (3cd)[2c] (Scheme 4): **Colorless solid**, R_f = 0.63 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 139-140 °C (Lit[2c] 140-142 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H; 4-H), 8.47 (d, ^3J = 8 Hz, 2H; 12-H), 7.98 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.54 (dd, ^3J = 8.0 Hz, 1H; 7-H), 7.33 (d, ^3J = 8 Hz, 2H; 13-H), 7.15 (d, ^4J = 2.8 Hz, 1H; 5-H), 3.97 (s, 3H; 15-H), 2.44 (s, 3H; 16-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.5 (C-2), 158.8 (C-4), 158.1 (C-6), 147.0 (C-9), 140.37 (C-11), 135.4 (C-14), 130.04 (C-8), 129.37 (C-13), 128.13 (C-12), 127.1 (C-7), 124.34 (C-10), 103.94 (C-5), 55.73 (C-15), 21.48 (C-16) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{16}H_{15}N_2O$: 251.1184; found: 251.1180.

Preparation of 6-Methoxy-2-(4-chlorophenyl)quinazoline (3ci)

According to the general procedure, reaction between 2-amino-5-methoxybenzylamine (**1c**) (1.0 mmol, 152 mg) and 4-chlorobenzonitrile (**2i**) (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6-methoxy-2-(4-chlorophenyl)quinazoline (**3ci**) in 76% (205 mg) yield as colorless solid (Scheme 4).

6-Methoxy-2-(4-chlorophenyl)quinazoline (3cd)[2c] (Scheme 4): **Colorless solid**, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 171-172 °C (Lit[2c] 172-173 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.30 (s, 1H; 4-H), 8.50 (d, ^3J = 8 Hz, 2H; 12-H), 7.94 (d, ^3J = 8.6 Hz, 1H; 8-H), 7.53 (dd, ^3J = 8.6 Hz, 1H; 7-H), 7.47 (d, ^3J = 8 Hz, 2H; 13-H), 7.10 (d, ^4J = 2.7 Hz, 1H; 5-H), 3.94 (s, 3H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.0 (C-2), 158.6 (C-4), 158.54 (C-6), 147.1 (C-9), 136.9 (C-14), 136.55 (C-11), 130.30 (C-8), 129.73 (C-13), 129.0 (C-12), 127.55 (C-7), 124.73 (C-10), 104.13 (C-5), 55.97 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{12}ClN_2O$: 271.0638; found: 271.0635.

Preparation of 6,7-Methylenedioxy-2-phenylquinazoline (3da)

According to the general procedure, reaction between 6-(aminomethyl)benzo[*d*][1,3]dioxol-5-amine (**1d**) (1.0 mmol, 166 mg) and benzonitrile (**2a**) (1.0 mmol, 103 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6,7-methylenedioxy-2-phenylquinazoline (**3da**) in 79% (198 mg) yield as colorless solid (Scheme 4).

6,7-Methylenedioxy-2-phenylquinazoline (3da)[2c] (Scheme 4): **Colorless solid**, R_f = 0.61 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 172-174 °C (Lit[2c] 172-173 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.15 (s, 1H; 4-H), 8.53 (d, ^3J = 9 Hz, 2H; 12-H), 7.54-7.44 (m, 3H; 13-H and 14-H), 7.33 (s, 1H; 8-H), 7.09 (s, 1H; 5-H), 6.13 (s, 2H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.3 (C-2), 157.7 (C-4), 154.37 (C-9), 150.53 (C-7), 148.5 (C-6), 138.4 (C-11), 130.43 (C-14), 128.8 (C-13), 128.4 (C-12), 120.97 (C-10), 105.23 (C-8), 102.43 (C-6), 102.08 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{11}N_2O_2$: 251.0821; found: 251.0818.

Preparation of 6,7-Methylenedioxy-2-(*p*-tolyl)quinazoline (3dd)

According to the general procedure, reaction between 6-(aminomethyl)benzo[*d*][1,3]dioxol-5-amine (**1d**) (1.0 mmol, 166 mg) and 4-methylbenzonitrile (**2d**) (1.0 mmol, 117 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6,7-methylenedioxy-

2-(*p*-tolyl)quinazoline (**3dd**) in 78% (206 mg) yield as colorless solid (Scheme 4).

6,7-Methylenedioxy-2-(*p*-tolyl)quinazoline (3dd)[2c] (Scheme 4): **Colorless solid**, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 186-188 °C (Lit[2c] 187-188 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.12 (s, 1H; 4-H), 8.42 (d, ^3J = 9 Hz, 2H; 12-H), 7.32-7.30 (m, 3H; 13-H and 8-H), 7.06 (s, 1H; 5-H), 6.11 (s, 2H; 15-H), 2.43 (s, 2H; 16-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.35 (C-2), 157.64 (C-4), 154.28 (C-9), 150.5 (C-7), 148.3 (C-6), 140.60 (C-11), 135.67 (C-14), 129.55 (C-13), 128.35 (C-12), 120.8 (C-10), 105.15 (C-8), 102.36 (C-6), 102.08 (C-15), 21.72 (C-16) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0974.

Preparation of 6,7-Methylenedioxy-2-(4-chlorophenyl)quinazoline (3di)

According to the general procedure, reaction between 6-(aminomethyl)benzo[*d*][1,3]dioxol-5-amine (**1d**) (1.0 mmol, 166 mg) and 4-chlorobenzonitrile (**2i**) (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6,7-methylenedioxy-2-(4-chlorophenyl)quinazoline (**3di**) in 76% (216 mg) yield as colorless solid (Scheme 4).

6,7-Methylenedioxy-2-(4-chlorophenyl)quinazoline (3di)[2c] (Scheme 4): **Colorless solid**, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 222-224 °C (Lit[2c] 223-225 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.14 (s, 1H; 4-H), 8.49 (d, ^3J = 9 Hz, 2H; 12-H), 7.47 (d, ^3J = 8 Hz, 2H; 13-H), 7.32 (s, 1H; 8-H), 7.11 (s, 1H; 5-H), 6.17 (s, 2H; 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.3 (C-2), 157.74 (C-4), 154.53 (C-9), 150.52 (C-7), 148.7 (C-6), 136.93 (C-14), 136.62 (C-11), 129.77 (C-13), 129.0 (C-12), 121.1 (C-10), 105.2 (C-8), 102.5 (C-6), 102.15 (C-15) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{10}ClN_2O_2$: 285.0431; found: 285.0428.

Preparation of 6,7-Methylenedioxy-2-(3-nitrophenyl)quinazoline (3dl)

According to the general procedure, reaction between 6-(aminomethyl)benzo[*d*][1,3]dioxol-5-amine (**1d**) (1.0 mmol, 166 mg) and 3-nitrobenzonitrile (**2l**) (1.0 mmol, 148 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6,7-methylenedioxy-2-(3-nitrophenyl)quinazoline (**3dl**) in 74% (218 mg) yield as yellow solid (Scheme 4).

6,7-Methylenedioxy-2-(3-nitrophenyl)quinazoline (3dl) (Scheme 4): **Yellow solid**, R_f = 0.40 (SiO_2, Hexane/EtOAc = 4:1); IR (KBr) ν = 3050, 2160, 1613, 1524, 1350, 768 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 9.42 (s, 1H; 4-H), 9.33 (d, *J* = 0.3 Hz, 1H; 12-H), 8.89 (dt, ^3J = 8.0 Hz, 1H; 16-H), 8.37 (ddd, ^3J = 8.0, 2.4, 1.2 Hz, 1H; 14-H), 7.85 (t, ^3J = 8.0 Hz, 1H; 15-H), 7.54 (s, 1H; 8-H), 7.49 (s, 1H; 5-H), 6.32 (s, 2H; 17-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.5 (C-2), 156.06 (C-4), 149.81 (C-9), 148.94 (C-7), 146.95 (C-6), 136.94 (C-16), 134.58 (C-11), 130.09 (C-15), 127.53, 124.0 (C-12), 123.87 (C-10), 108.71 (C-8), 103.57 (C-5), 102.07 (C-17) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{15}H_{10}N_3O_4$: 296.0671; found: 296.0666.

Preparation of 6-Fluoro-2-phenylquinazoline (3ea)

According to the general procedure, reaction between 2-amino-5-fluorobenzylamine (**1e**) (1.0 mmol, 140 mg) and benzonitrile (**2a**) (1.0 mmol, 103 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 6-fluoro-2-phenylquinazoline (**3ea**) in 77% (173 mg) yield as colorless solid (Scheme 4).

6-Fluoro-2-phenylquinazoline (3ea)[2c] (Scheme 4): **Colorless solid**, R_f = 0.66 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 137-138 °C (Lit[2c] 138-140 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.44 (s, 1H; 4-H), 8.59 (dd, ^3J = 9 Hz, 2H; 12-H), 8.11 (dd, ^3J = 9.2, 4.8 Hz, 1H; 8-H), 7.68 (td, ^3J = 8.8, 2.8 Hz, 1H; 7-H), 7.58-7.51 (m, 4H; 5-H, 13-H and 14-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.2 (d, *J* = 250.0 Hz, C-6), 160.1 (C-2), 159.04 (C-4), 148.23 (C-9), 138.0 (C-11), 131.68 (d, *J* = 12.0 Hz, C-8), 130.97 (C-14), 128.95 (C-13), 128.73 (C-12), 124.81 (d, *J* = 32.0 Hz, C-7), 124.2 (d, *J* = 12.0 Hz, C-10), 110.42 (d, *J* = 29 Hz, C-5) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0825.

Preparation of 2-(4-Chlorophenyl)-6-fluoroquinazoline (3ei)

According to the general procedure, reaction between 2-amino-5-fluorobenzylamine (**1e**) (1.0 mmol, 140 mg) and 4-chlorobenzonitrile (**2i**) (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 2-(4-chlorophenyl)-6-fluoroquinazoline (**3ei**) in 73% (189 mg) yield as colorless solid (Scheme 4).

2-(4-Chlorophenyl)-6-fluoroquinazoline (3ei)[2c] (Scheme 4): **Colorless solid**, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); **m.p** = 186-188 °C (Lit[2c] 187-188 °C);**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.41 (s, 1H; 4-H), 8.54 (dd, ^3J = 9 Hz, 2H; 12-H), 8.08 (dd, ^3J = 9.3, 5.0 Hz, 1H; 8-H), 7.68 (td, ^3J = 8.8, 2.8 Hz, 1H; 7-H), 7.55-7.47 (m, 3H; 5-H and 13-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.25 (d, *J* = 240 Hz, C-6), 160.12 (C-4), 159.11 (C-4), 148.12 (C-9), 137.2 (C-11), 136.46 (C-14), 131.62 (d, *J* = 11 Hz, C-8), 130.0 (C-13), 129.13 (C-12), 124.95 (d, *J* = 34 Hz, C-7), 124.22 (d, *J* = 12 Hz, C-10), 110.46 (d, *J* = 29 Hz, C-5) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_9ClFN_2$: 259.0438; found: 259.0435.

Preparation of 7-Fluoro-2-phenylquinazoline (3fa)

According to the general procedure, reaction between 2-amino-4-fluorobenzylamine (**1f**) (1.0 mmol, 140 mg) and benzonitrile (**2a**) (1.0 mmol, 103 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 7-fluoro-2-phenylquinazoline (**3fa**) in 75% (149 mg) yield as off-white solid (Scheme 4).

7-Fluoro-2-phenylquinazoline (3fa)[14] (Scheme 4): **Off-white solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.43 (s, 1H; 4-H), 8.63-8.60 (m, 1H; 12-H), 7.94 (dd, ^3J = 8.0 Hz, 1H; 5-H), 7.71 (d, ^3J = 8.0 Hz, 1H; 6-H), 7.58-7.49 (m, 3H; 8-H and 13-H), 7.38 (td, ^3J = 9.0 Hz, 1H; 14-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.06 (d, *J* = 272 Hz, C-7), 161.8 (C-2), 159.93 (C-4), 152.44 (d, *J* = 19 Hz, C-9), 137.55 (C-11), 131.03 (C-14), 129.8 (d, *J* = 14 Hz, C-5), 128.76 (C-13), 128.72 (C-12), 120.9 (C-10), 118.0 (d, *J* = 34 Hz, C-6), 112.5 (d, *J* = 27 Hz, C-8) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0824.

Preparation of 7-Fluoro-2-(3-nitrophenyl)quinazoline (3fl)

According to the general procedure, reaction between 2-amino-4-fluorobenzylamine (**1f**) (1.0 mmol, 140 mg) and 3-nitrobenzonitrile (**2l**) (1.0 mmol, 148 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 7-fluoro-2-(3-nitrophenyl)quinazoline (**3fl**) in 71% (191 mg) yield as white solid (Scheme 4).

7-Fluoro-2-(3-nitrophenyl)quinazoline (3fl) (Scheme 4): W**hite solid**, R_f = 0.50 (SiO_2, Hexane/EtOAc = 4:1); IR (KBr) ν = 3061, 2160, 1623, 1550, 1380, 1349, 1140, 1020, 768 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.49 (s, 1H; 4-H), 9.48 (s, 1H; 12-H), 8.96 (d, ^3J = 8.0 Hz, 1H; 16-H), 8.37 (d, ^3J = 8.0 Hz, 1H; 14-H), 8.02 (dd, ^3J = 8.0 Hz, 1H; 5-H), 7.77-7.69 (m, 2H; 6-H and 8-H), 7.46 (td, ^3J = 9.0 Hz, 1H; 15-H) ppm; **^{13}C NMR** (100

MHz, $CDCl_3$) δ = 166.25 (d, *J* = 272 Hz, C-7), 160.23 (C-2), 159.5 (C-4), 152.5 (d, *J* = 18 Hz, C-9), 148.9 (C-13), 139.46 (C-16), 134.37 (C-11), 129.94 (d, *J* = 14 Hz, C-5), 129.65 (C-15), 125.38 (C-14), 123.8 (C-12), 121.26 (C-10), 118.9 (d, *J* = 34 Hz, C-6), 112.7 (d, *J* = 27 Hz, C-8) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_9FN_3O_2$: 270.0678; found: 270.0674.

Preparation of 4-Chloro-*N*-(2-formylphenyl)benzimidamide (5aa)

According to the general procedure, reaction between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg) and 4-chlorobenzonitrile **2i** (1.0 mmol, 137.6 mg) were performed using Vitamin-B_3 (0.3 mmol, 37 mg) to obtain the desired 4-chloro-*N*-(2-formylphenyl)benzimidamide (**5aa)** in 54% (140 mg) yield as yellow solid (Scheme 2).

4-Chloro-*N*-(2-formylphenyl)benzimidamide (5aa) (Scheme 5): **Yellow solid**, R_f = 0.55 (SiO_2, Hexane/EtOAc = 4:1); IR (KBr) ν = 3458, 3309, 2916, 2850, 2710, 2160, 1730, 1620, 1590, 1352, 764 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 12.11 (s, 1H; 1-NH), 10.00 (d, *J* = 4.0 Hz, 1H; 4-H), 8.93 (d, ^3J = 8.0 Hz, 1H; 5-H), 8.02 (d, ^3J = 8.0 Hz, 1H; 13-H), 7.75 (dd, ^3J = 8.0 Hz, 1H; 7-H),7.69 (td, ^3J = 8.0 Hz, 1H; 6-H), 7.51 (dt, ^3J = 8.0 Hz, 1H; 12-H), 7.30 (td, ^3J = 8.0 Hz, 1H; 8-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 196.04 (C-4), 165.07 (C-2), 141.1 (C-9), 138.62 (C-14), 136.51 (C-7), 136.26 (C-5), 132.73 (C-6), 129.19 (C-12), 128.96 (C-13), 123.3, 122.0, 120.0 (C-8) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{12}ClN_2O$: 259.0638; found: 259.0630.

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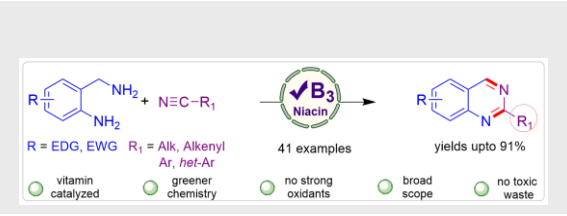

An organocatalyzed protocol has been described for the comprehensive synthesis of 2-substituted quinazolines using nitriles as C-N Source. The developed reaction conditions holds good for wide range of substrates by giving the desired products in excellent yields.

***N*-Heterocycles, Organocatalysis**

*Raghuram Gujjarappa, Nagaraju Vodnala, Velma Ganga Reddy and Chandi C. Malakar**

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Niacin as a Potent Organocatalyst towards the Synthesis of Quinazolines using Nitriles as C-N Source