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Divergent Synthesis of Quinazolines using Organocatalytic Domino Strategies under Aerobic Conditions

Raghuram Gujjarappa,[a]† Suvik K. Maity,[a]† Chinmoy K. Hazra,[b] Nagaraju Vodnala,[a] Shiv Dhiman,[c] Anil Kumar,[c] Uwe Beifuss,[d] Chandi C. Malakar*[a]

Abstract: Efficient organocatalytic platforms are described to accomplish the easy transformation towards 2-substituted quinazolines using the reaction between 2-aminobenzylamines and aldehydes or alcohols or amines. Three distinct organocatalytic platforms are investigated those rely on the use of 3-nitropyridine, pyridine-N-oxide and vitamin-B_3. Having established the novel catalytic systems, the tandem transformations of 2-aminobenzylamines to the substituted quinazolines are achieved with excellent yields and broad substrate scope that avoids the formation of toxic side-products. The investigated conditions are not only restricted to the use of aldehydes, rather the scope of the protocol can be extended to alcohols or amines as substrates which was *in-situ* oxidized to the corresponding aldehydes to realize the successful transformation. A mechanistic proposal has been drawn and based upon the control experiments. It was demonstrated that under the influence of aerobic conditions the catalytic amounts of H_2O_2 can be generated which plays a pivotal role towards efficacy of the described approach. The green chemistry merits of the developed method have been represented with the E-factor of 8.18 mg/1 mg, which shows the revealed method is an excellent complement to the previous protocols.

Introduction

Organocatalytic transformations for the elaboration of complex molecules have revised organic synthesis and during recent years the field has remarkably driven the effective synthesis of biologically active small molcules.[1] The area has been copiously documented and well-exercised in both academic as well as industrial sectors.[2,3] Recently, the well-recognized advantages in the reactivity and intellectual property positions of organocatalysis have lead many scientists to favor their application in the field of drug-discovery and medicinal chemistry.[4] In addition, the concept of organocatalysis has provided a surrogate and sustainable platform towards varieties of novel oxidative transformations.[5] Hence, the investigation of new organocatalytic system still remains challenging in multidisciplinary fields of research. Here we report three independent organocatalytic systems based on 3-nitropyridine, pyridine-N-oxide and vitamin-B_3. Under the aerobic conditions the described organocatalysts are found efficient to drive the oxidative transformations for the synthesis of 2-substituted quinazolines.

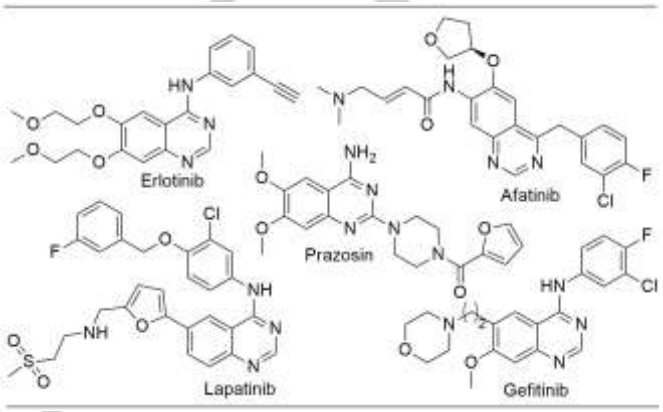
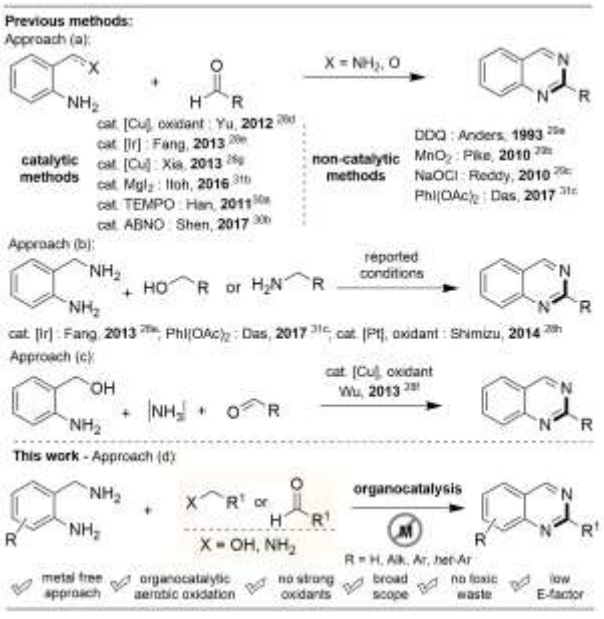


Figure 1. Selected quinazoline embodied FDA approved marketed drugs.



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

N-heterocyclic skeletons are often realized as the core structural units in both biologically and industrially due to their wide

[a] R. Gujjarappa, S. K. Maity, N. Vodnala, Dr. C. C. Malakar
Department of Chemistry, National Institute of Technology Manipur, Langol, Imphal - 795004, Manipur.
E-mail: cmalakar@nitmanipur.ac.in
[b] Dr. C. K. Hazra
Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305 - 701, South Korea.
[c] Shiv Dhiman, Prof. Anil Kumar
Department of Chemistry, BITS Pilani, Pilani Campus, Pilani, Rajasthan 333031, India.
[d] Prof. Dr. U. Beifuss
Institut für Chemie, Universität Hohenheim, Garbenstr. 30, D-70599 Stuttgart, Germany.
† R.G. and S.K.M. contributed equally to this work.
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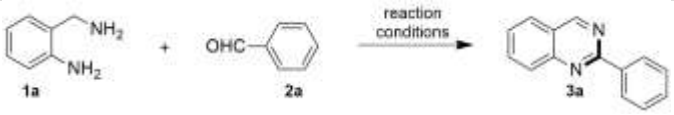
occurrence in natural products and valuable medicinal compounds (Figure 1).[6] Among the N-heterocyclic scaffolds, wide varieties of quinazoline embodied molecules are of immense biological relevance. These molecules witnessed for the pharmacological utilities like antiviral, antibacterial, anticancer, antitubercular, anticonvulsant, sedative, hypotensive, antidiabetic, and antitussive activities.[7-11]

Table 1. Screening of the conditions for the reaction between **1a** and **2a**.[a]

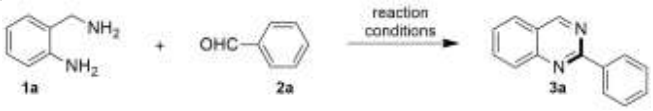


S.N	Catalyst (mol%)	Conditions	% Yield **3a** [b]
1	TBAI (30)	TBHP (1.5 equiv.), DMSO, air, 120 °C, 16 h	80
2	TBAI (30)	TBHP (1.5 equiv.), H_2O, air, 120 °C, 16 h	N.R
3	-	TBHP (1.5 equiv.), DMSO, 120 °C, 9 h	85
4	-	$K_2S_2O_8$ (1.5 equiv.), DMSO, 120 °C, 7 h	71
5	-	H_2O_2 (1.5 equiv.), DMSO, 120 °C, 10 h	83
6 [c]	Ph_2Se_2 (10)	NIS (1.0 equiv.), THF/HFIP, 50 °C, 12 h	0[d]
7	PhI (10)	mCPBA (1.5 equiv.), THF, 50 °C, 10 h	54
8	I_2 (30)	mCPBA (1.5 equiv.), THF, 50 °C, 15 h	47

[a] All reactions were performed using 1.0 mmol **1** and 1.0 mmol **2a**. [b] Isolated yields. [c] THF/HFIP (3:1) was used as solvent. [d] Mixture of unidentified compounds was formed; desired product was not observed.

Those molecules include the FDA approved active marketed drugs such as erlotinib,[12] afatinib,[13] gefitinib[14] and icotinib[15] for the treatment of lung cancer; lapatinib[16] as orally active drug used for the treatment of breast cancer and other solid tumors. Among the other pharmaceuticals, prazosin[17] a α-adrenergic blocker is valued for the treatment of anxiety, high blood pressure and panic disorder; etifoxine[18] used as GABA receptor inhibitor for the treatment of anxiolytic and anticonvulsant and cetilistat[19] as pancreatic lipase inhibitor to treat obesity. Additionally, some reported quinazoline containing alkaloids have immense importance in medicinal chemistry.[20-27] The well-known alkaloids of these type include Luotonin A,[20] tryptanthrin,[21] febrifugine,[22] peganidine,[23] (+)-anisotine,[24] (-)-vasicinone[25] and vasicine.[26] Another important quinazoline based alkaloid rutaecarpine[27] is actively used for the treatment of gastrointestinal disorders, antiinflammatory, headaches, and postpar tum haemorrhage. Therefore, the investigation of convenient approaches for the substituted quinazolines remain as one of the major topics of research in the synthesis of six-membered heterocycles.[6c] In this regards, a large number of transition metal-catalyzed transformations using Cu, Rh, Pt, Ir, and Zn have been devoted in recent years for the synthesis of these scaffolds (Scheme 1a).[28] Consequently, to serve the synthesis of these molecules, several strong as well as toxic organic and inorganic reagents were introduced to oxidize the derived intermediate from the reaction between 2-aminobenzyl alcohols or 2-aminobenzylamines and aldehydes (Scheme 1b).[29] The use of large excess of non-renewable, hazardous and toxic oxidants may restrict the novelty of these protocols.

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

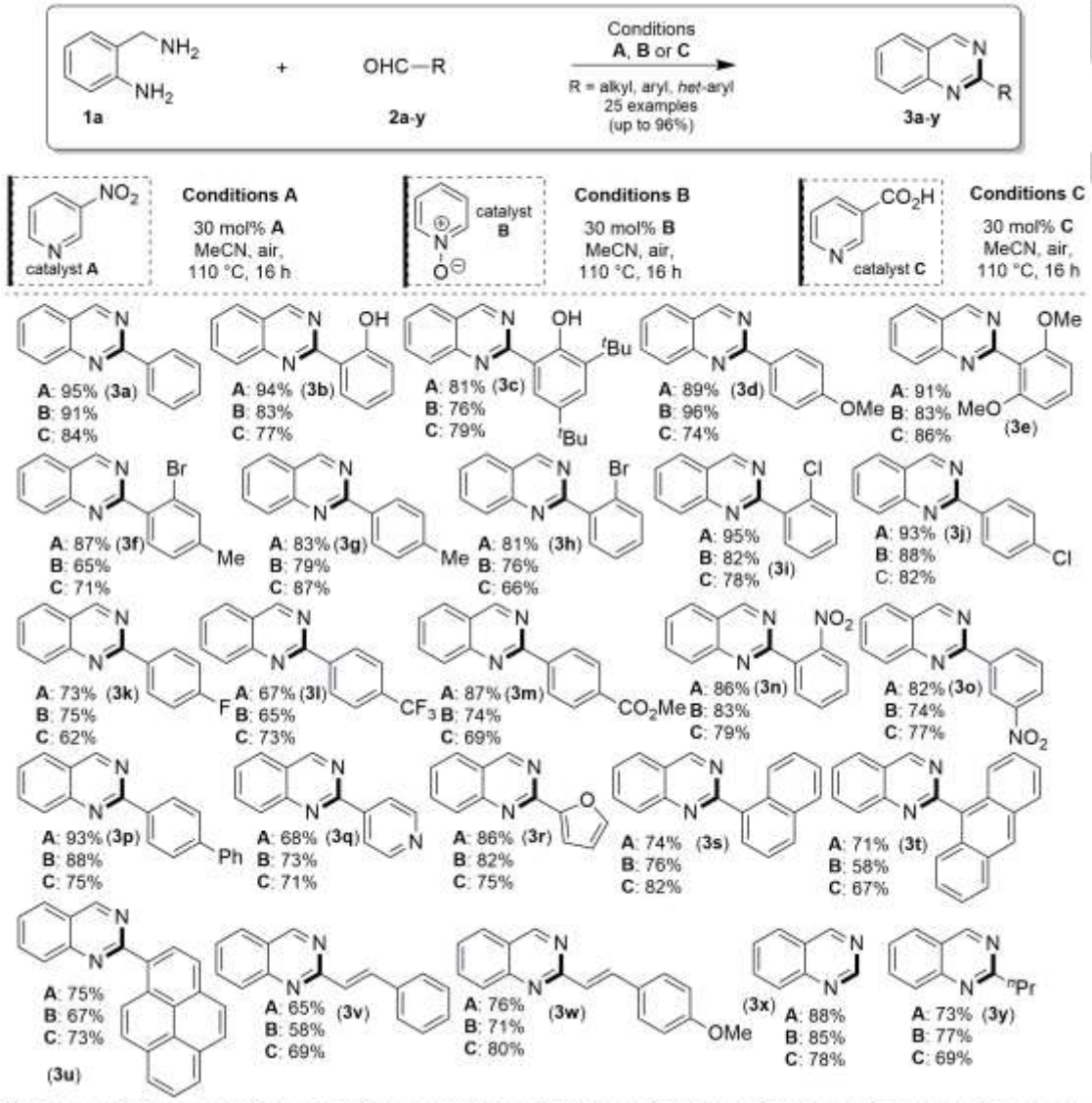


S.N.	Catalyst (mol%)	Conditions	% Yield **3a** [b]
1	vitamin-B_3 (30)	MeCN, air, 110 °C, 16 h	89
2	2-picolinic acid (30)	MeCN, air, 110 °C, 16 h	86
3	3-nitropyridine (30)	MeCN, air, 110 °C, 16 h	95
4	pyridine-N-oxide (30)	MeCN, air, 110 °C, 16 h	91
5	isonicotinic acid (30)	MeCN, air, 110 °C, 16 h	85
6	vitamin-B_3 (30)	H_2O, air, 110 °C, 16 h	N.R
7	vitamin-B_3 (30)	THF, air, 110 °C, 16 h	<5[c]
8	vitamin-B_3 (30)	Toluene, air, 110 °C, 16 h	<5[c]
9	vitamin-B_3 (30)	DMF, air, 110 °C, 16 h	77
10	vitamin-B_3 (30)	DMSO, air, 110 °C, 16 h	84
11[d]	vitamin-B_3 (30)	MeCN, N_2, 110 °C, 16 h	<5[c]
12	vitamin-B_3 (15)	MeCN, air, 110 °C, 16 h	49
13	-	MeCN, air, 120 °C, 16 h	7[c]
14	-	DMSO, air, 120 °C, 16 h	11[c]
15	vitamin-B_3 (30)	MeCN, air, 80 °C, 16 h	49
16	vitamin-B_3 (30)	DMSO, air, 110 °C, 10 h	61

[a] All reactions were performed using 1.0 mmol **1** and 1.0 mmol **2a**. [b] Isolated yields. [c] Starting material was recovered. [d] Reaction was carried out under nitrogen atmosphere.

More recently, the organocatalytic platforms are recognized for their synthesis.[30] These approaches rely on 9-azabicyclo[3.3.1]nonan-N-oxyl, TEMPO and rose Bengal as green organocatalytic systems.[30] Although, the mentioned previous methods[28-30] and some other reported methods[31] are useful, and have found extensive application in the synthesis;

the development of more general and practical organocatalytic



Scheme 2. Scope towards the synthesis of quinazolines using novel organocatalysts A, B and C under aerobic conditions.

platforms are highly desirable. As part of our on-going research program on developing novel catalytic approaches constraining the use of excess amounts of reagents, we aimed to investigate a surrogate protocol for the synthesis of these scaffolds using easy-to-operate synthetic tools. Hence, we describe that 3-nitropyridine, pyridine-N-oxide and vitamin-B_3 can be exclusively employed as independent organocatalyst in the reaction between 2-aminobenzylamines and aldehydes to furnish the corresponding 2-substituted quinazolines in excellent yields (Scheme 1, reactions (d)). The developed protocol has been extended to benzylalcohols and benzylamines as the easy-available substrates.

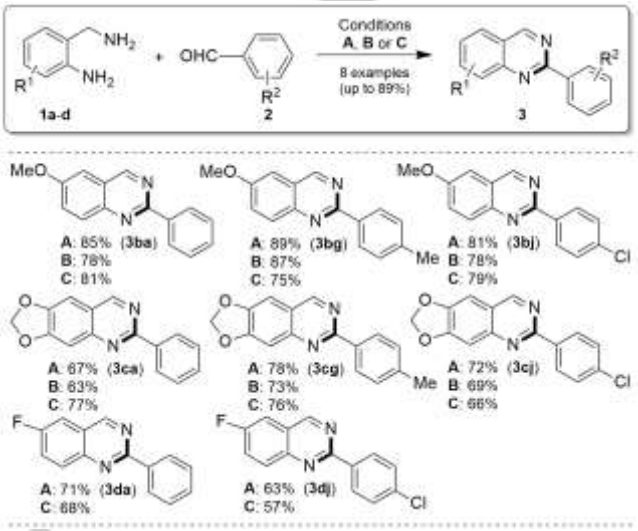
Results and Discussion

With the ideas in mind towards developing facile organocatalyzed aerobic oxidation protocol for the synthesis of quinazolines, we carried out several screening reactions between 2-aminobenzyl amine **1a** and benzaldehyde **2a**, (Table 1) and observed that the 2-phenylquinazoline **3a** was obtained in 80% yield in the presence of 30 mol% TBAI and 1.5 equiv. of TBHP, when the reaction was carried out in DMSO as solvent (Entry 1). However, the formation of the product was inhibited when DMSO was replaced with water as solvent (Entry 2). It was also observed that TBAI has no influence on successful completion of the reaction (Entry 3). Next, we have attempted to check the feasibility for the formation of desired product **3a** using equivalent amounts of alternative oxidants such as $K_2S_2O_8$, and H_2O_2 (Entries 4-5). It was found that among the oxidants screened, using 1.5 equiv. of TBHP the reaction between **1a** and **2a** delivered the highest yield of the expected product **3a** (Entry 3). Moreover, when the reaction between **1a** and **2a** was realized in the presence of 10 mol% Ph_2Se_2 and 1.5 equiv. NIS as oxidant using DMSO as solvent, desired product **3a** was not identified (Entry 6). Additionally, the desired product **3a** was obtained in moderate yields, when iodine sources as catalyst and mCPBA as oxidant were used for the reaction between **1a** and **2a** (Entries 7-8).

Albeit, under multiple screening conditions the formation of desired product **3a** was observed with high yields (Entries 1, 3-5); however, our aim still remains towards the optimization of the conditions that rely on identifying the new organocatalyst for the conversion of **1a** and **2a** into **3a**. To test the desired possibilities a series of test reactions were carried out (Table 2). In this regards, the screening reactions between **1a** and **2a** were attempted in presence of catalytic amounts of pyridine derivatives such as vitamin-B_3, 2-picolinic acid, 3-nitropyridine, pyridine N-oxide and
isonicotinic acid using MeCN as solvent under aerobic conditions at 110 °C for 16 hours (Entries 1-5). It was found that among the attempted pyridine derivatives, using 30 mol% of 3-nitropyridine as catalyst showed the highest efficiency (Entry 3). However, similar yields of the product **3a** were also observed when 30 mol% of vitamin-B_3 (Entry 1), 30 mol% of 2-picolinic acid (Entry 2), 30 mol% of pyridine N-oxide (Entry 4) and 30 mol% of isonicotinic acid (Entry 5), were used as catalysts. It was further observed that H_2O, THF and toluene as solvents were inactive to accomplish the transformation (Entries 6-8), while performing the reaction in DMF and DMSO as solvents obtain the high yields of the product **3a** (Entries 9-10). Interestingly, when the reaction was performed under nitrogen atmosphere, formation of the desired product **3a** was not observed (Entry 11). Moreover, the yield of product **3a** was decreased dramatically in the presence of low catalyst loading (Entry 12). Albeit in low yields, the product **3a** was formed in 7% and 11% respectively, when the reactions between **1a** and **2a** were carried out in absence of catalyst under the influence of MeCN and DMSO (Entries 13-14). Additionally, it was found that decreasing the reaction temperature and time resulted insufficient yields of the product **3a** (Entries 15-16). Having performed an extensive optimization of the reaction conditions, it was realized that the maximum yield of product **3a** was obtained when the reaction between 1 mmol of **1** and 1 mmol of **2a** was conducted in presence of 30 mol% 3-nitropyridine as catalyst using MeCN as solvent under aerobic conditions at 110 °C for 16 hours (Table 2, Entry 3). These conditions were then employed to execute the scope of the reaction (Conditions **A**). Additionally, the scope of the reactions has also been verified using 30 mol% pyridine N-oxide (conditions **B**: Table 2, Entry 4) or 30 mol% vitamin-B_3 (Conditions **C**: Table 2, Entry 1) as catalyst in MeCN as solvent under aerobic conditions at 110 °C for 16 hours.

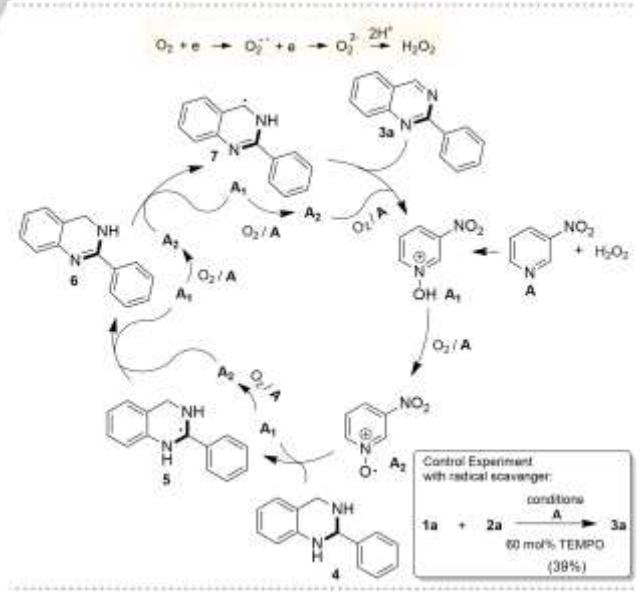
Having three independent optimized conditions in hand, further the reactivity of a broad range of aromatic, heteroaromatic and aliphatic aldehydes **2a**-**y** containing both electron donating groups and electron withdrawing groups were tested (Scheme 2). It has been described that electron donating groups such as hydroxy, methoxy and methyl residue on aromatic ring, as well as electron withdrawing substituents such as bromo, chloro, nitro, fluoro, trifluoromethyl and ester functionalities were well tolerated under the influence of developed organocatalytic conditions to furnish the desired products **3a**-**p** with good to excellent isolated yields. Interestingly, heteroaromatic aldehydes **2q**-**r** and polycyclic aromatic aldehydes **2s**-**u** also delivered the corresponding quinazolines **3q**-**u** in high yields. To extend the further scope of the developed methods, the reactivity of a range of non-aromatic aldehydes such as cinnamaldehydes **2v**-**w**, formaldehyde **2x** and butanal **2y** were investigated under the optimal conditions to obtain the desired quinazolines **3v**-**y** in high yields.

After having realized the successful application of a diverse range of aldehydes, we then envisioned to describe the scope of



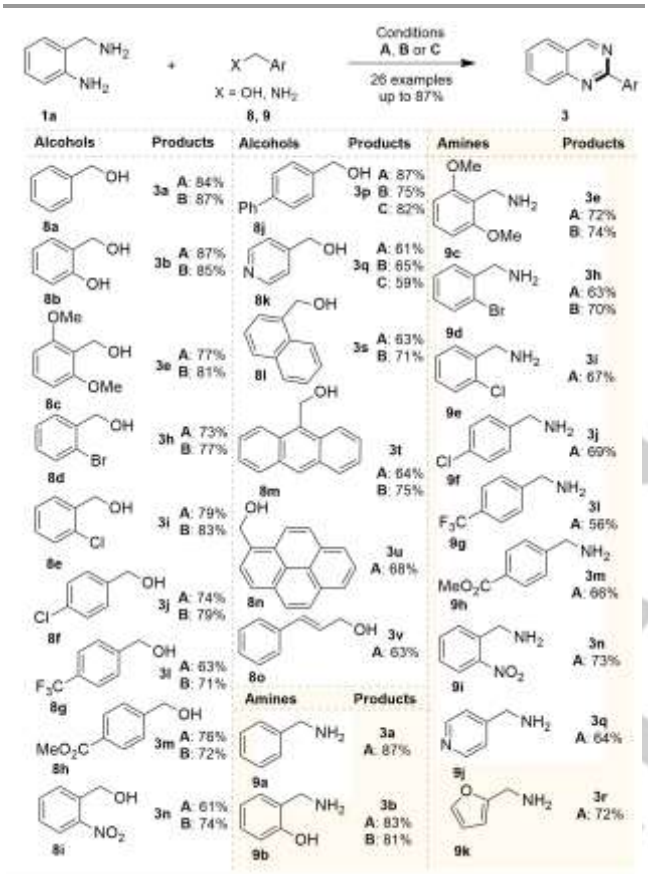
Scheme 3. Substrate scope for the synthesis of 2-substituted quinazolines.

2-aminobenzylamines **1** under the optimized conditions (Scheme 3). It was identified that 2-aminobenzylamines **1b**-**d** containing both electron-rich and electron-poor substituent were capable for the reaction with aromatic aldehydes **2** to afford the desired quinazolines **3** in high isolated yields.

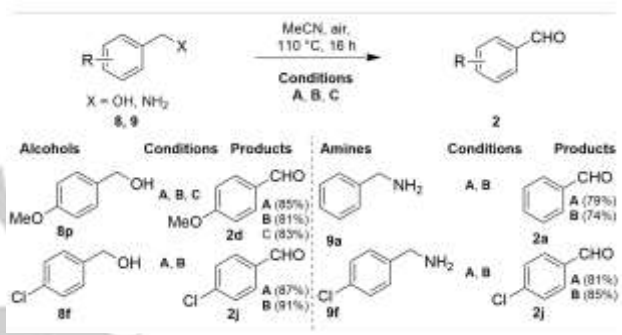


Scheme 4. Plausible mechanism for 3-nitropyridine catalyzed synthesis of 2-substituted quinazolines under aerobic conditions.

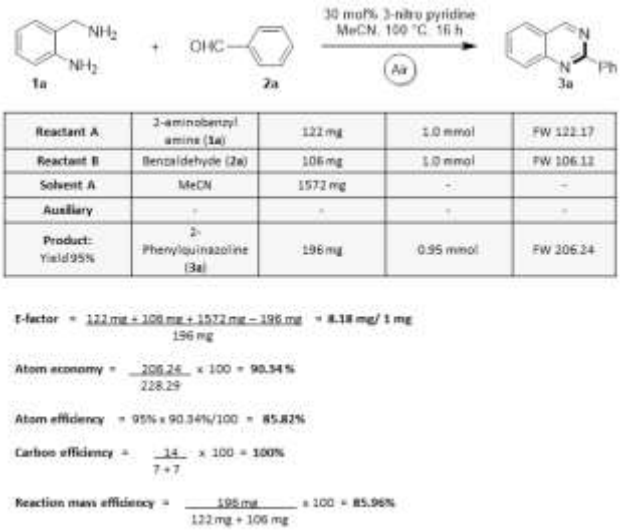
Next, our observation towards similar yields using catalysts **A**, **B** and **C** inspired us to question about the plausible mechanistic pathways for the formation of desired quinazolines **3**. In order to identify the plausible mechanism, we paid our attention towards the optimizations for the reaction between **1a** and **2a** (Table 1, 2). In this regards some screening reactions have been identified to conclude the plausible mechanism; these conditions are (i) the reaction delivered the desired product **3a** when peroxides have been used as oxidants (Table 1, Entries 1-3 and 5), (ii) formation of the desired product **3a** was reduced drastically when the reaction was performed under nitrogen atmosphere (Table 2, Entry 11), while a minor amounts of the product **3a** was formed when the reactions were carried out under aerobic conditions in absence of catalyst using MeCN and DMSO as solvent (Table 2, Entries 13-14), (iii) reaction delivered the desired product **3a** in presence of all pyridine derivatives those used as catalysts under the aerobic conditions (Table 2, Entries 1-5). On the basis of our experimental observations and literature evidence,[30b,32] a plausible mechanism has been drawn in scheme 4. It is expected that the intermediate **4**, can be formed by the condensation reaction between **1a** and **2a**. On the other hand, the catalytic amounts of H_2O_2 might be generated under aerobic conditions via the stepwise formation of superoxide ion and dioxygen dianion. Next, the catalytic amounts of 3-nitropyridine-N-hydroxide $\mathbf{A_1}$ can be formed *in-situ* by the reaction between 3-nitropyridine **A** and H_2O_2 which can be further converted to $\mathbf{A_2}$ in presence of aerial oxygen and 3-nitropyridine **A**. The intermediates **5**, **6** and **7** are formed via successive hydrogen abstraction by $\mathbf{A_2}$ which can be generated by re-oxidation of intermediate $\mathbf{A_1}$. Finally, the interaction between intermediate **7** and $\mathbf{A_2}$ leading to the formation of the product **3a** and $\mathbf{A_1}$. The proposed mechanism has been supported by the experiment performed in presence of nitrogen atmosphere that failed to deliver the product **3a** (Table 2, Entry 11). However, in absence of catalyst only catalytic amounts of H_2O_2 can be generated using aerial oxygen which could afford the minor amounts of product **3a** (Table 2, Entries 13-14) and the formation of the product **3a** can be accelerated using external peroxide as oxidant (Table 1, Entries 1-3 and 5). These observations align with the fair involvement of aerial oxygen with which the generation of H_2O_2 might be possible under aerobic conditions.



Scheme 5. Scope of benzylalcohols and benzylamines under developed conditions.



Scheme 6. Oxidation of benzylalcohols and benzylamines using developed organocatalytic conditions under aerobic conditions.



Scheme 7. Evaluation of green chemistry metrics for the synthesis.

Moreover, the yield of product **3a** was diminished when the reaction was carried out in the presence of 60 mol% of TEMPO as radical scavenger that indicates the radical nature of the reaction pathways for the formation of the desired product **3a (**Scheme 4).

To extend the further scope of the developed transformation, the reactivity of a broad spectrum of alcohols **8a**-**o** and amines **9a**-**k** have been examined under the optimized conditions (Scheme 5). It was identified that the developed conditions can effectively induce the reaction between **1a** and **8a**-**o** or **9a**-**k** to obtain the desired quinazolines **3** in high yields. These results guided to assume that using the organocatalytic conditions **A**, **B** or **C** the corresponding alcohols **8a**-**o** and amines **9a**-**k** can be *in-situ* oxidized to the corresponding aldehydes **2** under aerobic conditions to accomplish the transformation. To confirm the hypothesis, selected alcohols **8f**,**p** and amines **9a**,**f** were reacted under the optimized conditions that delivered the corresponding aldehydes **2a**,**d**,**j** in high yields (Scheme 6).

After the successful development and operation of the depicted approaches for the synthesis of the targeted N-heterocycles, we intended to verify the green chemistry merits of the described protocol (Scheme 7). It was found that the established method reveals the E-factor of 8.18 mg/1 mg with high atom-economy (90.34%), atom-efficiency (85.82%), carbon-efficiency (100%) and reaction mass-efficiency (85.96%).

Conclusions

In summary, we have studied in depth the novel organocatalytic synthesis of 2-substituted quinazolines under aerobic conditions using 2-aminobenzyl amines and aldehydes as substrates. The reactivity of a broad spectrum of alcohols and amines were also investigated under established conditions to introduce the surrogate of aldehydes as substrates. The proposed reaction mechanism has been verified by several control experiments. Considering the immense impact of 2-functionalized quinazolines, these facile and convenient organocatalytic approaches could be the excellent complements of current methods which represent a low E-factor, and high atom-economy, atom-efficiency, carbon-efficiency, and reaction mass-efficiency.

Experimental Section

General Method: All starting materials were purchased from commercial suppliers (Sigma-Aldrich, Alfa-Aesar, SD fine chemicals, Merck, HI Media) and were used without further purification unless otherwise indicated. All reactions were carried out under aerobic condition in oven-dried glassware with magnetic stirring. The reactions were performed in pressure tube purchased from Sigma-Aldrich glassware. 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. ^1H (^{13}C) NMR spectra were recorded at 600 (150) MHz and 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 (3a-**y or 3ba**-**dj) using aldehydes (2a**-**y)**: A 25 mL pressure tube was charged with a mixture of 2-aminobenzylamines **1a-d** (1.0 mmol), aldehydes **2a-y** (1.0 mmol), MeCN (2 mL) and 30 mol% catalyst **A** (37.2 mg) or **B** (28.5 mg) or **C** (37 mg). The pressure tube was then sealed and heated at 110 °C for 16 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 4:1), the mixture was diluted with hot ethyl acetate (15 mL) and water (25 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography over silica gel using hexane / ethyl acetate = 4:1 (*v/v*) as an eluent to obtain the desired products **3a-y** or **3ba**-**dj** in high yields.

General experimental procedure for the synthesis of quinazolines (3a-**t) using benzylalcohols (8a**-**o) or benzylamines (9a**-**k):** A 25 mL pressure tube was charged with a mixture of 2-aminobenzylamine **1a** (1.0 mmol, 122 mg), benzyl alcohols **8a**-**o** (1.0 mmol) or benzylamines **9a**-**k** (1.0 mmol), MeCN (2 mL) and 30 mol% catalyst **A** (37.2 mg) or **B** (28.5 mg) or **C** (37 mg). The pressure tube was then sealed and heated at 110 °C for 16 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 4:1), the mixture was diluted with hot ethyl acetate (15 mL) and water (25 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography over silica gel using hexane / ethyl acetate = 4:1 (*v/v*) as an eluent to obtain the desired products **3a**-**t** in high yields.

2-Phenylquinazoline (3a)[30b] (Table 1-2, Scheme 2,5)**:** Yellow solid, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); m.p = 100 - 102 °C (Lit[30b] 100 - 101 °C); ^1H NMR (400 MHz, DMSO-d_6): **δ** = 9.71 (s, 1H; 4-H), 8.57 (d, ^3J = 9 Hz, 2H; 12-H), 8.18 (d, ^3J = 7.96 Hz, 1H; 8-H), 8.08 – 8.02 (m, 2H; 5-H and 7-H), 7.75 (t, ^3J = 7.5 Hz, 1H; 6-H), 7.56 – 7.57 (m, 3H; 13-H, and 14-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) **δ** = 161.08 (C-2), 160.50 (C-4), 150.79 (C-9), 138.06 (C-11), 134.10 (C-7), 130.61 (C-14), 128.67 (C-8), 128.64 (C-13), 128.59 (C-12), 127.27 (C-6), 127.12 (C-5), 123.62 (C-10) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{11}N_2$: 207.0922; found: 207.0917.

2-(Quinazolin-2-yl)phenol (3b)[29d] (Scheme 2,5)**:** Pale **y**ellow solid, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); m.p = 136 - 137 °C (Lit[29d] 135 - 136 °C); ^1H NMR (400 MHz, $CDCl_3$) **δ** = 13.72 (s, 1H; 17-H), 9.47 (s, 1H; 4-H), 8.65 (d, ^3J = 8.4 Hz, 1H; 8-H), 8.01 (d, ^3J = 8.0 Hz, 1H; 16-H), 7.94 - 7.92 (overlapped, 2H; 5-H and 7-H), 7.64 (t, ^3J = 8.0 Hz, 1H; 6-H), 7.43 (t, ^3J = 7.2 Hz, 1H; 14-H), 7.07 (d, ^3J = 8.0 Hz, 1H; 13-H), 7.00 (t, ^3J = 8.0 Hz, 1H; 15-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) **δ** = 161.83 (C-2), 160.89 (C-4), 160.51 (C-2, 148.16 (C-9), 134.98 (C-16), 133.24 (C-7), 129.71 (C-14), 127.56 (C-8), 127.43 (C-5), 127.1 (C-6), 123.05 (C-10), 119.2 (C-15), 119.08 (C-11) 117.88 (C-13) ppm; MS (APCI): $[M + 1]^+$ = 223.1 (85.2%); HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0869.

3,5-Di-tert-butyl-2-(quinazolin-2-yl)phenol (3c) (Scheme 2)**:** Pale **y**ellow solid, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); m.p = 120 - 121 °C;

IR (KBr) v = 3315 (br, OH), 2917(s), 1572 (m C=N), 1348 (s), 1014 (s, C-O), 796 (m), 725 (m) cm^{-1}; ^1H NMR (599 MHz, $CDCl_3$) δ = 9.47 (s, 1H; 4-H), 8.62 (s, 1H; 16-H), 8.02 (d, ^3J = 8.4 Hz, 1H; 8-H), 7.93 – 7.90 (overlapped, 2H; 5-H and 7-H), 7.61 (t, ^3J = 8.0 Hz, 1H; 6-H), 7.51 (s, 1H; 14-H), 1.53 (s, 9H; 21-H), 1.40 (s, 9H; 19-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 178.42 (C-2), 162.70 (C-4), 160.41 (C-12), 158.23 (C-9), 147.73 (C-14), 140.06 (C-15), 134.77 (C-7), 128.18 (C-8), 127.35 (C-6), 127.22 (C-5), 126.86 (C-16), 123.99 (C-10), 122.72 (C-11), 117.99 (C-13), 35.25 (C-20), 34.44 (C-18), 31.62 (C-21), 29.65 (C-19) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{22}H_{27}N_2O$: 335.2123; found: 335.2119.

2-(4-Methoxyphenyl)quinazoline (3d)[29c] (Scheme 2)**:** Pale yellow solid, R_f = 0.63 (SiO_2, Hexane/EtOAc = 4:1); m.p = 89 - 91 °C (Lit[29d] 90 - 91 °C); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.42 (s, 1H; 4-H), 8.58 (d, ^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), 7.58 (d, ^3J = 8.0 Hz, 1H; 6-H), 7.04 (d, ^3J = 8.0 Hz, 2H; 13-H), 3.90 (s, 3H; 15-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.81 (C-2), 160.84 (C-4), 160.36 (C-14), 150.80 (C-9), 134.0 (C-11), 130.68 (C-7), 130.18 (C-12), 128.38 (C-8), 127.10 (C-6), 126.76 (C-5), 123.30 (C-10), 113.95 (C-13), 55.37 (C-15); HRMS (EI, $[M + H]^+$): calculated for $C_{15}H_{13}N_2O$: 237.1027; found: 237.1017.

2-(2,6-Dimethoxyphenyl)quinazoline (3e) (Scheme 2,5)**:** Light yellow solid, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); m.p = 58 - 59 °C; IR (KBr) v = 2921 (m), 1590 (s, C=N), 1149 (s), 1038 (s, C-O), 802 (s), 725 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 9.70 (s, 1H; 4-H), 8.17 (d, ^3J = 7.8 Hz, 1H; 8-H), 8.06 (overlapped, 2H; 5-H and 7-H), 7.75 (3H), 6.69 (1H), 3.86 (s, 6H; 15H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.09 (C-2), 160.69 (C-4), 160.37 (C-12), 150.71 (C-9), 140.14 (C-7), 134.09 (C-14), 128.71 (C-8), 127.35 (C-6), 127.10 (C-5), 123.72 (C-10), 106.24 (C-13), 103.84 (C-11), 55.60 (C-15) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{16}H_{15}N_2O_2$: 267.1134; found: 267.1130.

2-(2-Bromo-4-methylphenyl)quinazoline (3f) (Scheme 2)**:** Yellow solid, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); m.p = 49 - 50 °C; IR (KBr) v = 2930 (m), 1563 (s, C=N), 1287 (m), 799 (s), 769 (s), 729 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.52 (s, 1H; 4-H), 8.13 (d, ^3J = 7.2 Hz, 1H; 8-H), 8.00 – 7.93 (overlapped, 2H; 5-H and 7-H), 7.71 – 7.66 (overlapped, 2H; 6-H and 16-H), 7.57 (s, 1H; 13-H), 7.26 (d, ^3J = 7.9 Hz, 1H; 15-H), 2.41 (s, 3H; 17-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.79 (C-2), 160.15 (C-4), 150.32 (C-9), 140.86 (C-11), 137.26 (C-14), 134.32 (C-13), 134.21 (C-7), 131.57 (C-16), 128.62 (C-15), 128.29 (C-8), 127.92 (C-6), 127.14 (C-5), 123.23 (C-10), 121.69 (C-12), 20.97 (C-17) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{15}H_{12}BrN_2$: 299.0183; found: 299.0179.

2-(4-Methylphenyl)quinazoline (3g)[30b] (Scheme 2)**:** Pale yellow solid, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); m.p = 105 - 107 °C (Lit[30b] 104 - 106 °C); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.45 (s, 1H; 4-H), 8.52 (td, ^3J = 8.0 Hz, 2H; 12-H), 8.09 (d, ^3J = 8.6 Hz, 1H; 8-H), 7.94 – 7.87 (m, 2H; 5-H and 7-H), 7.60 (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 (75 MHz, $CDCl_3$) δ = 161.10 (C-2), 160.40 (C-4), 150.76 (C-9), 140.86 (C-11)135.25 (C-7), 134.02 (C-14), 129.38 (C-8), 128.52 (C-13), 128.50 (C-12), 127.09 (C-6), 127.01 (C-5), 123.49 (C-10), 21.49 (C-15) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{15}H_{13}N_2$: 221.1079; found: 221.1074.

2-(2-Bromophenyl)quinazoline (3h)[29f] (Scheme 2,5): Yellow solid, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); m.p = 71 - 72 °C (Lit[29f] 72 - 74 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 9.53 (s, 1H; 4-H), 8.14 (d, ^3J = 8.4 Hz, 1H; 8-H), 8.02 - 7.95 (overlapped, 2H; 5-H and 7- H), 7.79 (dd, ^4J = 9.6 Hz, 1H; 13H), 7.78 – 7.70 (overlapped, 2H; 6-H and 16-H), 7.46 (t, ^3J = 7.6 Hz, 1H; 14-H), 7.32 (t, ^3J = 8.0 Hz, 1H; 15-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.80 (C-2), 160.24 (C-4), 150.27 (C-9), 140.19 (C-11), 134.42 (C-14), 133.71 (C-13), 131.69 (C-7), 130.41 (C-16), 128.62 (C-15), 128.08 (C-8), 127.48 (C-6), 127.16 (C-5), 123.30 (C-10), 121.94 (C-12) ppm; MS (APCI): $[M + 1]^+$ = 285.00 (99.78%); HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{10}BrN_2$: 285.0027; found: 285.0020.

2-(2-Chlorophenyl)quinazoline (3i)[29f] (Scheme 2,5): Yellow solid, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); m.p = 67 - 68 °C (Lit[29f] 68 - 70 °C); ^1H NMR (400 MHz, DMSO-d_6) δ = 9.74 (s, 1H; 4-H), 8.23 (d, ^3J = 8 Hz, 1H; 8-H), 8.07 (s, 2H; 5-H and 7-H), 7.81 (overlapped, 2H; 13-H and 16-H), 7.62 (d, ^3J = 7 Hz, 1H; 6-H), 7.52 (t, ^3J = 5.36 Hz, 2H; 14-H and 15-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.97 (C-2), 160.24 (C-4), 150.36 (C-9), 138.29 (C-11), 134.39 (C-7), 132.92 (C-12), 131.81 (C-14), 130.55 (C-13), 130.33 (C-16), 128.64 (C-8), 128.06 (C-6), 127.15 (C-5), 126.89 (C-15), 123.28 (C-10) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{10}ClN_2$: 241.0532; found: 241.0528.

2-(4-Chlorophenyl)quinazoline (3j)[29c] (Scheme 2,5): Pale yellow solid, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); m.p = 130 - 132 °C (Lit[29d] 130 - 131 °C); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.46 (s, 1H; 4-H), 8.58 (td, ^3J = 8.0 Hz, 2H; 12-H), 8.08 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.95 - 7.89 (overlapped, 2H; 5-H and 7-H), 7.63 (dt, ^3J = 8.0 Hz, 1H; 6-H), 7.50 (td, ^3J = 8.0 Hz, 2H; 13-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.50 (C-2), 160.03 (C-4), 150.67 (C-9), 136.83 (C-14), 136.48 (C-11), 134.25 (C-7), 129.88 (C-13), 128.80 (C-12), 128.58 (C-8), 127.45 (C-6), 127.13 (C-5), 123.61 (C-10) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{10}ClN_2$: 241.0532; found: 241.0526.

2-(4-Fluorophenyl)quinazoline (3k)[30b] (Scheme 2): White solid, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); m.p = 130 - 132 °C (Lit[30b] 132 - 133 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 9.44 (s, 1H; 4-H), 8.94 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.09 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.75 (d, ^3J = 8.0 Hz, 1H), 7.70 (t, ^3J = 8.0 Hz, 2H), 7.21 (d, ^3J = 8.0 Hz, 2H; 13-H) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0818.

2-(4-(Trifluoromethyl)phenyl)quinazoline (3l)[29f] (Scheme 2,5)**:** Pale yellow solid, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); m.p = 136 - 137 °C (Lit[29f] 135 - 137 °C); ^1H 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 (overlapped, 2H; 5-H and 7-H), 7.62 (d, ^3J = 8.0 Hz, 1H; 6-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.61 (C-2), 159.60 (C-4), 150.65 (C-9), 141.31 (C-11), 134.37 (C-7), 132.27 (q, 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, C-13), 123.84 (C-15) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{15}H_{10}F_3N_2$: 275.0796; found: 275.0786.

Methyl 4-(quinazolin-2-yl)benzoate (3m) (Scheme 2,5)**:** Light brown solid, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); m.p = 120 - 121 °C; IR (KBr) v = 2918 (m), 1719 (s, C=O), 1547 (m, C=N), 1281 (s), 1014 (m, C-O), 768 (s), 710(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.50 (s, 1H; 4-H), 8.70 (d, ^3J = 8.0 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 (overlapped; 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 (101 MHz, $CDCl_3$) δ = 166.96 (C-15), 160.57 (C-2), 160.01 (C-4), 150.68 (C-9), 142.13 (C-11), 134.34 (C-7), 131.70 (C-14), 129.85 (C-12), 128.77 (C-8), 128.49 (C-13), 127.81 (C-6), 127.16 (C-5), 123.76 (C-10) 52.23 (C-16) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0971.

2-(2-Nitrophenyl)quinazoline (3n)[29f] (Scheme 2,5)**:** Yellow solid, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); m.p = 95 - 96 °C (Lit[29f] 93 - 95 °C); ^1H NMR (599 MHz, $CDCl_3$) δ = 9.42 (s, 1H; 4-H), 8.11 (dd, ^3J = 7.7, ^4J = 1.4 Hz, 1H; 8-H), 8.05 (d, ^3J = 8.4 Hz, 1H; 16-H), 7.95 – 7.91 (overlapped, 2H; 13-H and 15-H), 7.87 (d, ^3J = 8.0 Hz, 1H; 14-H), 7.72 – 7.66 (overlapped, 2H; 5-H and 7-H), 7.58 (td, ^3J = 7.8, ^4J = 1.4 Hz, 1H; 6-H)

ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.47 (C-2), 159.63 (C-4), 150.38 (C-12), 149.98 (C-9), 134.53 (C-15), 133.61 (C-16), 132.21 (C-7), 131.80 (C-14), 130.11 (C-8), 128.58 (C-6), 128.27 (C-5), 127.20 (C-11), 124.09 (C-10), 123.44 (C-13) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{10}N_3O_2$: 252.0773; found: 252.0765.

2-(3-Nitrophenyl)quinazoline (3o)[28m] (Scheme 2)**:** Pale yellow solid, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); m.p = 101 - 102 °C (Lit[28m] 103 - 103 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.52 – 9.50 (overlapped, 2H; 4-H and 12-H), 8.99 (dt, ^3J = 7.8, ^4J = 1.4 Hz, 1H; 16-H), 8.36 (ddd, ^3J = 8.2, 2.4, 1.1 Hz 1H; 14-H), 8.14 (d, ^3J = 8.0 Hz, 1H; 8-H), 8.00 – 7.95 (overlapped, 2H; 5-H and 15-H), 7.74 – 7.67 (overlapped, 2H; 6-H and 7-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.72 (C-2), 158.68 (C-4), 150.60 (C-9), 148.84 (C-13), 139.87 (C-16), 134.55 (C-7), 134.19 (C-11), 129.50 (C-15), 128.75 (C-8), 128.06 (C-6), 127.20 (C-5), 124.99 (C-10), 123.94 (C-14), 123.59 (C-12) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{14}H_{10}N_3O_2$: 252.0773; found: 252.0764.

2-([1,1'-Biphenyl]-4-yl)quinazoline (3p)[28k] (Scheme 2,5)**:** White solid, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); m.p = 116 - 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.49 (s, 1H; 4-H), 8.70 (d, ^3J = 8.0 Hz, 2H; 12-H), 8.11 (d, ^3J = 8.0 Hz, 1H; 8-H), 7.96 – 7.91 (overlapped, 2H; 5-H and 7-H), 7.79 (d, ^3J = 8.0 Hz, 2H; 16-H), 7.71 (d, ^3J = 8.0 Hz, 2H; 13-H), 7.63 (t, ^3J = 8.0 Hz, 1H; 6-H), 7.49 (t, ^3J = 8.0 Hz, 2H; 17-H), 7.39 (t, ^3J = 8.0 Hz, 1H; 18-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.85 (C-2), 160.50 (C-4), 150.85 (C-9), 143.27 (C-14), 140.64 (C-15), 137.00 (C-11), 134.14 (C-7), 129.04 (C-17), 128.83 (C-12), 128.66 (C-8), 127.67 (C-6), 127.35 (C-16), 127.25 (C-18), 127.20 (C-13), 127.16 (C-5), 123.64 (C-10) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{20}H_{15}N_2$: 283.1235; found: 283.1231.

2-(Pyridin-4-yl)quinazoline (3q)[29f] (Scheme 2,5)**:** Pale yellow solid, R_f = 0.60 (SiO_2, Hexane/EtOAc = 4:1); m.p = 125 - 127 °C (Lit[29f] 124 - 126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.53 (s, 1H; 4-H), 8.81 (d, *J* = 4 Hz, 2H; 13-H), 8.47 (d, *J* = 4 Hz, 2H; 12-H), 8.15 (d, ^3J = 8 Hz, 1H; 8-H), 8.01 - 7.96 (m, 2H; 5-H and 7-H), 7.75 - 7.69 (m, 1H; 6-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.77 (C-2), 158.94 (C-4), 150.91 (C-13), 150.39 (C-9), 145.40 (C-11), 134.55 (C-7), 128.91 (C-8), 128.34 (C-6), 127.21 (C-5), 124.20 (C-10), 122.40 (C-12) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{13}H_{10}N_3$: 208.0874; found: 208.0864.

2-(Furan-2-yl)quinazoline (3r)[30b] (Scheme 2,5)**:** Pale yellow solid, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); m.p = 126 - 127 °C (Lit[30b] 127 - 129 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.40 (s, 1H; 4-H), 8.11 (d, ^3J = 8 Hz, 1H; 8-H), 7.93 - 7.90 (overlapped, 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 = 8 Hz, 1H; 15-H), 6.63 (s, 1H; 14-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.74 (C-2), 154.09 (C-4), 152.50 (C-11), 150.43 (C-9), 145.35 (C-13), 134.54 (C-7), 128.38 (C-8), 127.29 (C-6), 127.28 (C-5), 123.28 (C-10), 114.12 (C-14), 112.23 (C-15) ppm; HRMS (EI, M^+): calculated for $C_{12}H_9N_2O$: 197.0714; found: 197.0706.

2-(Naphthalen-1-yl)quinazoline (3s)[30b] (Scheme 2,5)**:** Pale yellow solid, R_f = 0.66 (SiO_2, Hexane/EtOAc = 4:1); m.p = 123 - 124 °C (Lit[30b] 124 - 125 °C); ^{1}H NMR (599 MHz, $CDCl_3$) δ = 9.58 (s, 1H; 4-H), 8.69 (d, ^3J = 8.2 Hz, 1H; 18-H), 8.17 (d, ^3J = 7.7 Hz, 2H; 14-H and 15-H), 8.00 – 7.92 (overlapped, 4H; 5-H, 8-H, 12-H and 13-H), 7.68 (t, ^3J = 7.5 Hz, 1H; 7-H), 7.62 (t, ^3J = 7.6 Hz, 1H; 17-H), 7.56 – 7.51 (m, 2H; 6-H and 16-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.42 (C-2), 160.38 (C-4), 150.54 (C-9), 136.23 (C-11), 134.33 (C-20), 134.17 (C-19), 131.20 (C-7), 130.38 (C-8), 129.63 (C-15), 128.64 (C-14), 128.47 (C-5), 127.74 (C-6), 127.13 (C-16), 126.84 (C-17), 125.88 (C-13), 125.28 (C-10), 123.11 (C-12) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{18}H_{13}N_2$: 257.1078; found: 257.1071.

2-(Anthracen-9-yl)quinazoline (3t) (Scheme 2,5)**:** Yellow solid, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); m.p = 112 - 114 °C; IR (KBr) ν = 2920 (w), 1664 (s), 1550 (m, C=N), 1253 (m), 725 (s), 698 (s) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ = 9.69 (s, 1H), 8.99 (d, ^3J = 9.0 Hz, 1H; 8-H), 8.59 (s, 1H; 18-H), 8.19 (d, ^3J = 8.5 Hz, 1H; 5-H), 8.12 (d, ^3J = 8.2 Hz, 1H; 7-H), 8.07 (d, ^3J = 8.6 Hz, 2H; 13-H), 7.80 (t, ^3J = 7.5 Hz, 1H; 6-H), 7.59 (d, ^3J = 9.0 Hz, 2H; 16-H), 7.45 (t, ^3J = 7.6 Hz, 2H; 15-H), 7.36 (t, ^3J = 7.6 Hz, 2H; 14-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.68 (C-2 and C-4), 150.60 (C-9), 134.63 (C-11), 134.12 (C-17), 131.48 (C-7), 129.99 (C-12), 129.15 (C-18), 128.80 (C-6), 128.60 (C-16), 128.30 (C-5), 127.29 (C-8), 126.48 (C-15), 125.71 (C-10), 125.61 (C-14), 125.14 (C-13), ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{22}H_{15}N_2$: 307.1235; found: 307.1152.

2-(Pyren-1-yl)quinazoline (3u) (Scheme 2,5)**:** Yellow solid, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); m.p = 145 - 147 °C; IR (KBr) ν = 3016 (w), 1624 (s, C=N), 1375 (m), 839 (s), 765 (s), 702 (s) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ = 9.68 (s, 1H; 4-H), 9.08 (d, ^3J = 9.3 Hz, 1H; 13-H), 8.73 (d, ^3J = 8.0 Hz, 1H; 18-H), 8.33 (d, ^3J = 7.9 Hz, 1H; 12-H), 8.26 – 8.22 (m, 3H; 8-H, 15-H and 16-H), 8.19 – 8.13 (m, 3H; 19-H, 20-H and 22-H), 8.07 – 8.00 (m, 3H; 5-H, 7-H and 23-H), 7.73 (t, ^3J = 8.1 Hz, 6.7 Hz, 1H; 6-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.65 (C-2), 160.44 (C-4), 150.61 (C-9), 134.52 (C-11), 133.03 (C-14), 132.49 (C-17), 131.30 (C-7), 130.84 (C-13), 129.52 (C-8), 129.06 (C-18), 128.61 (C-6), 128.47 (C-5), 127.85 (C-15 and C-16), 127.43 (C-19), 127.21 (C-22), 126.00 (C-20), 125.58 (C-25), 125.32 (C-21), 125.25 (C-10), 125.18 (C-26), 124.88 (C-12), 124.72 (C-23), 122.93 (C-24) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{24}H_{15}N_2$: 331.1235; found: 331.1228.

(E)-2-Styrylquinazoline (3v)[29c] (Scheme 2,5)**:** White solid, R_f = 0.59 (SiO_2, Hexane/EtOAc = 4:1); m.p = 122 - 123 °C (Lit[29c] 120 - 121 °C); ^{1}H NMR (599 MHz, $CDCl_3$) δ = 9.27 (s, 1H 4-H), 8.06 (d, ^3J = 15.9 Hz, 1H; 11-H), 7.89 (d, ^3J = 8.5 Hz, 1H; 8-H), 7.78 (d, ^3J = 7.5, 1.3 Hz, 2H; 5-H and 7-H), 7.58 (d, ^3J = 7.6 Hz, 2H; 14-H), 7.48 (td, ^3J = 7.5, ^4J = 1.3 Hz, 1H; 6-H), 7.35 – 7.28 (m, 3H; 12-H and 15-H), 7.24 (t, ^3J = 7.3 Hz, 1H; 16-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.25 (C-2), 160.22 (C-4), 150.52 (C-9), 138.58 (C-13), 136.17 (C-12), 134.21 (C-7), 129.04 (C-15), 128.78 (C-14), 128.08 (C-8), 127.85 (C-16), 127.66 (C-6), 127.20 (C-5), 127.13 (C-10), 123.34 (C-11) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{16}H_{13}N_2$: 233.1078; found: 233.1070.

(E)-2-(4-Methoxystyryl)quinazoline (3w) (Scheme 2)**:** White solid, R_f = 0.61 (SiO_2, Hexane/EtOAc = 4:1); m.p = 102 - 103 °C; IR (KBr) ν = 2961 (m), 1584 (m, C=N), 1547 (m, C=C), 1256 (s), 1020 (s, C-O), 966 (s), 825(s), 750 (s) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ = 9.34 (s, 1H; 4-H), 8.11 (d, ^3J = 12.0 Hz, 1H; 11-H), 7.96 (d, 1H; 8-H), 7.86 (d, ^3J = 7.7 Hz, 2H; 6-H and 7-H), 7.61 (d, 2H; 14-H), 7.55 (td, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H; 5-H), 7.28 (d, ^3J = 8.0 Hz, 1H; 12-H), 6.93 (d, ^3J = 8.0 Hz, 2H; 15-H), 3.78 (s, 3H; 17-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.57 (C-2), 159.48 (C-16), 159.19 (C-4), 149.54 (C-9), 137.29 (C-12), 133.17 (C-7), 128.14 (C-14), 127.96 (C-13), 126.94 (C-8), 126.20 (C-6), 125.89 (C-5), 124.57 (C-10), 122.22 (C-11), 113.27 (C-15), 54.33 (C-17) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_{17}H_{15}N_2O$: 263.1184; found: 263.1177.

Quinazoline (3x)[29f] (Scheme 2)**:** White solid, R_f = 0.48 (SiO_2, Hexane/EtOAc = 4:1); m.p = 48 - 49 °C (Lit [29g] 45 - 47 °C); ^{1}H NMR (599 MHz, $CDCl_3$) δ = 9.43 (s, 1H; 4-H), 9.353 (s, 1H; 2-H), 8.07 (d, ^3J = 8.5 Hz, 1H; 8-H), 7.95 (t, ^3J = 7.5 Hz, 2H; 5-H and 7-H), 7.69 (t, ^3J = 7.6 Hz, 1H; 6-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.21 (C-2), 155.21 (C-4), 150.00 (C-9), 134.20 (C-7), 128.40 (C-8), 127.95 (C-6), 127.19(C-5), 125.10 (C-10) ppm; HRMS (EI, $[M + H]^+$): calculated for $C_8H_7N_2$: 131.0609; found: 131.0600.

2-Propylquinazoline (3y)[30b] (Scheme 2)**:** Pale brown liquid, R_f = 0.58 (SiO_2, Hexane/EtOAc = 4:1); b.p = 120 - 122 °C; ^{1}H NMR (599 MHz,

$CDCl_3$) δ = 9.36 (s, 1H; 4-H), 8.00 (d, ^3J = 8.4 Hz, 1H; 8-H), 7.91 – 7.90 (m, 2H; 5-H and 7-H), 7.61 (t, ^3J = 7.5 Hz, 1H; 6-H), 3.11 (t, ^3J = 7.7 Hz, 2H; 11-H), 1.98 – 1.94 (m, 2H; 12-H), 1.05 (t, ^3J = 7.4 Hz, 3H; 13-H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.62 (C-2), 160.39 (C-4), 150.16 (C-9), 134.07 (C-7), 127.78 (C-8), 127.07 (C-6), 126.97 (C-5), 123.04 (C-10), 41.76 (C-11), 22.27 (C-12), 13.96 (C-13) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{11}H_{13}N_2$: 173.1078; found: 173.1076.

6-Methoxy-2-phenylquinazoline (3ba)[28m] (Scheme 3)**:** Colorless solid**,** R_f = 0.63 (SiO_2, Hexane/EtOAc = 4:1); m.p = 118 - 119 °C (Lit[28m] 119 - 121 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.38 (s, 1H; 4-H), 8.57 (d, ^3J = 9 Hz, 2H; 12-H), 8.05 (d, ^3J = 7.96 Hz, 1H; 8-H), 7.58 – 7.46 (m, 4H; 7-H, 13-H and 14-H), 7.16 (d, ^4J = 2.8 Hz, 1H; 5-H), 3.98 (s, 3H; 15-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.37 (C-2), 158.78 (C-4), 158.24 (C-6), 146.98 (C-9), 138.11 (C-11), 130.17 (C-14), 130.11 (C-8), 128.58 (C-13), 128.16 (C-12), 127.19 (C-7), 124.45 (C-10), 103.88 (C-5), 55.72 (C-15) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1021.

6-Methoxy-2-(p-tolyl)quinazoline (3bg)[28m] (Scheme 3): Colorless solid, R_f = 0.62 (SiO_2, Hexane/EtOAc = 4:1); m.p = 140 - 142 °C (Lit[28m] 142 - 143 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.35 (s, 1H; 4-H), 8.47 (d, ^3J = 8 Hz, 2H; 12-H), 7.98 (d, ^3J = 7.96 Hz, 1H; 8-H), 7.54 (dd, ^3J = 7.96 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 (75 MHz, $CDCl_3$) δ = 159.47 (C-2), 158.74 (C-4), 158.07 (C-6), 146.99 (C-9), 140.35 (C-11), 135.38 (C-14), 130.02 (C-8), 129.34 (C-13), 128.10 (C-12), 127.09 (C-7), 124.31 (C-10), 103.91 (C-5), 55.70 (C-15), 21.45 (C-16) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{16}H_{15}N_2O$: 251.1184; found: 251.1180.

2-(4-chlorophenyl)-6-methoxyquinazoline (3bj)[28m] (Scheme 3)**:** Colorless solid, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); m.p = 172 – 173 °C (Lit[28m] 173 - 175 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.30 (s, 1H; 4-H), 8.50 (d, ^3J = 8 Hz, 2H; 12-H), 7.94 (d, ^3J = 7.96 Hz, 1H; 8-H), 7.53 (dd, ^3J = 9.2, 2.7 Hz, 1H; 7-H), 7.46 (d, ^3J = 8 Hz, 2H; 13-H), 7.15 (d, ^4J = 2.8 Hz, 1H; 5-H), 3.94 (s, 3H; 15-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.02 (C-2), 158.61 (C-4), 158.55 (C-6), 147.12 (C-9), 136.91 (C-14), 136.56 (C-11), 130.30 (C-8), 129.74 (C-13), 128.99 (C-12), 127.56 (C-7), 124.74 (C-10), 104.14 (C-5), 55.98 (C-15) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{15}H_{12}ClN_2O$: 271.0638; found: 271.0630.

6,7-Methylenedioxy-2-phenylquinazoline (3ca)[28m] (Scheme 3)**:** Colorless solid, R_f = 0.61 (SiO_2, Hexane/EtOAc = 4:1); m.p = 172 - 173 °C (Lit[28m] 173 - 175 °C); ^{1}H NMR (300 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 (75 MHz, $CDCl_3$) δ = 160.28 (C-2), 157.71 (C-4), 154.38 (C-9), 150.53 (C-7), 148.51 (C-6), 138.41 (C-11), 130.44 (C-14), 128.81 (C-13), 128.43 (C-12), 120.98 (C-10), 105.23 (C-8), 102.43 (C-6), 102.09 (C-15) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{15}H_{11}N_2O_2$: 251.0821; found: 251.0815.

6,7-Methylenedioxy-2-(4-methylphenyl)quinazoline (3cg)[28m] (Scheme 3)**:** Colorless solid, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); m.p = 187 - 188 °C (Lit[28m] 187 - 189 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.12 (s, 1H; 4-H), 8.42 (d, ^3J = 9 Hz, 2H; 12-H), 7.32 – 7.30 (overlapped, 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 (75 MHz, $CDCl_3$) δ = 160.36 (C-2), 157.66 (C-4), 154.29 (C-9), 150.53 (C-7), 148.32 (C-6), 140.60 (C-11), 135.69 (C-14), 129.57 (C-13), 128.37 (C-12), 120.82 (C-10), 105.16 (C-8), 102.38 (C-6), 102.10 (C-15), 21.74 (C-16) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{16}H_{13}N_2O_2$: 265.0927; found: 265.0923.

6,7-Methylenedioxy-2-(4-chlorophenyl)quinazoline (3cj)[28m] (Scheme 3)**:** Colorless solid, R_f = 0.65 (SiO_2, Hexane/EtOAc = 4:1); m.p = 223 - 225 °C (Lit[28m] 224 - 226 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.14 (s, 1H; 4-H), 8.48 (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 (75 MHz, $CDCl_3$) δ = 159.29 (C-2), 157.72 (C-4), 154.52 (C-9), 150.50 (C-7), 148.69 (C-6), 136.92 (C-14), 136.61 (C-11), 129.76 (C-13), 128.98 (C-12), 121.06 (C-10), 105.19 (C-8), 102.51 (C-6), 102.13 (C-15) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{15}H_{10}ClN_2O_2$: 285.0431; found: 285.0423.

6-Fluoro-2-phenylquinazoline (3da)[28m] (Scheme 3)**:** (Scheme 3) Colorless solid, R_f = 0.66 (SiO_2, Hexane/EtOAc = 4:1); m.p = 138 - 140 °C (Lit [28m] 140 - 141 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.44 (s, 1H; 4-H), 8.59 (dd, ^3J = 9 Hz, 2H; 12-H), 8.11 (dd, ^3J = 9.3, 5.0 Hz, 1H; 8-H), 7.68 (td, ^3J = 8.8, 2.8 Hz, 1H; 7-H), 7.57 – 7.50 (m, 4H; 5-H, 13-H and 14-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.35 (C-4), 160.08 (d, J = 250 Hz, C-6), 159.01 (C-4), 148.21 (C-9), 137.97 (C-11), 131.71 (d, J = 35 Hz, C-8), 130.95 (C-14), 128.93 (C-13), 128.71 (C-12), 124.96 (d, J = 104.2 Hz, C-7), 124.24 (d, J = 38.2 Hz, C-10), 110.25 (d, J = 88 Hz, C-5) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{14}H_{10}FN_2$: 225.0828; found: 225.0819.

2-(4-chlorophenyl)-6-fluoroquinazoline (3dj)[28m] (Scheme 3)**:** Colorless solid, R_f = 0.64 (SiO_2, Hexane/EtOAc = 4:1); m.p = 187 - 188 °C (Lit[28m] 185 - 187 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.44 (s, 1H; 4-H), 8.57 (dd, ^3J = 9 Hz, 2H; 12-H), 8.11 (dd, ^3J = 9.3, 5.0 Hz, 1H; 8-H), 7.68 (td, ^3J = 8.8, 2.8 Hz, 1H; 7-H), 7.59 – 7.50 (overlapped, 3H; 5-H and 13-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.43 (C-4), 160.11 (d, J = 250 Hz, C-6), 159.1 (C-4), 148.11 (C-9), 137.18 (C-11), 136.45 (C-14), 131.67 (d, J = 34 Hz, C-8), 128.93 (C-13), 128.71 (C-12), 125.11 (d, J = 103.4 Hz, C-7), 124.27 (d, J = 37.8 Hz, C-10), 110.59 (d, J = 87 Hz, C-5) ppm; HRMS (EI, [M + H]$^+$): calculated for $C_{14}H_9ClFN_2$: 259.0438; found: 259.0433.

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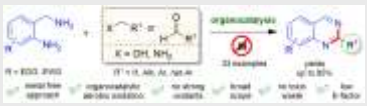

A convenient approach towards synthesis of 2-substituted quinazolines is described using organocatalytic domino reaction. Under the developed conditions a broad range of substrates were explored to afford the desired products in high yields.

*Organocatalysis, Domino cyclization

N-Heterocycles*

*Raghuram Gujjarappa, Suvik K. Maity, Chinmoy K. Hazra, Nagaraju Vodnala, Shiv Dhiman, Anil Kumar, Uwe Beifuss, Chandi C. Malakar**

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Divergent Synthesis of Quinazolines using Organocatalytic Domino Strategies under Aerobic Conditions