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Nickel-Catalyzed Aerobic Oxidative Isocyanide Insertion: Access to Benzimidazoquinazoline Derivatives *via* Sequential Double Annulation Cascade (SDAC) strategy

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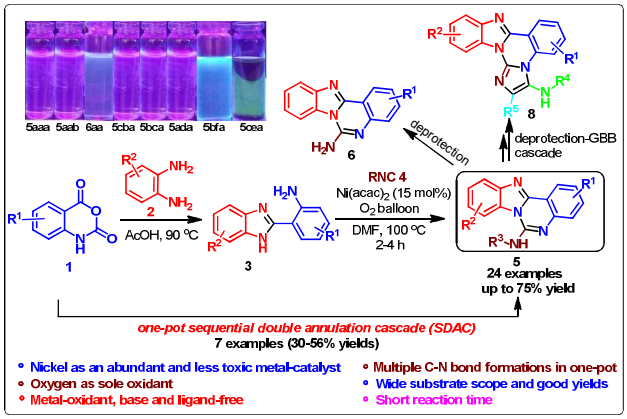


Abstract: An efficient protocol for the synthesis of quinazoline derivatives through nickel-catalyzed ligand/base-free oxidative isocyanide insertion under aerobic conditions with intramolecular bis-amine nucleophiles has been developed. A one-pot sequential double annulation cascade (SDAC) strategy involving an opening of isatoic anhydride and annulation to benzimidazole and further nickel-catalyzed intramolecular isocyanide insertion has also been demonstrated. The method is operationally simple to implement with wide substrates and represents a new approach for multiple C-N bond formations. The methodology has been successfully applied for the syntheses of hitherto unreported imidazo fused benzimidazoquinazoline *via* deprotection-GBB reaction sequence. Further, the florescence study reveals the potential of the present strategy for discovery of highly fluorescent probes.

Introduction

Transition metal catalyzed C-hetero bond formation *via* CH/NH functionalization has attracted much attention compared to traditional methods for heterocyclic synthesis as it provides a direct and atom economical synthetic strategy to structurally diverse and complex molecules from simple substrate.[1] The development of new chemical approaches for in situ generation of template/substrate for rapid and straightforward access to structurally complex molecules *via* CH/XH functionalization under eco-benign conditions is one of the prime focuses in contemporary science. Directing group approaches have achieved much progress in CH/NH functionalization. To overcome the drawbacks of directing group approaches such as prefunctionalization, removal of directing group, various other alternative approaches such as cross-dehydrogenative coupling (CDC),[2] metal-free redox-neutral,[3] non-directed CH bond activation[4] and direct atom insertion strategies[5] have been explored. Among the various atom insertions[5] such as nitrogen, carbon and sulphur, the carbon insertion using isocyanide is in limelight. In contrast to reaction using other CO surrogates, isocyanide insertion offers functionally diverse molecules by providing extra nitrogen functionality which could be diversified further and might also result in improved activity as pharmaceuticals.

In the past decades, precious late transition metals, for example, palladium, ruthenium, rhenium and iridium catalysts have been shown to be effective catalytic systems for CH or XH activation. However, cost and toxicity of these noble metals limit their practical applications. Owing to this, the development of new catalytic routes by switching to non-precious metals such as nickel/cobalt has become a challenging and active area of research, and drastic shift is taking place in industrial process from precious to non-precious transition metals.[6] Especially, nickel continued to shine by carrying out a broader array of reactions, and has proved to play key role to facilitate highly efficient transformations through C-H activation.[6a-c,7]

Several transition metals such as palladium, cobalt, and Lewis acid catalyzed isocyanide insertion reactions have been reported which use various kinds of bisnucleophiles either in inter or intramolecular

fashion.[8] However, nickel catalyzed isocyanide insertions are in their infancy.[9] Among various intramolecular isocyanide insertions leading to heteroannulations, isocyanide insertion in NH bond is unique as it provides a useful and convenient tool for the construction of *N*-heterocycles.

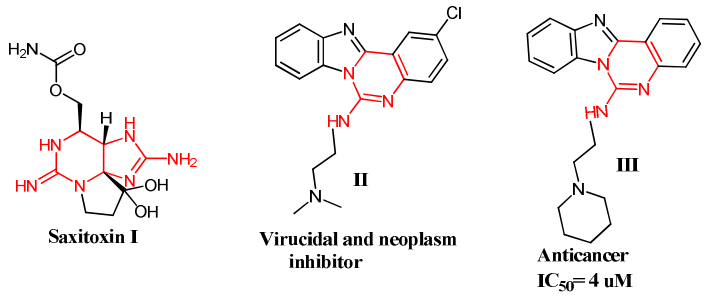


Figure 1. Cyclic guanidine containing alkaloid (I) and cyclic guanidine containing bioactive benzimidazoquinazoline skeletons (II and III).

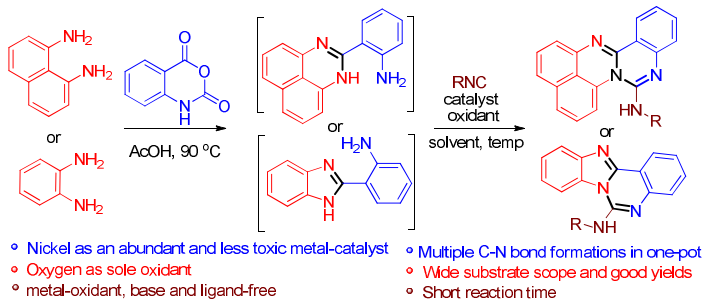
Aza-heterocyclic compounds[10] especially cyclic guanidine containing compounds have attracted considerable interest due to its wide variety of biological activities.[11] As a result, molecules containing this structural motif have recently emerged as important pharmacophores in biomedical research. The cyclic guanidine containing alkaloid Saxitoxin **I** (Fig 1) is a potent neurotoxin and sodium channel blocker.[12] Moreover, cyclic guanidines have also been employed as synthetically useful organocatalysts and reagents in organic synthesis.[13] Quinazoline containing cyclic guanidines such as **II** and **III** (Fig 1) are highly potent virucidal and neoplasm inhibitors and are found to be active against breast cancer.[14]

Cyclic guanidine is typically synthesized from acyclic precursor or guanidinylation of amine. The literature reveals several traditional approaches including the coupling of 2-aminophenylbenzimidazole with cyanogen bromide or alkyl nitrile,[15] low valent titanium catalyzed reaction,[16] and copper catalyzed cascade.[17] On the other hand, the strategies involving isocyanide insertion under transition metal catalysis have also been reported.[18] However, most precedents still rely on ligands as well as stoichiometric metal oxidants and bases, which limits its use in organic synthesis. Although oxidants such as $Cu(OAc)_2$, AgOAc, $K_2S_2O_8$ etc. have been proven to be excellent and practical, dioxygen is an ideal oxidant which offers attractive industrial prospects in terms of green and sustainable chemistry.[19] These reported

protocols also suffer from several drawbacks such as limited substrate scope, multistep processes and poorly available starting materials. On the other hand, amine substrates could poison catalytic activity of the metals by forming stable complexes, which in turn makes C-N bond formation reactions challenging and achieving such transformations in one-pot efficiently from simple substrate is even most challenging due to the compatibility issues with further sensitive catalytic processes, which are inevitable to carry out these cascade reactions.

In continuation of our research interest in annulation cascade strategies[20a,20b] and transition metal catalyzed isocyanide insertion,[20c, 20d] herein, we report for the first time a novel SDAC strategy involving nickel-catalyzed metal-oxidant and base-free isocyanide insertion between NH/NH under aerobic conditions for the synthesis of benzimidazoquinazoline derivatives from isatoic anhydride in one-pot fashion (Scheme 1).

Scheme 1. Designed SDAC strategy involving nickel-catalyzed isocyanide insertion between active NH bonds.

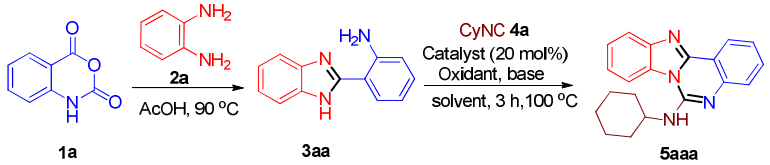


Results and Discussion:

We initiated our study by investigating the isocyanide insertion reaction into the 2-aminophenylbenzimidazole **3aa** system. It is noted that there was no product formation in absence of the catalyst and oxidant (Table 1, entry 1). When the model reaction was performed in the presence of $NiCl_2.6H_2O$ as catalyst, $K_2S_2O_8$ as oxidant and Na_2CO_3 as base in DMF solvent, afforded the desired product **5aab** albeit in 42% yield and little improvement was observed in presence of anhydrous $NiCl_2$ (Table 1, entries 2 and 3). But, unfortunately reaction under $Ni(ClO_4)_2$, $Ni(C_2O_4)$ as catalyst or with

change of base as NaOAc as well could not improve the yield (Table 1, entries 4-6). When we used peroxide based oxidants, there was improvement in yield as well as reaction profile especially with DTPB as oxidant (Table 1, entries 7 and 8). To our delight, the reaction under dioxygen as sole oxidant gave the product in much better yield (55%) (Table 1, entry 9). To our surprise the reaction under $Ni(acac)_2$ catalysis under aerobic conditions gave the product in 61% yield (Table 1, entry 10).

Table 1. Screening of reaction conditions for Ni-catalysed isocyanide insertion 5aaa [a]

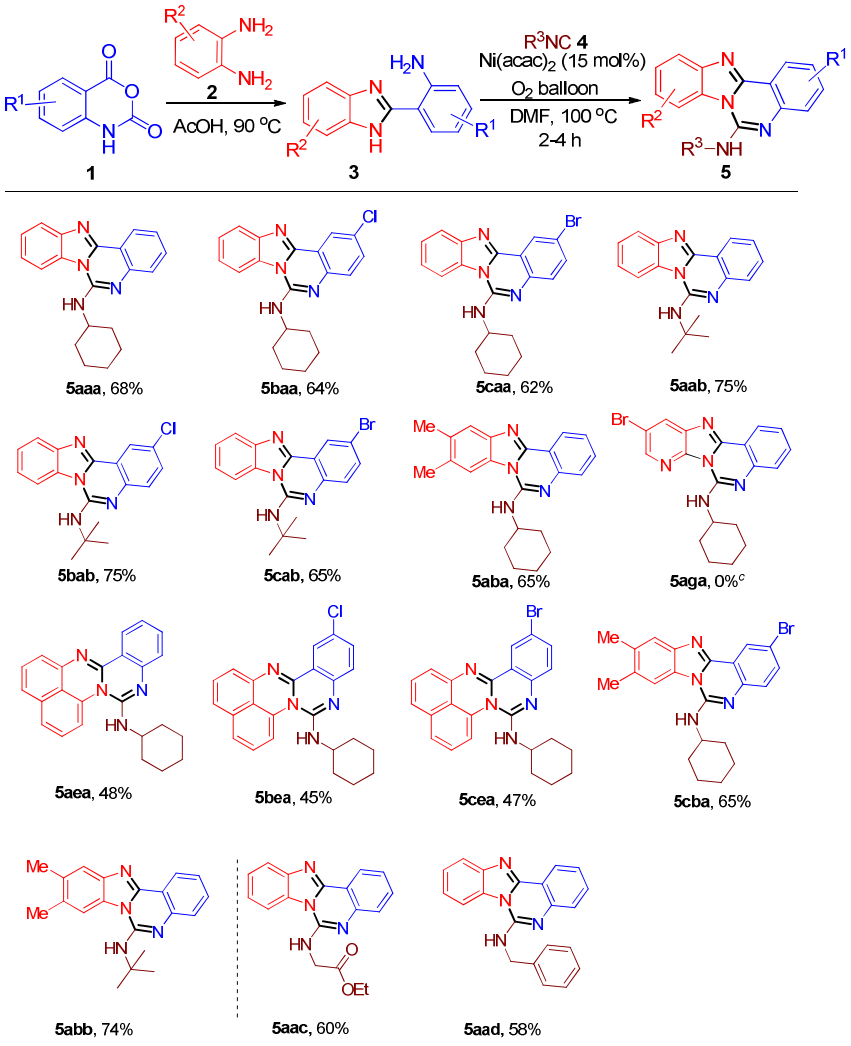


Entry	Catalyst	Oxidant	Base	Solvent	Yield (%)[b]
1[c]	-	-	Na_2CO_3	DMF	trace
2	$NiCl_2.6H_2O$	$K_2S_2O_8$	Na_2CO_3	DMF	42
3	$NiCl_2$	$K_2S_2O_8$	Na_2CO_3	DMF	45
4	$Ni(ClO_4)_2$	$K_2S_2O_8$	Na_2CO_3	DMF	5
5	$Ni(C_2O_4)$	$K_2S_2O_8$	Na_2CO_3	DMF	trace
6	$NiCl_2$	$K_2S_2O_8$	NaOAc	DMF	42
7	$NiCl_2$	DTPB	Na_2CO_3	DMF	49
8	$NiCl_2$	TBPB	Na_2CO_3	DMF	40
9	$NiCl_2$	O_2	Na_2CO_3	DMF	55
10	$Ni(acac)_2$	O_2	Na_2CO_3	DMF	61
11	$Ni(acac)_2$	O_2	Na_2CO_3	Toluene	0
12	$Ni(acac)_2$	O_2	Na_2CO_3	DCE	30
13	$Ni(acac)_2$	O_2	Na_2CO_3	MeCN	20
14	$Ni(acac)_2$	O_2	Na_2CO_3	H_2O	trace
15	$Ni(acac)_2$	O_2	Na_2CO_3	DMF:H_2O	trace
16	$Ni(acac)_2$	O_2	Na_2CO_3	DMSO	30
17	$Ni(acac)_2$	O_2	-	DMF	65
18[d]	**$Ni(acac)_2$**	**O_2**	**-**	**DMF**	**68**
19[e,f]	$Ni(acac)_2$	O_2	-	DMF	60
20[d]	$Ni(acac)_2$	-	-	DMF	0
21[g]	$Ni(acac)_2$	O_2	-	DMF	60
22[h]	$Ni(acac)_2$	O_2	-	DMF	58

a) *General conditions:* amine **3aa** (0.2 mmol), CyNC **4a** (0.2 mmol), catalyst (20 mol%), base (1.5 equiv.), oxidant (1.5 equiv.), and solvent (2 mL); b) Isolated yields; c) Without catalyst/oxidant; d) 15 mol% of $Ni(acac)_2$; e) 10 mol% of $Ni(acac)_2$; f) Reaction time = 8 h; g) Reaction temperature = 120 °C; h) Reaction temperature = 80 °C; DTPB= di-*tert*-butylperoxide; TBPB= *tert*-butylperoxybenzoate; For compound **5aaa** first letter refers to isatoic anhydride part **1a**, second letter refers to diamine part **2a** and third letter refers to part coming from isocyanide **4a**.

Further, reaction under various solvents such as toluene, DCE, acetonitrile, water and DMSO was unsatisfactory (Table 1, entries 11-16). When we tested the reaction under base-free condition, resulted in comparable yield of the product (65%) (Table 1, entry 17). Further, when we tested the effect of varied catalyst loading (Table 1, entries 18 and 19), we found 15 mol% of $Ni(acac)_2$ led to the best yield (68%) of the product efficiently (Table 1, entry 18). For understanding the role of oxidant, when we performed

Table 2. Scope of diamines 2 and Isocyanides 4 for the synthesis of quinazolines 5 [a,b]



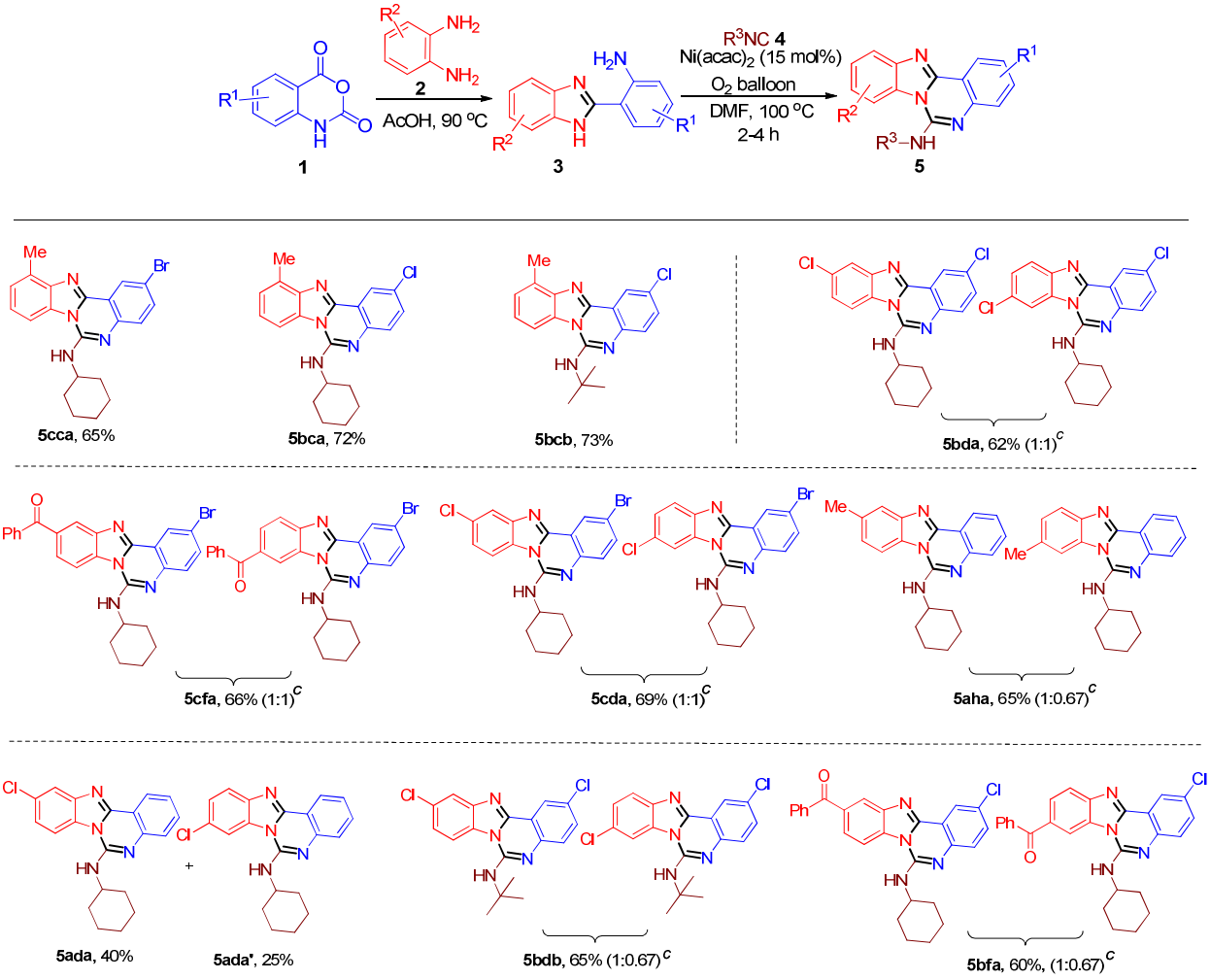
a) *General conditions:* Amine **3** (0.2 mmol), isocyanide **4** (0.2 mmol), $Ni(acac)_2$ (15 mol%), O_2 balloon, and DMF (2 mL); b) Isolated yields after column chromatography; c) Failed to give the intermediate **3ag**; For compound **5** first letter refers to isatoic anhydride part **1a-1c**, second letter refers to diamine part **2a-2g** and third letter refers to part coming from isocyanides **4a-4d**.

the reaction using $Ni(acac)_2$ in absence of oxidant, there was no progress in the reaction and 90% of the starting material was recovered suggesting that the oxygen is essential for the present transformation (Table 1, entry 20). The reaction under varying temperature could not able to improve the yield further (Table 1, entries 21 and 22). So we chose the 15 mol% of $Ni(acac)_2$ as catalyst and dioxygen as oxidant in DMF solvent as optimum condition for further study.

After having the optimized conditions in hand, we turned our attention to explore the scope of the present methodology with respect to *o*-phenylenediamines **2** and variety of isocyanides **4**. We have successfully extended the methodology to various electron donating as well as electron withdrawing *o*-phenylenediamines **2** and 1^o, 2^o and 3^o isocyanides (Table 2). When we have used the neutral unsubstituted *o*-phenylenediamine **2a** for the Ni-catalyzed isocyanide insertion it resulted in products with good to high yields (Table 2, entries **5aaa-5cab**). The donating dimethyl substituted *o*-phenylenediamine **2b** provided the desired products in high yields (Table 2, entries **5aba**, **5abb** and **5cba**). Interestingly, 1,8 diaminonaphthalene **2e** as an amine variant gave the products in moderate yields demonstrating the diversity of our methodology (Table 2, entries **5aea**, **5bea** and **5cea**). However, 2-bromo-2,3-diaminopyridine **2g** failed to give the desired product, which might be due to the side reactions involving pyridinium complex (Table 2, entry **5aga**). In general, both the 2^o cyclohexyl and 3^o *t*-butyl isocyanides worked well and provided the desired products in moderate to good yields (Table 2, entries **5aaa-5abb**). Our further motto to introduce different 1^o isocyanides such as ethylisocyanoacetate **4c** and benzylisocyanide **4d** was successful resulting in the desired products with moderate to good yields (Table 2, entries **5aac** and **5aad**).

When the application of this methodology is considered for the synthesis of quinazoline **5**, potential regioselectivity issues exist in case of unsymmetrically substituted *o*-phenylenediamines. Consequently, various unsymmetrically substituted *o*-phenylenediamines **2** were used to investigate the regioselectivity of the process (Table 3). When electron donating methyl substituted *o*-phenylenediamine was treated with chloro or bromo substituted isatoic anhydrides **1**, to our surprise gave the desired products as a single

Table 3. Regioselectivity in Ni-catalyzed isocyanide insertion and scope of isatoic anhydrides 1 and *o*-phenylenediamines 2 for the synthesis of quinazolines 5 [a,b]



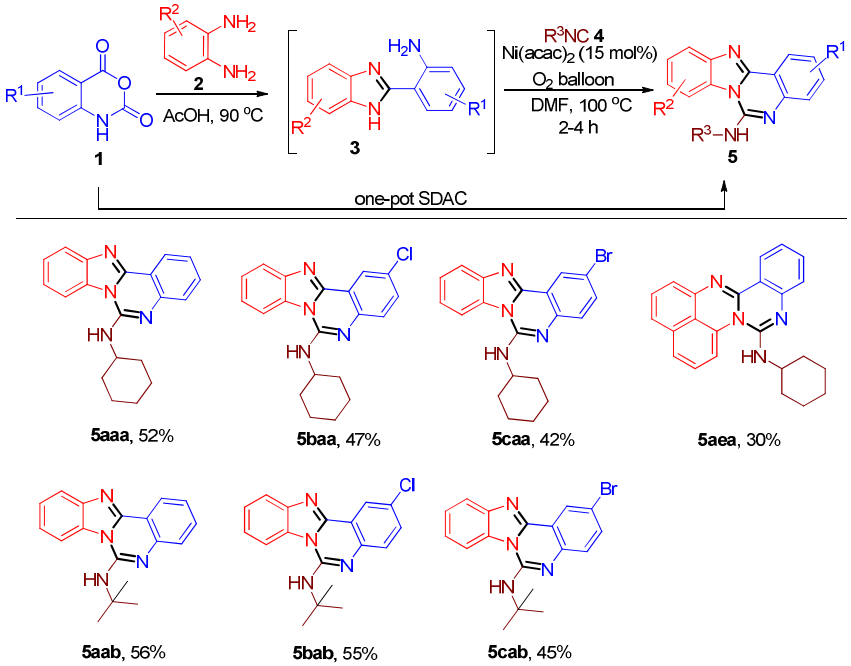
a) *General conditions:* Amine **3** (0. 2 mmol), isocyanide **4** (0.2 mmol), $Ni(acac)_2$ (15 mol%), O_2 balloon, and DMF (2mL); b) Isolated yields after column chromatography; c) Ratio was determined by NMR spectroscopy; For compound **5** first letter refers to isatoic anhydride part **1a-1c**, second letter refers to diamine part **2a-2h** and third letter refers to part coming from isocyanides **4a, 4b**.

regioisomer with good yields (Table 3, entries **5cca-5bcb**). However, *o*-phenylenediamines such as **2d** and **2f** with electron withdrawing group at 4-position provided the unisolable mixture of regioisomers (1:1) (Table 3, entries **5bda**, **5cfa** and **5cda**) in good yields. A satisfactory improvement in regioselectivity was observed in case of **5aha**, **5bdb** and **5bfa**, which gave the desired products with good

yields however as inseparable regioisomeric mixture (1:0.67) (Table 3, entries **5aha**, **5bdb** and **5bfa**). The isolable mixture of regioisomer was observed in case of **5ada** and **5ada'** which gave the product in overall 57% yield. The structure of the isomers **5ada** and **5ada'** was assigned by NOE experiments. The observed high regioselectivity in case of methyl substituted *o*-phenylenediamine **2c** might be due to the ortho-substituent effect leading to predominant existence of single tautomer. The structures of the products were confirmed by spectral analyses and X-ray crystal structure analysis of one of the compounds **5abb** (see the SI† for X-ray data of **5abb**).

After having successfully developed the methodology, we were keen to examine the feasibility of a sequential double annulation cascade (SDAC) protocol for the synthesis of quinazolines **5** directly from

Table 4. One-pot synthesis of quinazolines 5 *via* sequential double annulation cascade (SDAC) strategy [a,b]

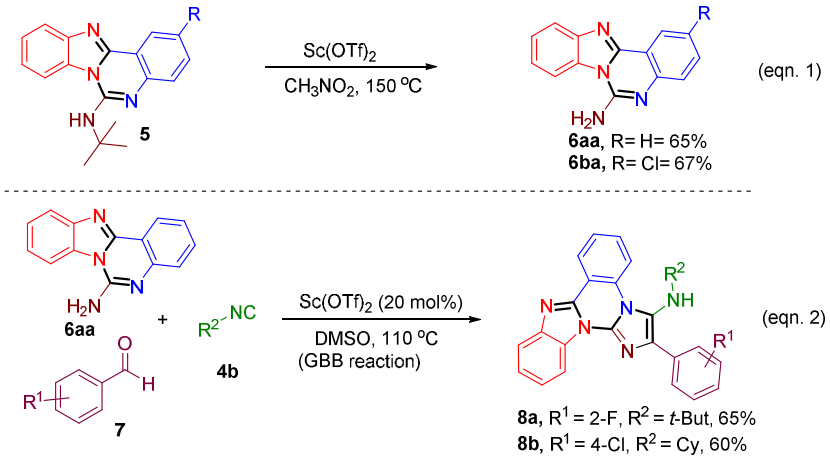


a) *General conditions:* Isatoic anhydride **1** (0.25 mmol), *o*-phenylenediamine **2** (0.25 mmol), amine **3** (0. 0.25 mmol), isocyanide **4** (0.25 mmol), $Ni(acac)_2$ (15 mol%), O_2 balloon, and DMF (2 mL); b) Isolated yields after column chromatography; For compound **5** first letter refers to isatoic anhydride part **1a-1c**, second letter refers to diamine part **2a, 2e** and third letter refers to part coming from isocyanides **4a, 4b**.

isatoic anhydride **1** and *o*-phenylenediamine **2** involving opening-cyclization of isatoic anhydride and Ni-catalyzed isocyanide insertion. To our delight, this one-pot sequence has resulted in desired product with moderate to good yield (30-56%, Table 4, entries **5aaa-5cab**).

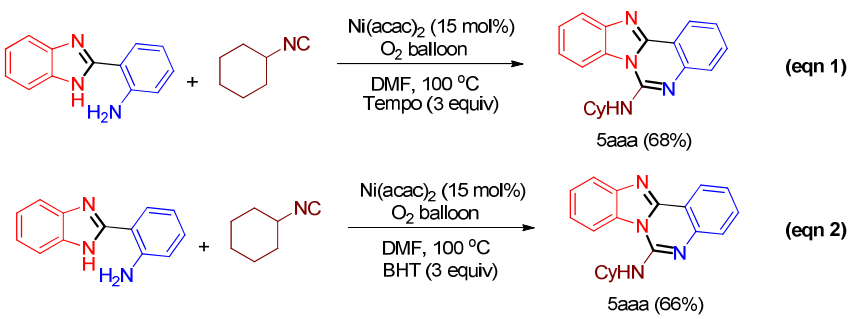
Next, to illustrate the synthetic viability of our methodology, we converted the quinazoline **5** into free aminoquinazoline **6aa** and **6ba** in good yields *via* scandium triflate mediated *tert*-butyl deprotection reaction (Scheme 2, eqn 1).[21] These resulting compounds with aminoazine moiety could be suitable substrate for many of the organic transformations. We have accordingly demonstrated the synthetic utility of one of the aminoazines **6aa** by employing in Groebke-Blackburn-Bienayme (GBB) reaction[22] to provide interesting hitherto unreported imidazo fused pentacyclic scaffolds **8a** and **8b** in good yields under scandium triflate catalysis (Scheme 2, eqn 2).[23] This isatoic opening-cyclization and Ni-catalysed isocyanide insertion (SDAC) protocol/t-butyl deprotection/GBB reaction approach can be systematically used for the synthesis of library of privileged benzimidazoquinazoline fused imidazole hybrids **8** for the biological screening in four-step reaction sequence.

Scheme 2. Synthetic applicability of products generated through Ni-catalyzed isocyanide insertion.



To gain some insights into the reaction mechanism, radical trapping experiments were carried out. The commonly used radical scavengers such as TEMPO and BHT were introduced into the standard reaction system to trap possible radical intermediates. Interestingly, the desired products could still be obtained in 66% and 68% yields respectively (Scheme 3), thus, implicating the ionic mechanism.

Scheme 3. TEMPO and BHT trapping experiments.



Based on the literature reports,[18] and TEMPO/ BHT trapping experiments, a plausible ionic mechanism is proposed in Figure 2 in two possible pathways. Path **I** consists of the Ni(II) salt reacting with isocyanide **4** to furnish complex **A**. Then, **3aa** adds to give nickel(II) complex **B** (Figure 2, path I). The other possible pathway for the formation of **B** involves a direct reaction of Ni(II) salt with **3aa** to give nickel(II) complex **D** (Figure 2, path **II**), which on further isocyanide insertion forms complex **B**. Further, complex **B** undergoes aerobic oxidation to provide nickel (III) complex **C**, which on reductive elimination affords the desired product **5** with further regeneration of Ni(II) catalyst *via* aerobic oxidation to complete the catalytic cycle.

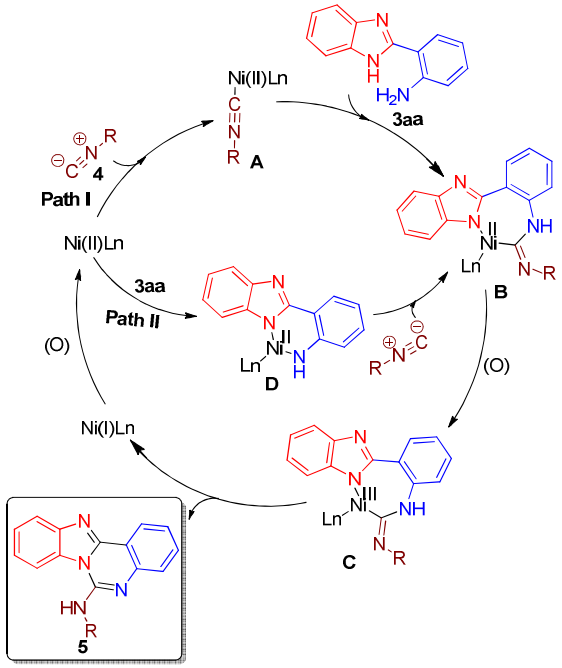


Figure 2. Plausible reaction mechanism for the formation of benzimidazoquinazoline 5.

After having developed the strategy, we were keen to study the fluorescent properties of the synthesized molecules. The absorption and fluorescent spectra of chosen molecules were measured in DCM as shown in Table 5 and Figure 3. Initially, when the parent compounds **5aaa** and **5aab** were measured, there was only 2 nm change by changing the substituent on nitrogen (Tabel 5, entries 1 and 2). However, in comparison to **5aab**, a longer wavelength of the absorption maximum peak (λ_{max}) was obtained in case of free amine compound **6aa** (Tabel 5, entry 3); as well a longer wavelength was obtained when there was substituent over phenyl rings of benzimidazoquinazoline moiety irrespective of donating or withdrawing groups (Tabel 5, entries 4-7). The napthalene fused quinazoline compound **5cea** gave a shorter wavelength of the absorption maximum peak (λ_{max}), however, it showed the stronger yellow fluorescence among all at 532 (λ_{em}) (Tabel 5, entry 8). The compounds **6aa** and **5bfa** showed green-blue fluorescence, while compounds **5aaa**, **5aab** and **5cba-5ada** showed blue fluorescence. The withdrawing phenoxy substituted compound **5bfa** showed the higher fluorescence emission at 445 (λ_{em}) (Tabel 5, entry 7). The compounds **5aaa**-**5ada** showed the fluorescence emission in the range of 381-407 (λ_{em}) (Tabel 5, entries 1-6). Overall, fluorescence study showed that the electron withdrawing groups on benzimidazole and *t*-butyl substituent on amine increases the fluorescence properties of the molecule.

Table 5. Photophysical properties of benzimidazoquinazoline 5.

entry	compd	λ_{max} (nm)[ε (M^{-1} cm^{-1})]^{a}	λ_{em} (nm)^{a,b}
1	**5aaa**	271 [3115]	388
2	**5aab**	273 [3263]	407
3	**6aa**	284 [1294]	381
4	**5cba**	284 [3389]	401
5	**5bca**	283 [1320]	400
6	**5ada**	284 [1295]	393
7	**5bfa**	284 [1288]	445
8	**5cea**	242 [2516]	532

a) Concentration:1x10^{-3} M in DCM; b) Excited at 285 nm.

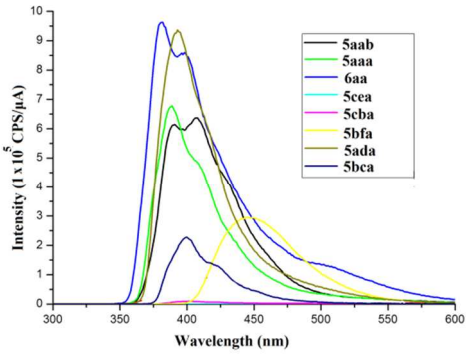


Figure 3. Fluorescence spectra of the compounds 5 recorded in DCM.

In conclusion, we have developed a novel and highly efficient sequential double annulation cascade (SDAC) protocol involving isatoic anhydride opening-cyclization and $Ni(acac)_2$ catalyzed isocyanide insertion for the synthesis of complex and diverse benzimidazoquinazoline **5**. The use of dioxygen as sole oxidant, and base/ligand-free features make this strategy unique. The diverse potential of the present SDAC strategy has been demonstrated by synthesizing naphthalene fused quinazoline compounds. The utility of the present SDAC is showed by synthesizing privileged benzimidazoquinazoline fused imidazole hybrids through GBB reaction and which can be further utilized for synthesizing a library of compounds for biological screening. The present SDAC technique shows wide substrate scope with moderate to good yields. The salient features of this method are formation of four new C-N bonds in one-pot, rapid access to biologically relevant heterocyclic scaffolds, short reaction time, high bond forming index (BFI), and the use of inexpensive, readily available starting materials. The UV-Visible and fluorescence studies reveal the possible application for the discovery of highly fluorescent probes. Further, studies on nickel-catalyzed isocyanide insertion and exploration of SDAC strategy are currently under way.

Experimental Section

General Considerations

In this section the preparations of all the compounds that have been made in the course have been discussed. For the experiments, all starting material and reagents are purchased from standard

commercial sources or were prepared in laboratory. All the glassware was cleaned with soap water followed by acetone and dried in hot air oven at 100 ˚C for 2h. Solvents were distilled prior to use.

IR spectra were recorded on the FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295K in $CDCl_3$ or DMSO d_6; chemical shifts value (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either tetramethylsilane (TMS) (δ-H = 0.00 ppm) or $CHCl_3$ (δ-H = 7.26 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at 298K in $CDCl_3$ or DMSO d_6; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [(δ-C = 77.00 ppm) central line of triplet] or DMSO [(δ-C = 39.52 ppm) central line of septet]. In ^{13}C NMR the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT- 135 spectra. In ^{1}H NMR, the following abbreviations were used throughout the experimental; s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet. The assignment of the signals was confirmed by ^{1}H, ^{13}C and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents.

(I) General Procedure 1: Synthesis of 2-aminophenylbenzimidazoles 3 *via* opening of isatoic anhydride with diamines 2.

To the mixture of isatoic anhydride **1** (1 mmol) and diamine **2** (1 mmol) was added glacial acetic acid (2 mL) and stirred at 90 ^{o}C for 1-3 h and monitored by TLC. After completion of the reaction the acetic acid was evaporated. The reaction mixture was quenched with saturated solution of $NaHCO_3$, extracted with ethyl acetate (2 X 20 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated and then purified by silica gel column chromatography using ethyl acetate and hexane (15:85) as eluents to afford the corresponding product **3**. The compounds (**3aa-3ad**) are already known in the literature and compounds (**3ca-3bf**) are newly synthesized according to general procedure 1.

(II) Spectral data for the 2-aminopheylbenzimidazole compounds 3ca-3bf:

2-(1H-Benzo[d]imidazol-2-yl)-4-bromoaniline **(3ca):** Following the general procedure 1, **3ca** was isolated as a colorless solid; Yield: 207 mg (72%); mp 184-186 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3186, 2973, 2926, 1610, 1527, 1451, 1283, 811, 732 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 6.83 (d, *J* = 8.80 Hz, 1H), 7.20 - 7.31 (m, 3H), 7.60 (dd, *J* = 5.62 and 3.18 Hz, 2H), 8.05 (d, *J* = 2.45 Hz, 1H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm = 105.4, 111.7, 118.1, 122.2, 129.1, 132.7, 147.3, 151.0; HR-MS (ESI+) *m/z* calculated for $C_{13}H_{10}BrN_3^+$ [M + H$^+$]: 288.0131; found: 288.0135.

2-(1H-Perimidin-2-yl)aniline **(3ae):** Following the general procedure 1, **3ae** was isolated as a yellow solid; Yield: 168 mg (65%); mp 138-140 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3399, 3271, 3046, 1616, 1592, 1370, 1260, 821, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 5.87 (br. s., 1H), 6.46 (br. s., 2H), 6.63 - 6.70 (m, 2H), 7.02 - 7.19 (m, 6H), 7.27 - 7.30 (m, 1H) ;^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 115.3, 117.1, 117.5, 119.6, 121.2, 126.1, 128.3, 131.7, 135.3, 147.9, 153.1; HR-MS (ESI+) *m/z* calculated for $C_{17}H_{14}N_3^+$ [M + H$^+$]: 260.1182; found: 260.1185.

4-Chloro-2-(1H-perimidin-2-yl)aniline **(3be):** Following the general procedure 1, **3be** was isolated as a orange solid; Yield: 176 mg (60%); mp 144-146 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3398, 3286, 3048, 1632, 1593, 1489, 1371, 1256, 820, 767 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 5.91 (br. s., 2H), 6.64 (d, 8.8 Hz, 2H), 7.07 - 7.14 (m, 6H), 7.28 (d, 2.4 Hz, 2H) ;^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 116.1, 118.6, 121.2, 121.4, 125.6, 131.5, 135.3, 146.5, 152.0; HR-MS (ESI+) *m/z* calculated for $C_{17}H_{13}ClN_3^+$ [M + H$^+$]: 294.0793; found: 294.0780.

4-Bromo-2-(1H-perimidin-2-yl)aniline **(3ce):** Following the general procedure 1, **3ce** was isolated as a yellow solid; Yield: 222 mg (66%); mp 184-186 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3289, 3049, 1632, 1564, 1408, 1237, 822, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 5.96 (br s, 2H), 6.17 - 6.44 (m, 1H), 6.61 (d, *J* = 8.80 Hz, 1H), 6.69 - 6.94 (m, 1H), 7.11 (br s, 2H), 7.18 - 7.30 (m, 3H), 7.44 (d, *J*=1.96 Hz, 2H) ;^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 108.1, 116.6, 119.0, 121.2, 128.4, 134.3, 135.3, 147.0, 151.8; HR-MS (ESI+) *m/z* calculated for $C_{17}H_{13}BrN_3^+$ [M + H$^+$]: 338.0287; found: 338.0285.

4-Bromo-2-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)aniline **(3cb):** Following the general procedure 1, **3cb** was isolated as a colorless solid; Yield: 198 mg (63%); mp 236-238 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3609, 3368, 3054, 1680, 1264, 731 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 2.34 (s, 3H), 2.32 (s, 3H), 6.81 (s, 1H), 7.16 - 7.30 (m, 2H), 7.37 - 7.49 (m, 3H), 8.02 (br. s., 1H), 12.54 (s, 1H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm = 19.9, 20.0,105.3, 111.0, 112.1, 118.0, 118.4, 128.8, 129.8, 131.4, 132.0, 132.2, 141.4, 147.1, 150.2; HR-MS (ESI+) *m/z* calculated for $C_{15}H_{15}BrN_3^+$ [M + H$^+$]: 316.0444; found: 316.0441.

2-(1H-Benzo[d]imidazol-2-yl)-4-bromoaniline **(3cc):** Following the general procedure 1, **3cc** was isolated as a colorless solid; Yield: 195 mg (65%); mp 158-160 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3310, 3263, 1606, 1484, 1160, 815, 754 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 2.58 (s, 3H), 6.83 (dd, 8.8 and 3.9 Hz, 1H), 7.01 (t, 6.4 Hz, 1H), 7.11 (dt, 7.4 and 6.4 Hz, 1H), 7.28 (dd, 6.4 and 2.4 Hz, 1H), 7.34 (d, 8 Hz, 0.5H), 7.50 (d, 4 Hz, 2.5H), 7.47 (d, 4 Hz, 0.5H), 8.06 (d, 2 Hz, 0.5H), 8.26 (d, 2 Hz, 0.5H), 12.76 (s, 0.5H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm 16.5, 17.2, 108.4, 115.8, 118.0, 118.1, 121.7, 121.8, 122.6, 123.4, 128.9, 129.4, 132.5, 132.5; HR-MS (ESI+) *m/z* calculated for $C_{14}H_{13}BrN_3^+$ [M + H$^+$]: 302.0288; found: 302.0286.

(2-(2-Amino-5-bromophenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone **(3cf):** Following the general procedure 1, **3cf** was isolated as a light yellow solid; Yield: 226 mg (58%); mp 236-238 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3441, 3250, 1640, 1611, 1315, 1315, 1261, 805, 710 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 6.85 (d, 8.8 Hz, 1H), 7.32 (dd, 8.4 and 2.4 Hz, 1H), 7.47 (br. s., 2H), 7.55 - 7.63 (m, 2H), 7.69 (t, 7.3 Hz, 2H), 7.74 - 7.82 (m, 3H), 8.07 (s, 1H), 13.16 (br. s., 1H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm 105.4, 110.9, 118.3, 128.4, 129.3, 129.4, 132.1, 138.1, 147.7, 195.5; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{15}BrN_3O^+$ [M + H$^+$]: 392.0393; found: 392.0384.

4-Bromo-2-(5-chloro-1H-benzo[d]imidazol-2-yl)aniline **(3cd):** Following the general procedure 1, **3cd** was isolated as a colorless solid; Yield: 173 mg (54%); mp 198-200 °C; IR (MIR-ATR, 4000-600cm-1): νmax = 3302, 3198, 2925, 1603, 1482, 1406, 1233, 864, 817, 745 cm-1; 1H NMR (DMSO d_6, 400 MHz):

δ ppm = 6.83 (d, 8.8 Hz, 1H), 7.24 (br. s., 1H), 7.30 (dd, 8.8 and 2 Hz, 1H), 7.43 (br. s., 2H), 7.54 (br. s., 1H), 7.65-7.72 (m, 1H), 8.04 (d, 2 Hz, 1H), 12.99 (br. s., 1H) ; 13C NMR (DMSO d_6, 100 MHz): δ ppm 105.4, 111.2, 118.2, 129.2, 133.0, 147.5; HR-MS (ESI+) m/z calculated for $C_{13}H_{10}BrClN_3$+ [M + H+]: 321.9741; found: 321.9745.

(2-(2-Amino-5-chlorophenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone **(3bf):** Following the general procedure 1, **3bf** was isolated as a light yellow solid; Yield: 201 mg (58%); mp 222-224 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3251, 2923, 1601, 1278, 805, 712 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 6.89 (d, 8.8 Hz, 1H), 7.22 (d, 8.8 Hz, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.59 (t, 7.8 Hz, 2H), 7.69 (t, 6.8 Hz, 2H), 7.71 - 7.83 (m, 3H), 7.83 - 8.06 (m, 2H), 13.21 (br. s., 1H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm 110.2, 111.0, 112.8, 118.0, 121.0, 123.8, 124.8, 126.5, 128.4, 129.4, 130.6, 130.8, 132.1, 133.1, 137.0, 138.1, 142.2, 147.3, 195.6; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{15}ClN_3O^+$ [M + H^+]: 348.0899; found: 348.0890.

(III) General procedure 2: Synthesis of quinazolines 5 *via* Ni-catalyzed isocyanide insertion:

To the mixture of 2-aminophenylbenzimidazole **3** (0.2 mmol), isocyanide **4** (0.2 mmol) and $Ni(acac)_2$ (15 mol%) in an 10 mL Schlenk tube was added 2mL of DMF and the mixture was stirred at 100 ^oC for 2-4 h (monitored by TLC) under oxygen balloon. After the completion of the reaction, the reaction mixture was allowed to cool and was quenched with ice cold water. Then the reaction mixture was extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using hexane and ethyl acetate (9:1) as eluents to yield the desired products quinazolines **5**.

(IV) General procedure 3: One-pot SDAC synthesis of quinazolines 5 *via* isatoic anhydride opening/ring closing to 2-aminophenylbenzimidazole/Ni-catalyzed isocyanide insertion:

To the mixture of isatoic anhydride **1** (0.25 mmol) and diamine **2** (0.25 mmol) in a 10 mL Schenk tube was added glacial acetic acid (2 mL) and stirred at 90 ^oC for 2-3 h and monitored by TLC. After

completion of the reaction the acetic acid was evaporated using rotary evaporator and dried under vacuum. To this was added isocyanide **4** (0.25 mmol), $Ni(acac)_2$ (15 mol%), and 2 mL of DMF and the mixture was stirred at 100 ^oC for 2-3 h (monitored by TLC) under oxygen balloon. After the completion of the reaction, the reaction mixture was allowed to cool and was quenched with ice cold water. Then the reaction mixture was extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using hexane and ethyl acetate (9:1) as eluents to yield the desired products quinazolines **5**.

(V) Spectral data for the quinazolines compounds 5aaa-5bfa:

N-Cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5aaa):** Following the general procedure 2, **5aaa** was isolated as a colorless solid; Yield: 54 mg (68%); mp 158-160 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3446, 3054, 2925, 2852, 1626, 1598, 1527, 1446, 1339, 758, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.53 - 1.62 (m, 5H), 1.70 - 1.76 (m, 1H), 1.82 - 1.87 (m, 2H), 2.16-2.31 (m, 2H), 4.33 (m, 1H), 5.29 (d, 1H), 7.34 - 7.43 (m, 2H), 7.54 (t, 7.6 Hz, 1H), 7.60 - 7.65 (m, 2H), 7.82 (d, 8Hz, 1H), 8.02 (d, 8Hz 1H), 8.54 (d, 8Hz 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.8, 33.2, 50.3, 76.7, 77.0, 77.4, 112.1, 120.4, 122.6, 123.7, 124.3, 125.2, 125.4, 131.9; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{21}N_4^+$ $[M + H^+]$: 317.1761; found: 317.1754.

2-Chloro-*N*-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine (5baa): Following the general procedure 2, **5baa** was isolated as a colorless solid; Yield: 56 mg (64%); mp 178-180 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3449, 3054, 2928, 2852, 1625, 1598, 1528, 1208, 823, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.44 - 1.61 ppm (m, 4H), 1.73 (dt, J = 12.6, 3.7 Hz, 1H), 1.78 - 1.90 (m, 3H), 2.28 (dd, J = 12.0 and 3.2 Hz, 2H), 4.22 - 4.38 (m, 1H), 5.29 (d, J = 6.8 Hz, 1H), 7.37 - 7.45 (m, 1H), 7.48 - 7.58 (m, 3H), 7.78 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 8.47 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.7, 33.1, 50.4, 112.1, 116.1, 120.5, 122.9, 123.5, 125.4, 126.9, 128.0,

128.9, 132.0, 143.0, 144.5, 148.2; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{20}ClN_4^+$ [M + H$^+$]: 351.1371; found: 351.1375.

2-Bromo-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5caa):** Following the general procedure 2, **5caa** was isolated as a colorless solid; Yield: 61 mg (62%); mp 140-142°C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3444, 3055, 2929, 2853, 1627, 1599, 1528, 1263, 822, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.32 - 1.38 ppm (m, 1H), 1.44 - 1.60 (m, 4H), 1.77 - 1.90 (m, 3H), 2.28 (dd, *J* = 12.0 and 3.2 Hz, 2H), 4.24 - 4.37 (m, 1 H), 5.30 (d, *J* = 7.3 Hz, 1H), 7.39 - 7.45 (m, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.50 - 7.56 (m, 1H), 7.65 (dd, *J* = 8.6 and 2.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.64 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.7, 33.1, 50.4, 112.1, 116.4, 116.6, 120.6, 123.0, 125.4, 126.6, 127.1, 128.0, 134.8, 143.4, 144.5, 144.6, 148.1; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{20}BrN_4^+$ [M + H$^+$]: 395.0866; found:395.0860.

N-(Tert-butyl)benzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5aab):** Following the general procedure 2, **5aab** was isolated as a colorless solid; Yield: 54 mg (75%); mp 134-136 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3452, 3273, 3055, 2962, 2925, 1628, 1600, 1528, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.72 (s, 9H), 5.29 (s, 1H), 7.44 - 7.31 (m, 2H), 7.57 - 7.48 (m, 1H), 7.68 - 7.59 (m, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 8.53 (dd, *J* = 1.2 and 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 29.2, 53.2, 112.0, 115.2, 120.3, 122.5, 123.7, 124.2, 125.1, 125.7, 128.1, 131.8, 143.5, 144.2, 144.6, 149.5; HR-MS (ESI+) *m/z* calculated for $C_{18}H_{19}N_4^+$ [M + H$^+$]: 291.1604; found: 291.1606.

N-(Tert-butyl)-2-chlorobenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5bab):** Following the general procedure 2, **5bab** was isolated as a colorless solid; Yield: 61 mg (75%); mp 168-170 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3451, 2961, 2924, 1626, 1529, 1470, 1197, 822, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.71 (s, 9H), 5.33 (s, 1H), 7.41 - 7.49 (m, 1H), 7.52 - 7.62 (m, 4H), 7.79 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 29.1, 53.3, 112.0, 120.6, 122.9, 123.5, 125.4, 127.1, 128.0, 129.0, 132.0, 142.7, 143.6, 144.5; HR-MS (ESI+) *m/z* calculated for $C_{18}H_{18}ClN_4^+$ [M + H$^+$]: 325.1215; found: 325.1214.

2-Bromo-N-(tert-butyl)benzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5cab):** Following the general procedure 2, **5cab** was isolated as a colorless solid; Yield: 60 mg (65%); mp 188-190 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3364, 2921, 2851, 1631, 1601, 1529, 814, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.71 (s, 9H) 5.34 (s, 1H) 7.40 - 7.47 (m, 1H) 7.50 (d, J = 8.80 Hz, 1H) 7.55 (td, J = 7.83 and 0.98 Hz, 1H) 7.66 (dd, J = 8.56 and 2.20 Hz, 1H) 7.77 (d, J = 8.31 Hz, 1H) 8.00 (d, J = 7.82 Hz, 1H) 8.66 (d, J = 2.45 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 29.1, 53.3, 112.0, 116.5, 116.6, 120.6, 122.9, 125.4, 126.6, 127.4, 128.0, 134.7, 143.0, 143.7, 144.5, 148.2; HR-MS (ESI+) *m/z* calculated for $C_{18}H_{18}BrN_4^+$ [M + H$^+$]: 369.0709; found: 369.0708.

N-Cyclohexyl-9,10-dimethylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5aba):** Following the general procedure 2, **5aba** was isolated as a light yellow solid; Yield: 56 mg (65%); mp 208-210 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3338, 2926, 2853, 1604, 1529, 1453, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.44 - 1.65 ppm (m, 4H), 1.68 - 1.78 (m, 1H), 1.81 - 1.91 (m, 2H), 2.26 - 2.34 (m, 4H), 2.38 (d, J = 9.8 Hz, 6H), 4.23 - 4.41 (m, 1H), 5.22 (d, J = 6.4 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.45 (br. s., 1H), 7.54 - 7.65 (m, 2H), 7.69 (br. s., 1H), 8.47 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 20.5, 21.0, 24.8, 25.8, 33.2, 50.3, 112.4, 115.5, 120.4, 123.5, 124.1, 125.3, 126.4, 131.5, 131.7, 134.3, 143.2, 144.4, 144.5, 148.8; HR-MS (ESI+) *m/z* calculated for $C_{22}H_{25}N_4^+$ [M + H$^+$]: 345.2074; found: 345.2072.

N-Cyclohexylquinazolino[3,4-a]perimidin-6-amine **(5aea):** Following the general procedure 3, **5aea** was isolated as a yellow solid; Yield: 44 mg (48%); mp 178-180°C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3432, 2928, 1609, 1496, 825, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.21 - 1.33 (m, 5H), 1.45 - 1.55 (m, 2H), 1.75 (dt, J = 13.6 and 4.0 Hz, 3H), 2.09 - 2.19 (m, 2H), 4.09 - 4.22 (m, 1H), 5.13 (d, J = 7.3 Hz, 1H), 7.10 - 7.19 (m, 3H), 7.26 - 7.35 (m, 3H), 7.39 - 7.45 (m, 2H), 7.49 (td, J = 7.6 and 1.5 Hz, 1H), 8.24 (dd, J = 8.3 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.7, 33.0, 50.1, 111.1, 117.4, 119.1, 120.7, 122.8, 122.8, 123.9, 124.0, 125.6, 126.3, 129.0, 133.1, 135.1, 140.9, 145.0, 146.1, 148.9; HR-MS (ESI+) *m/z* calculated for $C_{24}H_{23}N_4^+$ [M + H$^+$]: 367.1917; found: 367.1916.

2-Chloro-N-cyclohexylquinazolino[3,4-a]perimidin-6-amine **(5bea):** Following the general procedure 2, **5bea** was isolated as a yellow solid; Yield: 45 mg (45%); mp 136-138 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3424, 2923, 2852, 1621, 1509, 823, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.23 - 1.30 (m, 5H), 1.41 - 1.51 (m, 3H), 1.75 (dt, *J* = 13.3 and 3.9 Hz, 3H), 2.12 (dd, *J* = 12.2 and 3.4 Hz, 2H), 7.09 - 7.22 (m, 3H), 7.28 - 7.36 (m, 2H), 7.39 - 7.46 (m, 3H), 8.20 (d, *J* = 2.4 Hz, 1H),; ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.7, 32.9, 50.2, 111.2, 117.6, 120.1, 121.0, 123.0, 123.9, 124.9, 125.5, 126.3, 128.0, 129.1, 132.8, 133.1, 135.1, 140.5, 145.1; HR-MS (ESI+) *m/z* calculated for $C_{24}H_{22}ClN_4^+$ [M + H$^+$]: 401.1528; found: 401.1524.

2-Bromo-N-cyclohexylquinazolino[3,4-a]perimidin-6-amine **(5cea):** Following the general procedure 2, **5cea** was isolated as a yellow solid; Yield: 52 mg (47%); mp 204-206 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3420, 2926, 2852, 1619, 1566, 1509, 822, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.20 - 1.33 (m, 3H), 1.41 - 1.54 (m, 2H), 1.66 (dt, *J* = 12.84 and 4.10 Hz, 1H), 1.75 (dt, *J* = 13.33 and 3.85 Hz, 2H), 2.07 - 2.16 (m, 2H), 4.13 (td, *J* = 6.97 and 3.18 Hz, 1H), 5.18 (d, *J* = 7.83 Hz, 1H), 7.10 - 7.18 (m, 3H), 7.26 - 7.34 (m, 1H), 7.34 - 7.36 (m, 1H), 7.40 - 7.46 (m, 2H), 7.55 (dd, *J* = 8.56 and 2.20 Hz, 1H), 8.36 (d, *J* = 2.45 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.6, 32.9, 50.2,111.2, 115.4, 117.7, 120.3, 120.6, 121.1, 123.0, 123.9, 125.8, 126.3, 128.0, 129.1, 132.8, 135.1, 135.9, 140.5, 145.2, 147.6; HR-MS (ESI+) *m/z* calculated for $C_{24}H_{22}BrN_4^+$ [M + H$^+$]: 445.1022; found: 445.1020.

2-Bromo-N-cyclohexyl-9,10-dimethylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5cba):** Following the general procedure 2, **5cba** was isolated as a colorless solid; Yield: 68 mg (65%); mp 216-218 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3443, 2925, 2852, 1631, 1603, 1527, 1464, 821, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.49 - 1.61 (m, 4H), 1.71 - 1.77 (m, 2H), 1.86 (dt, *J* = 13.1 and 3.7 Hz, 2H), 2.25 - 2.33 (m, 2H), 2.41 (s, 3H), 2.44 (s, 3H), 4.21 - 4.37 (m, 1H), 5.25 (d, *J* = 6.8 Hz, 1H), 7.42 - 7.49 (m, 2H), 7.63 (dd, *J* = 8.8 and 2.4 Hz, 1H), 7.69 (s, 1H), 8.59 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 20.5, 21.0, 24.8, 25.8, 33.1, 50.4, 112.3, 116.2, 116.9, 120.4, 126.3, 126.4, 127.0, 132.2, 134.3, 134.6, 143.0, 143.2, 144.7, 147.3; HR-MS (ESI+) *m/z* calculated for $C_{22}H_{24}BrN_4^+$ [M + H$^+$]: 423.1179; found: 423.1182.

N-(Tert-butyl)-9,10-dimethylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5abb):** Following the general procedure 2, **5abb** was isolated as a colorless solid; Yield: 59 mg (74%); mp 228-230 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3412, 2962, 2918, 1605, 1562, 1529, 1452, 1201, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.72 (s, 9H), 2.41 (d, J = 8.31 Hz, 6H), 5.25 (s, 1H), 7.34 (ddd, J = 7.95, 6.72 and 1.47 Hz, 1H), 7.46 (s, 1H), 7.55 - 7.65 (m, 2H), 7.72 (s, 1H), 8.48 (dd, J = 7.82 and 0.98 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 20.4, 21.0, 29.2, 53.0, 112.3, 115.4, 120.3, 123.5, 124.0, 125.6, 126.4, 131.3, 131.5, 134.1, 143.1, 143.6, 144.1, 148.8; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{23}N_4^+$ [M + H$^+$]: 319.1917; found: 319.1909.

Ethyl 2-(benzo[4,5]imidazo[1,2-c]quinazolin-6-ylamino)acetate **(5aac):** Following the general procedure 2, **5aac** was isolated as a colorless solid; Yield: 48 mg (60%); mp 152-154 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3432, 2927, 1736, 1628, 1602, 1535, 1450, 1203, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.39 (t, 7.3 Hz, 3H), 4.37 (q, 7.3 Hz, 2H), 4.52 (d, 4.4 Hz, 2H), 6.19 (br. s., 1H), 7.38 - 7.43 (m, 1H), 7.45 (d, 8.3 Hz, 1H), 7.50 - 7.56 (m, 1H), 7.60 - 7.65 (m, 2H), 8.01 (dd, 7.6 and 6.1 Hz, 2H), 8.53 (d, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 14.2, 44.0, 62.1, 112.4, 115.5, 120.3, 123.1, 124.3, 124.3, 125.4, 125.5, 128.0, 131.9, 144.0, 144.3, 144.4, 148.9, 170.6.; HR-MS (ESI+) *m/z* calculated for $C_{18}H_{17}N_4O_2^+$ [M + H$^+$]: 321.1346; found: 321.1346.

N-Benzylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5aad):** Following the general procedure 2, **5aad** was isolated as a colorless solid; Yield: 47 mg (58%); mp 168-170 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3398, 1626, 1599, 1530, 1447, 1264,734, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 4.98 (d, 4.9 Hz, 2H), 5.62 (br. s., 1H), 7.34 - 7.46 (m, 5H), 7.48 - 7.57 (m, 3H), 7.62 - 7.71 (m, 2H), 7.75 - 7.80 (m, 1H), 8.01 (d, 7.8 Hz, 1H), 8.56 (d, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 46.4, 112.2, 114.4, 114.5, 115.5, 120.4, 122.6, 122.8, 124.2, 124.3, 125.3, 125.6, 128.0, 128.1, 129.0, 131.0, 132.0, 137.9, 144.2, 145.1, 149.2; HR-MS (ESI+) *m/z* calculated for $C_{21}H_{17}N_4^+$ [M + H$^+$]: 325.1448; found: 325.1449.

2-Bromo-N-cyclohexyl-11-methylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5cca):**

Following the general procedure 2, **5cca** was isolated as a colorless solid; Yield: 66 mg (65%); mp 208-210 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3442, 2924, 2850, 1624, 1593, 820, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.43 - 1.60 (m, 4H), 1.70 - 1.76 (m, 2H), 1.84 (dt, J = 13.2 and 3.9 Hz, 2H), 2.27 (dd, J = 11.7 and 2.9 Hz, 2H), 2.81 (s, 3H), 4.23 - 4.37 (m, 1H), 5.33 (d, J = 6.8 Hz, 1H), 7.30 - 7.36 (m, 2H), 7.47 (d, J = 8.8 Hz, 1H), 7.58 - 7.68 (m, 2H), 8.68 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 17.1, 24.8, 25.8, 33.1, 50.3, 109.5, 116.2, 116.9, 122.8, 125.7, 126.6, 127.0, 127.6, 130.9, 134.5, 143.3, 143.9, 144.7, 147.3; HR-MS (ESI+) *m/z* calculated for $C_{21}H_{22}BrN_4^+$ [M + H$^+$]: 409.1022; found: 409.1005.

2-Chloro-N-cyclohexyl-11-methylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5bca):**

Following the general procedure 2, **5bca** was isolated as a colorless solid; Yield: 65 mg (72%); mp 184-186 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3397, 2922, 2851, 1617, 1591, 1227, 1071, 822, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.32 - 1.62 (m, 6H), 1.72 (m, 1H), 1.84 (m, 2H), 2.27 (m, 2H), 2.78 (s, 3H), 4.26 (td, 10.6, 6.6 and 3.2 Hz, 1H), 5.28 (d, 7.3 Hz, 1H), 7.24 - 7.31 (m, 2H), 7.44 - 7.48 (m, 1H), 7.48 - 7.52 (m, 1H), 7.54 - 7.58 (m, 1H), 8.49 (d, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 17.1, 24.8, 25.8, 33.1, 50.3, 109.4, 116.4, 122.7, 123.5, 125.6, 126.7, 127.5, 128.7, 130.8, 131.7, 142.9, 143.8, 144.6, 147.4; HR-MS (ESI+) *m/z* calculated for $C_{21}H_{22}ClN_4^+$ [M + H$^+$]: 365.1528; found: 365.1522.

N-(tert-butyl)-2-chloro-11-methylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5bcb):**

Following the general procedure 2, **5bcb** was isolated as a colorless solid; Yield: 62 mg (73%); mp 210-212 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3448, 2961, 1627, 1599, 1530, 1470, 1206, 820, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.70 (s, 9H), 2.80 (s, 3H), 5.33 (s, 1H), 7.29 - 7.35 (m, 2H), 7.46 - 7.51 (m, 1H), 7.51 - 7.55 (m, 1H), 7.55 - 7.60 (m, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 17.1, 29.1, 53.2, 109.4, 116.3, 122.7, 123.5, 125.6, 127.0, 127.5, 128.7, 130.3, 130.8, 131.7, 142.5, 143.7, 147.5; HR-MS (ESI+) *m/z* calculated for $C_{19}H_{20}ClN_4^+$ [M + H$^+$]: 339.1371; found: 339.1371.

Mixture of 2,10-dichloro-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine and 2,9-dichloro-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5bda):**

Following the general procedure 2, **5bda** was isolated as a colorless inseparable solid mixture; Yield: 60 mg (62%); mp 178-180 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3444, 2929, 2854, 1629, 1598, 1524, 934, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.42 - 1.60 (m, 4H), 1.69 - 1.81 (m, 2H), 1.86 (m, 2H), 2.25 - 2.34 (m, 2H), 4.21 - 4.32 (m, 1H), 5.02 (d, 6.6 Hz, 0.5H), 5.10 (d, 6.6 Hz, 0.5H), 7.28 - 7.35 (m, 0.5H), 7.43 - 7.49 (m, 0.5H), 7.49 - 7.55 (m, 2H), 7.59 - 7.65 (m, 0.5H), 7.71 (br. s., 0.5H), 7.80 - 7.86 (m, 0.5H), 7.88 (br. s., 0.5H), 8.37 (br. s., 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 24.9, 25.5, 25.7, 33.1, 50.6, 50.8, 112.4, 112.7, 115.7, 115.9, 120.1, 121.1, 123.1, 123.4, 123.5, 126.0, 126.5, 127.0, 128.3, 128.4, 129.1, 129.2, 131.0, 132.3, 132.4, 142.8, 143.0, 144.1, 145.4, 148.8, 149.2; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{19}Cl_2N_4^+$ [M + H$^+$]: 385.0981; found: 385.0996.

Mixture of (2-bromo-6-(cyclohexylamino)benzo[4,5]imidazo[1,2-c]quinazolin-10-yl (phenyl) methanone and (2-bromo-6-(cyclohexylamino)benzo[4,5]imidazo[1,2-c]quinazolin-9-yl) (phenyl)methanone **(5cfa):**

Following the general procedure 2, **5cfa** was isolated as a yellow color inseparable solid mixture; Yield: 82 mg (66%); mp 210-212 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3339, 3061, 2928, 2853, 1628, 1599, 1525, 1276, 823, 718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.32 - 1.51 (m, 1H), 1.53 - 1.56 (m, 3H), 1.71 - 1.82 (m, 3H), 1.87 (dd, *J* = 9.3, 3.9 Hz, 1H), 2.22 (d, *J* = 9.8 Hz, 1H), 2.27 - 2.36 (m, 1H), 4.32 (dd, *J* = 6.1, 3.2 Hz, 1H), 5.33 (d, *J* = 6.8 Hz, 0.5H), 5.42 (d, *J* = 6.8 Hz, 0.5H), 7.46 - 7.56 (m, 3H), 7.59 - 7.72 (m, 2H), 7.79 - 7.91 (m, 3H), 8.34 (d, *J* = 1.5 Hz, 1H), 8.42 (s, 1H), 8.56 - 8.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.6, 24.8, 25.7, 25.7, 32.7, 33.1, 50.5, 50.7, 112.3, 114.8, 116.2, 116.3, 116.7, 116.7, 119.4, 123.2, 124.5, 126.7, 126.8, 127.3, 127.3, 128.1, 128.4, 129.9, 130.2, 130.5, 131.8, 132.4, 132.6, 134.6, 135.3, 135.6, 137.5, 137.8, 143.4, 143.8, 143.9, 144.3, 144.4, 147.7, 149.4, 195.8, 196.0 ; HR-MS (ESI+) *m/z* calculated for $C_{27}H_{24}BrN_4O^+$ [M + H$^+$]: 499.1128; found: 499.1107.

Mixture of 2-bromo-10-chloro-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine and 2-bromo-9-chloro-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(5cda):**

Following the general procedure 2, **5cda** was isolated as a inseparable colorless solid mixture; Yield: 74 mg (69%); mp 190-192 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3445, 2927, 2853, 1626, 1597, 1522,

1466, 1422, 1207, 821, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.33 - 1.63 ppm (m, 6H), 1.86 (td, J = 8.6 and 3.9 Hz, 2H), 2.25 - 2.36 (m, 2H), 4.27 (dd, J = 6.1 and 3.2 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 5.10 (d, J = 6.8 Hz, 1H), 7.42 - 7.49 (m, 1H), 7.59 - 7.67 (m, 2H), 7.70 (d, J = 2.0 Hz, 1H), 7.81 - 7.90 (m, 1H), 8.54 (t, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 149.1, 148.6, 145.4, 144.2, 144.1, 143.4, 143.2, 143.0, 135.1, 135.0, 131.0, 128.3, 128.3, 127.2, 126.5, 126.5, 126.0, 123.1, 121.1, 120.1, 116.7, 116.6, 116.4, 116.2, 112.7, 112.4, 77.3, 77.0, 76.7, 50.8, 50.6, 33.1, 25.7, 24.9, 24.8; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{19}BrClN_4^+$ [M + H^+]: 429.0476; found: 429.0487.

***Mixture of N-cyclohexyl-10-methylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine and N-cyclohexyl-9-methylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine* (5aha):**

Following the general procedure 2, **5aha** was isolated as a colorless inseparable solid mixture; Yield: 54 mg (65%); mp 174-176 °C. IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3408, 2920, 1607, 1482, 834, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.29 - 1.42 (m, 1H), 1.43 - 1.65 (m, 3H), 1.67 - 1.78 (m, 2H), 1.80 - 1.91 (m, 2H), 2.24 - 2.36 (m, 2H), 2.56 (s, 1H), 2.61 (s, 2H), 4.27 - 4.40 (m, 1H), 5.20 - 5.31 (m, 1H), 7.31 - 7.39 (m, 2H), 7.54 - 7.69 (m, 3H), 7.89 (d, 8.3 Hz, 1H), 8.47 - 8.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 21.7, 22.3, 24.8, 24.9, 25.8, 33.2, 50.2, 50.3, 76.7, 77.0, 77.2, 77.3, 111.5, 112.2, 115.4, 119.9, 120.2, 123.6, 123.6, 124.0, 124.1, 124.2, 125.3, 126.7, 128.3, 131.6, 131.7, 132.6, 135.2, 144.4; HR-MS (ESI+) *m/z* calculated for $C_{21}H_{23}N_4^+$ [M + H^+]: 331.1917; found: 331.1917.

***Isolated Mixture of 10-chloro-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine (5ada) and 9-chloro-N-cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine* (5ada'):**

Following the general procedure 2, **5ada** and **5ada'** were isolated as colorless solids;

Data for **5ada**: Yield: 35 mg (40%); mp 186-188 °C, IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3444, 3062, 2927, 2853, 1627, 1599, 1525, 1428, 1208, 1068, 865, 761; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.32 - 1.39 (m, 1H), 1.43 - 1.52 (m, 2H), 1.55 - 1.61 (m, 2H), 1.67 - 1.79 (m, 3H), 1.85 (dt, J = 13.3 and 3.9 Hz, 2H), 2.30 (dd, J = 12.0 and 3.2 Hz, 2H), 4.32 (dtd, J = 10.1, 6.6 and 3.7 Hz, 1H), 5.10 (d, J = 6.8 Hz, 1H), 7.30 - 7.43 (m, 2H), 7.60 - 7.67 (m, 2H), 7.68 - 7.75 (m, 1H), 7.92 - 7.99 (m, 1H), 8.42 - 8.54 (m, 1H); ^{13}C

NMR ($CDCl_3$, 100 MHz): δ ppm = 24.8, 25.8, 33.2, 50.5, 112.7, 114.9, 120.0, 122.7, 123.9, 124.3, 125.5, 126.7, 130.8, 132.2, 144.1, 144.6, 145.6, 150.6;

Data for **5ada'**: Yield: 22 mg (25%); mp 196-198 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3431, 2927, 2852, 1625, 1598, 1528, 1450, 1340, 814, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.32 - 1.42 (m, 1H), 1.45 - 1.61 (m, 4H), 1.75 (dt, *J* = 13.0 and 3.5 Hz, 1H), 1.87 (dt, *J* = 13.1 and 3.7 Hz, 2H), 2.31 (dd, *J* = 12.0 and 3.2 Hz, 2H), 4.26 - 4.38 (m, 1H), 5.03 (d, *J* = 7.3 Hz, 1H), 7.38 (ddd, *J* = 8.1, 4.6 and 3.4 Hz, 1H), 7.49 - 7.52 (dd, 8.5 and 2Hz, 1H), 7.62 - 7.67 (m, 2H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 8.45 - 8.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.9, 25.7, 33.2, 50.6, 112.4, 115.1, 121.0, 124.0, 124.2, 125.5, 125.8, 127.9, 128.5, 132.2, 143.2, 144.0, 144.5, 150.1; HR-MS (ESI+) *m/z* calculated for $C_{20}H_{20}ClN_4^+$ [M + H^+]: 351.1371; found: 351.1368.

***Mixture of N-(tert-butyl)-2,10-dichlorobenzo[4,5]imidazo[1,2-c]quinazolin-6-amine and N-(tert-butyl)-2,9-dichlorobenzo[4,5]imidazo[1,2-c]quinazolin-6-amine* (5bdb):**

Following the general procedure 2, **5bdb** was isolated as colorless inseparable solid mixture; Yield: 58 mg (65%); mp 206-208 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3450, 2967, 2928, 1631, 1600, 1526, 1198, 822, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.71 (s, 9H), 5.1 (s, 0.4H), 5.1 (s, 0.6H), 7.39 (dd, 8.8 and 2 Hz, 0.5H), 7.50 - 7.55 (m, 0.5H), 7.55 - 7.60 (m, 2H), 7.7 (m, 0.6H), 7.7 (m, 0.4H), 7.96 (d, 8.8 Hz, 0.4H), 8.1(m, 0.6H), 8.45 - 8.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 29.1, 53.5, 53.5, 76.7, 77.0, 77.2, 77.3, 112.4, 112.7, 115.8, 116.0, 120.1, 121.1, 123.0, 123.4, 123.4, 125.9, 126.6, 127.2, 128.3, 128.4, 129.2, 129.2, 130.9, 132.2, 132.3, 142.5, 142.7, 143.0, 143.1, 143.2, 145.4, 148.9, 149.4; HR-MS (ESI+) *m/z* calculated for $C_{18}H_{17}Cl_2N_4^+$ [M + H^+]: 359.0825; found: 359.0825.

***Mixture of (2-chloro-6-(cyclohexylamino)benzo[4,5]imidazo[1,2-c]quinazolin-10-yl)(phenyl)methanone and (2-chloro-6-(cyclohexylamino)benzo[4,5]imidazo[1,2-c]quinazolin-9-yl)(phenyl)methanone* (5bfa):**

Following the general procedure 2, **5bfa** was isolated as a yellow inseparable solid mixture; Yield: 68 mg (60%); mp 192-194 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3338, 3056, 2928, 2853, 1628, 1598, 1275, 824, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.29 - 1.42 (m, 1H), 1.42 - 1.62 (m, 4H), 1.72 - 1.83

(m, 2H), 1.87 (m, 1H), 2.22 (m, 1H), 2.26 - 2.35 (m, 1H), 4.18 - 4.44 (m, 1H), 5.31 (s, 0.5H), 5.41 (s, 0.5H), 7.48 - 7.54 (m, 2H), 7.54 - 7.60 (m, 2H), 7.60 - 7.67 (m, 1H), 7.80 - 7.88 (m, 2H), 7.95 - 8.04 (m, 2H), 8.42 - 8.47 (m, 1H), 8.50 (t, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 24.6, 24.8, 25.7, 25.7, 32.8, 33.1, 50.4, 50.7, 76.7, 77.0, 77.2, 77.4, 112.3, 114.8, 115.7, 115.9, 119.5, 123.3, 123.6, 123.8, 124.6, 127.1, 128.1, 128.4, 129.2, 129.9, 130.2, 130.5, 131.8, 132.4, 132.6, 132.9, 134.6, 137.5, 137.9, 143.0, 143.6, 143.9, 144.2, 144.3, 147.8, 150.9, 195.9, 196.0; HR-MS (ESI+) *m/z* calculated for $C_{27}H_{24}ClN_4O^+$ [M + H^+]: 455.1633; found: 455.1615.

(VI) General procedure 4: Synthesis of free amine 6-aminobenzimidazoquinazolines 6aa and 6ba from 5aab and 5bab by tert-butyl deprotection:

In an 10 mL sealed tube was taken compounds **5aab** or **5bab** (0.5 mmol) and added 2 mL of nitro methane followed by addition of $Sc(OTf)_2$ (0.75 mmol). The tube was heated at 150 ^oC for 6 h. Then the solvent was evaporated using rotary evaporator. The crude was dissolved in ethyl acetate and filtered through a pad of Celite and the crude was purified through a silica gel (100-200 mesh) column using hexane and ethyl acetate (4:1) as eluents to yield the desired products **6aa** or **6ba** as free amines.

(VII) Spectral data for the compounds 6aa and 6ba:

Benzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(6aa):** Following the general procedure 4, **6aa** was isolated as a colorless solid; Yield: 76 mg (65%); mp > 300 ^oC; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3056, 2926, 2851, 1607, 1525, 1449, 1264, 736 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 7.37 (t, 7.6 Hz, 1H), 7.41 - 7.48 (m, 3H), 7.50 - 7.56 (m, 2H), 7.62 - 7.68 (m, 1H), 7.91 (d, 8.3 Hz, 1H), 8.42 (t, 8.8 Hz, 2H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm = 114.3, 114.6, 119.0, 122.3, 123.2, 123.8, 124.3, 125.0, 128.1, 131.8, 143.8, 144.6, 146.5, 148.4; HR-MS (ESI+) *m/z* calculated for $C_{14}H_{11}N_4^+$ [M + H^+]: 235.0978; found: 235.0977.

2-Chlorobenzo[4,5]imidazo[1,2-c]quinazolin-6-amine **(6ba):** Following the general procedure 4, **6ba** was isolated as a colorless solid; Yield: 90 mg (67%); mp 268-270 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3398, 3057, 1658, 1518, 1258, 822, 732 cm^{-1}; ^{1}H NMR (DMSO d_6, 400 MHz): δ ppm = 7.45 - 7.54

(m, 2H), 7.54 - 7.59 (m, 3H), 7.65 (dd, 8.8 and 2.4 Hz, 1H), 7.92 (d, 7.8 Hz, 1H), 8.32 (d, 2.4 Hz, 1H), 8.44 (d, 8.3 Hz, 1H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm = 38.8, 39.0, 39.2, 39.4, 39.6, 39.8, 40.0, 114.3, 115.7, 119.2, 122.5, 122.8, 125.3, 126.4, 126.8, 128.1, 131.7, 143.4, 143.6, 146.7, 147.3; HR-MS (ESI+) *m/z* calculated for $C_{14}H_{10}ClN_4^+$ [M + H$^+$]: 269.0589; found: 269.0590

(VIII) General procedure 5: Synthesis of compound 8a and 8b *via* Groebke-Blackburn-Bienayme (GBB) type reaction:

To a mixture of amine (**6**, 0.2 mmol), 4-chlorobenzaldehyde (**7**, 0.2 mmol) and *t*-butylisocyanide (**4b,** 0.2 mmol) was added Scandium triflate (20 mol%) and 2 mL of DMSO and the mixture was heated at 110 ^{o}C for 8 h. After completion of the reaction (checked by TLC), the ice cold water was added and extracted with ethyl acetate (3x 15mL) and the extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude extract was purified by filtration through short pad of a silica gel (60-120 mesh) column using hexane/ EtOAc (5:1) to give compound **8a** or **8b**.

(IX) Spectral data for the compounds 8a and 8b:

***N-cyclohexyl-2-(2-fluorophenyl)benzo[4,5]imidazo[1,2-c]imidazo[1,2-a]quinazolin-3-amine* (8a):**

Following the general procedure 5, **8a** was isolated as a yellow solid; Yield: 58 mg (65%); mp 188-190 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3334, 2960, 1609, 1478, 1374, 823, 732 cm^{-1}; ^{1}H NMR (DMSO d6, 400 MHz): δ ppm = 0.62 - 0.82 (m, 2H), 1.00 - 1.30 (m, 3H), 1.45 (m, 3H), 1.62 - 1.88 (m, 2H), 3.85 (t, 9.5 Hz, 1H), 7.12 (dd, 11.5 and 8.1 Hz, 1H), 7.32 - 7.54 (m, 5H), 7.66 (s, 1H), 7.72 - 7.79 (m, 1H), 7.91 (m, 1H), 7.99 - 8.10 (m, 1H), 8.27 (d, 7.8 Hz, 1H), 8.44 (m, 1H), 9.40 (d, 1H); ^{13}C NMR (DMSO d_6, 100 MHz): δ ppm = 23.6, 23.8, 25.1, 33.3, 34.1, 57.0, 62.7, 89.2, 112.2, 114.9, 115.4, 115.6, 115.9, 119.6, 124.3, 124.5, 124.6, 125.2, 125.5, 127.4, 129.0, 129.1, 130.2, 130.4, 132.7, 134.4, 143.8, 147.6 (d, $^1J_{C\text{-}F}$ = 190.0 Hz), 158.2; HR-MS (ESI+) *m/z* calculated for $C_{28}H_{25}FN_5^+$ [M + H$^+$]: 450.2089; found: 450.2083.

***N-(tert-butyl)-2-(4-chlorophenyl)benzo[4,5]imidazo[1,2-c]imidazo[1,2-a]quinazolin-3-amine* (8b):**

Following the general procedure 5, **8b** was isolated as a yellow solid; Yield: 53 mg (60%); mp 236-238 °C; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3369, 2968, 1603, 1474, 1365, 1203, 835, 746 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz): δ ppm 0.97 (s, 9H), 3.20 (s, 1H), 7.43 (d, 8.3 Hz, 3H), 7.46 - 7.52 (m, 2H), 7.53 - 7.59 (m, 1H), 7.80 (d, 8.3 Hz, 2H), 7.89 - 7.97 (m, 1H), 8.62 (d, 7.8 Hz, 1H), 8.65 - 8.73 (m, 1H), 9.37 (d, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 29.7, 57.1, 114.7, 115.1, 117.5, 119.4, 123.8, 124.9, 125.6, 125.9, 127.6, 128.6, 129.3, 129.9, 130.5, 133.1, 133.2, 134.5, 134.9, 143.7, 144.3; HR-MS (ESI+) *m/z* calculated for $C_{26}H_{23}ClN_5^+$ [M + H^+]: 440.1636; found: 440.1631.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

Experimental procedures and characterization for all new compounds; NMR spectra (PDF)

X-ray data for **5abb** (CIF)

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