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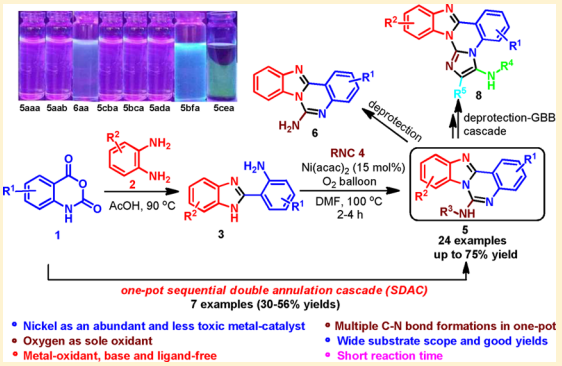
Nickel-Catalyzed Aerobic Oxidative Isocyanide Insertion: Access to Benzimidazoquinazoline Derivatives via a Sequential Double Annulation Cascade (SDAC) Strategy

Anand H. Shinde, Sagar Arepally, Mayur D. Baravkar, and Duddu S. Sharada*

Department of Chemistry, Indian Institute of Technology Hyderabad (IITH), Kandi, Sangareddy 502 285, Telangana, India

Supporting Information

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 a wide variety of substrates and represents a new approach for multiple C−N bond formations. The methodology has been successfully applied to the syntheses of hitherto unreported imidazo-fused benzimidazoquinazolines via a deprotection−GBB reaction sequence. Further, a florescence study reveals the potential of the present strategy for the discovery of highly fluorescent probes.



INTRODUCTION

Transition-metal-catalyzed C−heteroatom bond formation via CH/NH functionalization has attracted much attention in comparison to traditional methods for heterocyclic synthesis, as it provides a direct and atom-economical synthetic strategy to structurally diverse and complex molecules from simple substrates.[1] The development of new chemical approaches for in situ generation of templates/substrates for rapid and straightforward access to structurally complex molecules via CH/XH functionalization under ecologically 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 and removal of the directing group, various other alternative approaches such as cross-dehydrogenative coupling (CDC),[2] metal-free redox-neutral methods,[3] nondirected CH bond activation,[4] and direct atom insertion strategies[5] have been explored. Among the insertions of various atoms[5] such as nitrogen, carbon, and sulfur, carbon insertion using isocyanide has been in the limelight. In contrast to reactions using other CO surrogates, isocyanide insertion offers functionally diverse molecules by providing an extra nitrogen functionality which can be diversified further and might also result in improved activity as pharmaceuticals.

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

Several transition metals such as palladium and cobalt and Lewis acid catalyzed isocyanide insertion reactions have been reported which use various kinds of bis-nucleophiles in either an inter- or intramolecular fashion.[8] However, nickel-catalyzed isocyanide insertions are in their infancy.[9] Among the various intramolecular isocyanide insertions leading to heteroannulations, isocyanide insertion in an NH bond is unique, as it provides a useful and convenient tool for the construction of N-heterocycles.

Aza-heterocyclic compounds,[10] especially cyclic guanidine containing compounds, have attracted considerable interest due to their 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 (Figure 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 (Figure 1)

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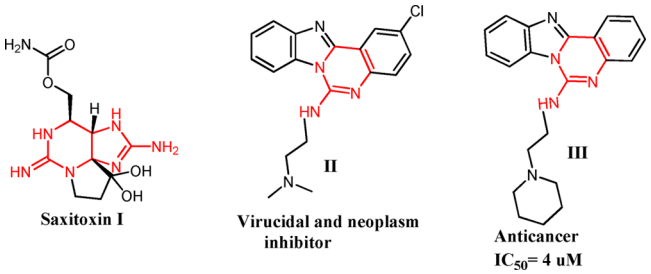


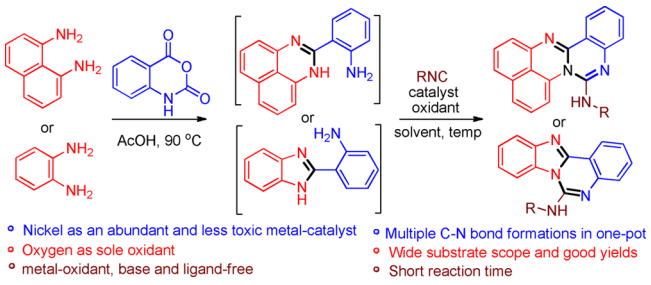
Figure 1. Cyclic guanidine containing alkaloid (I) and cyclic guanidine containing bioactive benzimidazoquinazoline skeletons (II and III).

are highly potent virucidal and neoplasm inhibitors and are found to be active against breast cancer.[14]

Cyclic guanidine is typically synthesized from an 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 reactions,[16] and copper-catalyzed cascades.[17] On the other hand, 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 limit their 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 the catalytic activity of the metals by forming stable complexes, which in turn make C−N bond formation reactions challenging, and achieving such transformations in one pot efficiently from a simple substrate is even most challenging due to the compatibility issues with further sensitive catalytic processes, which are inevitable in carrying out these cascade reactions.

In continuation of our research interest in annulation cascade strategies[20a,b] and transition-metal-catalyzed isocyanide insertion,[20c,d] herein we report for the first time a novel SDAC strategy involving nickel-catalyzed metal oxidant and base-free isocyanide insertion in NH/NH under aerobic conditions for the synthesis of benzimidazoquinazoline derivatives from isatoic anhydride in a 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 system **3aa**. It is noted that there was no product formation in the 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, it afforded the desired product **5aab**, albeit in 42% yield, and little improvement was observed in the presence of anhydrous $NiCl_2$ (Table 1, entries 2 and 3). Unfortunately, however, reaction with $Ni(ClO_4)_2$ or $Ni(C_2O_4)$ as catalyst or with a change of base to NaOAc also did not improve the yield (Table 1, entries 4−6). When we used peroxide-based oxidants, there was an improvement in yield as well as reaction profile, especially with DTPB as oxidant (Table 1, entries 7 and 8). To our delight, the reaction with dioxygen as the sole oxidant gave the product in much better yield (55%) (Table 1, entry 9). To our surprise, the reaction with $Ni(acac)_2$ catalysis under aerobic conditions gave the product in 61% yield (Table 1, entry 10).

Further, reactions in various solvents such as toluene, DCE, acetonitrile, water, and DMSO were unsatisfactory (Table 1, entries 11−16). When we tested the reaction under base-free conditions, it resulted in a comparable yield of the product (65%) (Table 1, entry 17). Further, when we tested the effect of varied catalyst loadings (Table 1, entries 18 and 19), we found that 15 mol % of $Ni(acac)_2$ led efficiently to the best yield (68%) of the product (Table 1, entry 18). To understand the role of the oxidant, when we performed the reaction using $Ni(acac)_2$ in the absence of oxidant, there was no progress in the reaction and 90% of the starting material was recovered, suggesting that oxygen is essential for the present transformation (Table 1, entry 20). Carrying out the reaction at varying temperatures did not improve the yield further (Table 1, entries 21 and 22). Therefore, we chose 15 mol % of $Ni(acac)_2$ as catalyst and dioxygen as oxidant in DMF solvent as optimum conditions 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 a variety of isocyanides **4**. We have successfully extended the methodology to various electron-donating as well as electron-withdrawing *o*-phenylenediamines **2** and 1°, 2°, and 3° isocyanides (Table 2). When we 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**−**cab**). The donating dimethyl-substituted *o*-phenylenediamine **2b** provided the desired products in high yields (Table 2, entries **5aba**,**abb**,**cba**). 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**,**bea**,**cea**). However, 2-bromo-2,3-diaminopyridine **2g** failed to give the desired product, which might be due to the side reactions involving a pyridinium complex (Table 2, entry **5aga**). In general, both the 2° cyclohexyl and 3° *tert*-butyl isocyanides worked well and provided the desired products in moderate to good yields (Table 2, entries **5aaa**−**abb**). Our further attempt to introduce different 1° isocyanides such as ethyl isocyanoacetate **4c** and benzyl isocyanide **4d** was successful, resulting in the desired products with moderate to good yields (Table 2, entries **5aac**,**aad**).

When the application of this methodology is considered for the synthesis of quinazoline **5**, potential regioselectivity issues exist in the 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

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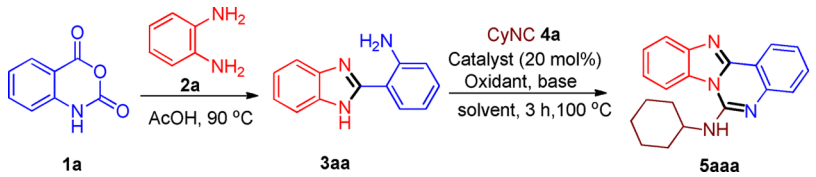
Table 1. Screening of Reaction Conditions for Ni-Catalyzed Isocyanide Insertion To Give 5aaa[a]



1a 3aa 5aaa

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). Abbreviations: DTPB = di-*tert*-butyl peroxide; TBPB = *tert*-butyl peroxybenzoate. For compound **5aaa** the first letter refers to isatoic anhydride part **1a**, the second letter refers to diamine part **2a**, and the third letter refers to the part coming from isocyanide **4a**. [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.

methyl-substituted *o*-phenylenediamine was treated with chloro- or bromo-substituted isatoic anhydrides **1**, to our surprise it gave the desired products as a single regioisomer with good yields (Table 3, entries **5cca**–**bcb**). However, *o*-phenylenediamines such as **2d**,**f** with an electron-withdrawing group at the 4-position provided an unisolable mixture of regioisomers (1:1) (Table 3, entries **5bda**,**cfa**,**cda**) in good yields. A satisfactory improvement in regioselectivity was observed in the case of **5aha**,**bdb**,**bfa**, which gave the desired products with good yields; however, the products were obtained as an inseparable regioisomeric mixture (1:0.67) (Table 3, entries **5aha**,**bdb**,**bfa**). An isolable mixture of regioisomers was observed in the case of **5ada**,**ada′**, which gave the product in overall 57% yield. The structures of the isomers **5ada**,**ada′** were assigned by NOE experiments. The observed high regioselectivity in the case of methyl-substituted *o*-phenylenediamine **2c** might be due to the ortho-substituent effect leading to the predominant existence of a 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 Supporting Information 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 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 the desired products with moderate to good yield (30–56%, Table 4, entries **5aaa**–**cab**).

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

To gain some insights into the reaction mechanism, radical trapping experiments were carried out. The commonly used radical scavengers 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.

On the basis of the literature reports[18] and TEMPO/BHT trapping experiments, a plausible ionic mechanism is proposed

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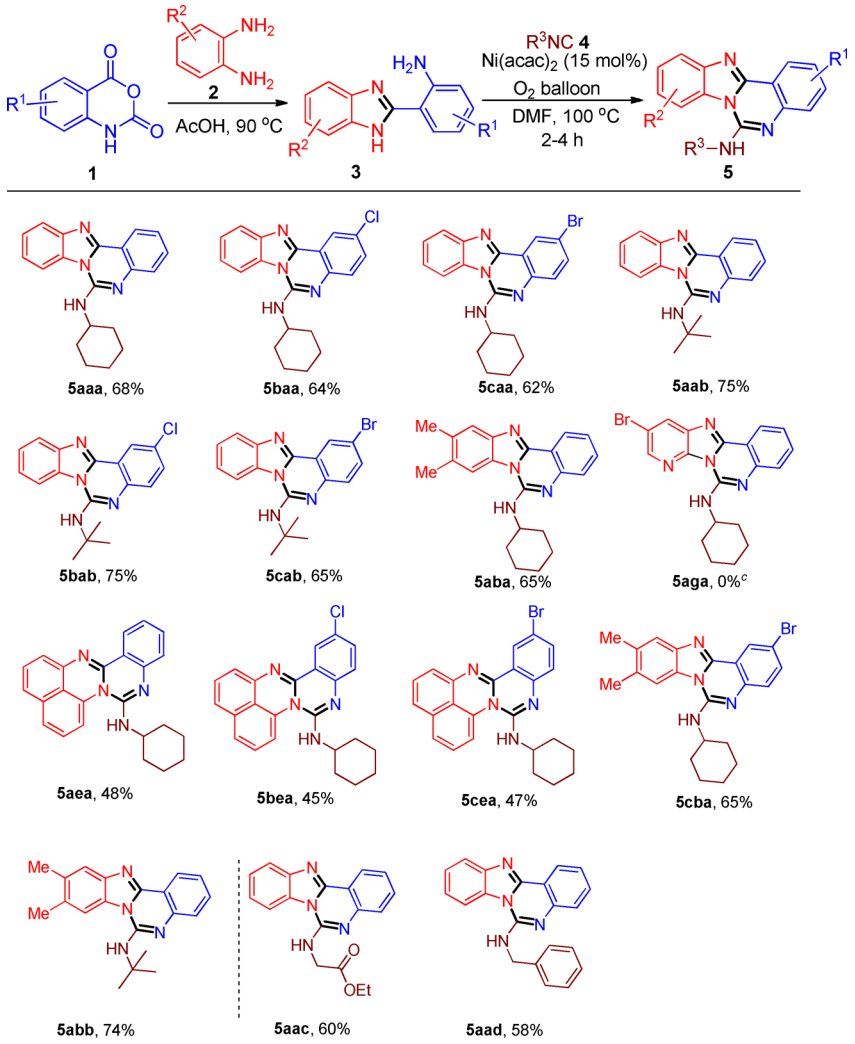
Table 2. Scope of Diamines 2 and Isocyanides 4 for the Synthesis of Quinazolines 5[a,b]



[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). For compound **5** the first letter refers to isatoic anhydride parts **1a−c**, the second letter refers to diamine parts **2a−g**, and the third letter refers to parts coming from isocyanides **4a−d**. [b]Isolated yields after column chromatography. [c]Failed to give the intermediate **3ag**.

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 the 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.

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,aab** were measured, there was only a 2 nm change on changing the substituent on nitrogen (Table 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** (Table 5, entry 3); in addition, a longer wavelength was obtained when there was a substituent on the phenyl rings of the benzimidazoquinazoline moiety irrespective of electron-donating or -withdrawing groups (Table 5, entries 4−7). The naphthalene-fused quinazoline compound **5cea** gave a shorter wavelength of the absorption maximum peak (λ_{max}); however, it showed the strongest yellow fluorescence among all compounds at 532 nm (λ_{em}) (Table 5, entry 8). The compounds **6aa** and **5bfa** showed green-blue fluorescence, while compounds **5aaa,aab,cba−ada** showed blue fluorescence. The electron-withdrawing phenoxy-substituted compound **5bfa** showed the highest fluorescence emission at 445 (λ_{em}) (Table 5, entry 7). The compounds **5aaa−ada** showed fluorescence emission in the range of 381−407 nm (λ_{em}) (Table 5, entries 1−6). Overall, the fluorescence study showed that electron-withdrawing groups on benzimidazole and a *tert*-butyl substituent on the amine increase the fluorescence properties of the molecule.

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 benzimidazoquinazolines **5**. The use of dioxygen as the sole oxidant and base-/ligand-free features make this strategy unique. The diverse potential of the present SDAC

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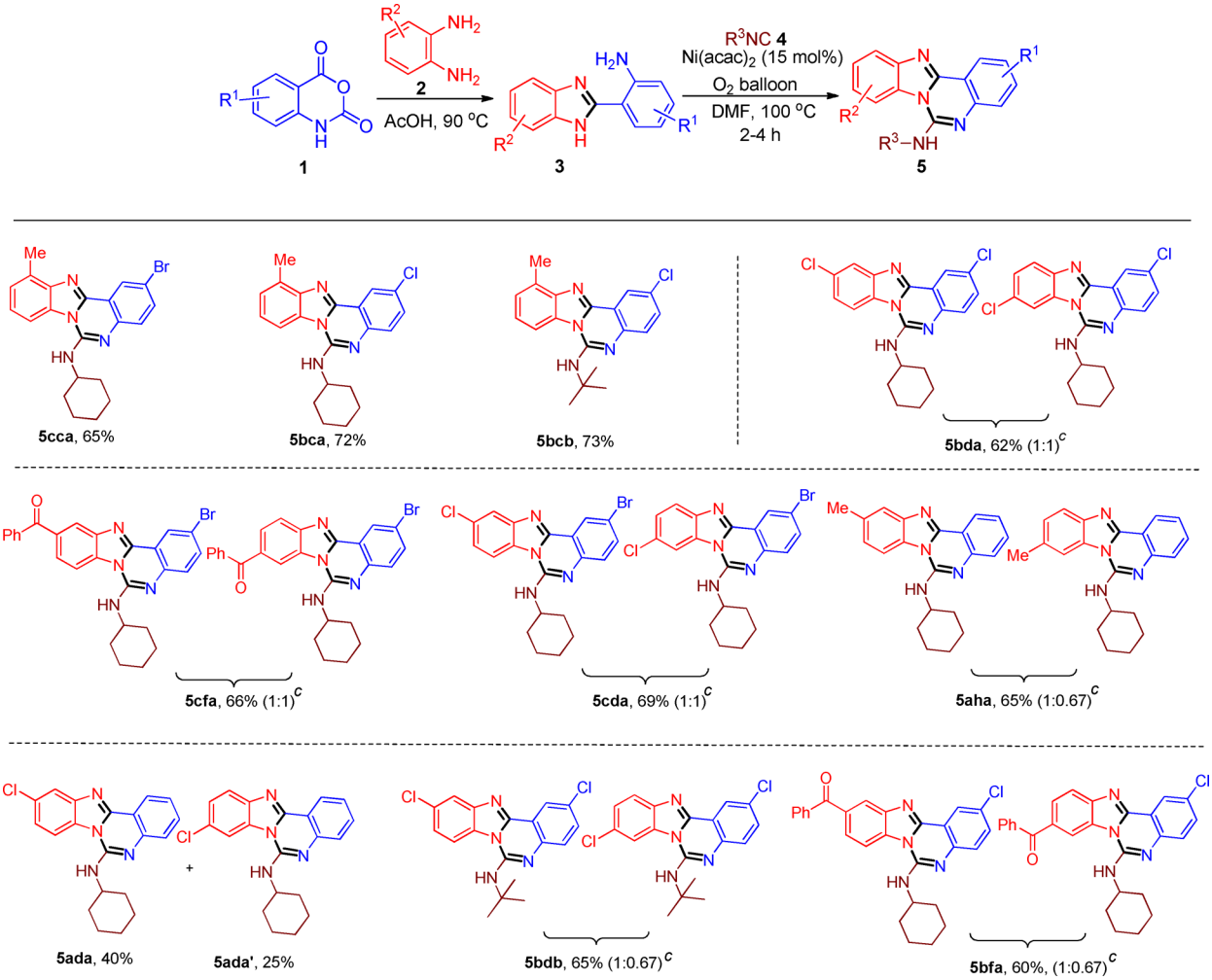
Table 3. Regioselectivity in Ni-Catalyzed Isocyanide Insertion and Scope of Isatoic Anhydrides 1 and *o*-Phenylenediamines 2 for the Synthesis of Quinazolines 5[a,b]



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

strategy has been demonstrated by synthesizing naphthalene-fused quinazoline compounds. The utility of the present SDAC has been shown by synthesizing through GBB reactions privileged benzimidazoquinazoline-fused imidazole hybrids that 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 the 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. UV–visible and fluorescence studies reveal possible applications for the discovery of highly fluorescent probes. Studies on nickel-catalyzed isocyanide insertions and exploration of the SDAC strategy are currently under way.

EXPEIMENTAL SECTION

General Considerations. In this section the preparations of all the compounds that have been made in the course of our studies have been discussed. For the experiments, all starting materials and reagents were purchased from standard commercial sources or were prepared in the laboratory. All glassware was cleaned with soapy water followed by acetone and dried in a hot air oven at 100 °C for 2 h. Solvents were distilled prior to use.

IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at 295 K in $CDCl_3$ or DMSO-d_6; chemical shift values (δ, ppm) and coupling constants (Hz) are reported in the 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 a 100 MHz spectrometer at 298 K 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 the carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra. In ^{1}H NMR, the following abbreviations are used throughout: 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 in Q-TOF electron spray ionization (ESI) 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.

General Procedure 1: Synthesis of 2-Aminophenylbenzimidazoles 3 via Opening of Isatoic Anhydride with Diamines 2. To a mixture of isatoic anhydride **1** (1 mmol) and diamine **2** (1 mmol)

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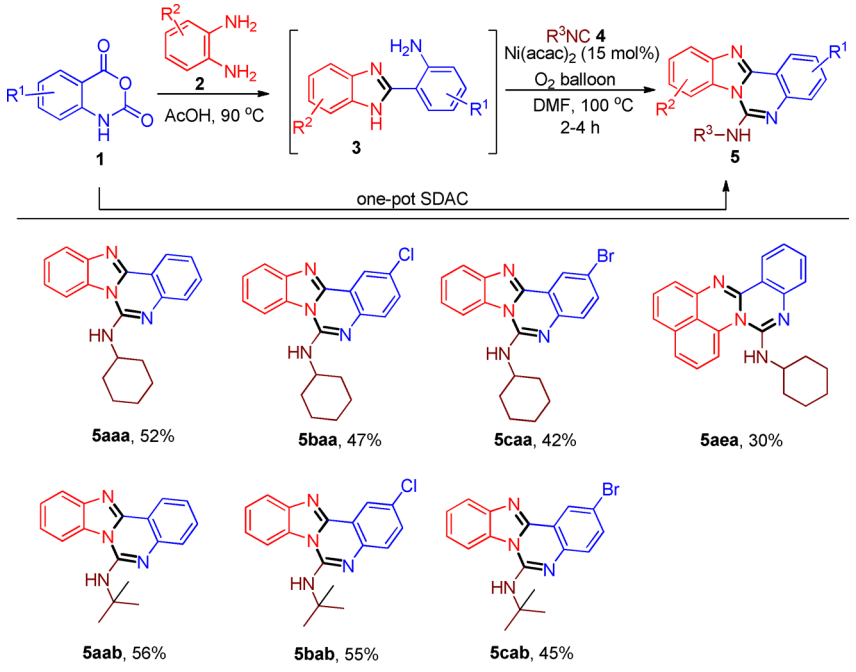
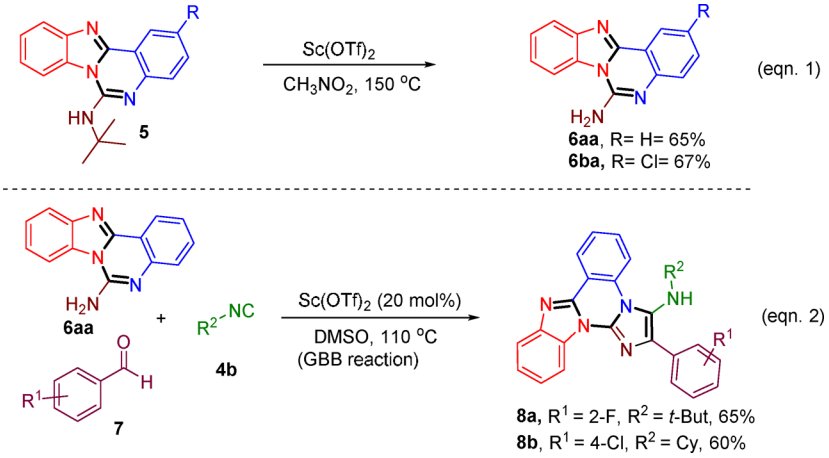
Table 4. One-Pot Synthesis of Quinazolines 5 via Sequential Double Annulation Cascade (SDAC) Strategy[a,b]

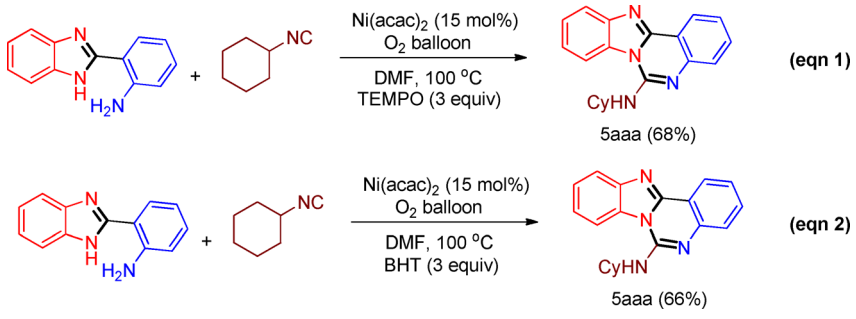


[a]*General conditions:* isatoic anhydride **1** (0.25 mmol), *o*-phenylenediamine **2** (0.25 mmol), amine **3** (0.25 mmol), isocyanide **4** (0.25 mmol), $Ni(acac)_2$ (15 mol %), O_2 balloon, and DMF (2 mL). For compound **5** the first letter refers to isatoic anhydride parts **1a−c**, the second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

Scheme 2. Synthetic Applicability of Products Generated through Ni-Catalyzed Isocyanide Insertion



Scheme 3. TEMPO and BHT Trapping Experiments



was added glacial acetic acid (2 mL), and the mixture was stirred at 90 °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 a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and then purified by silica gel column chromatography using ethyl acetate and hexane (15/85) as eluents to afford the corresponding product **3**.

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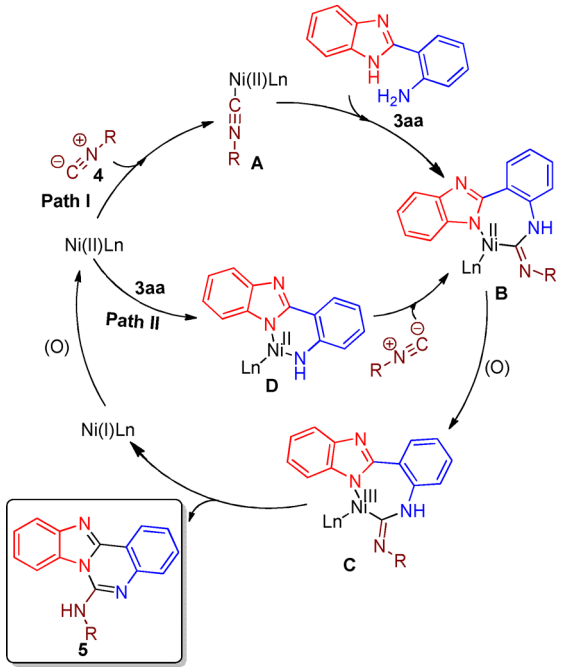

Figure 2. Plausible reaction mechanism for the formation of benzimidazoquinazoline **5**.

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 1×10^{-3} M in DCM. [b]Excited at 285 nm.

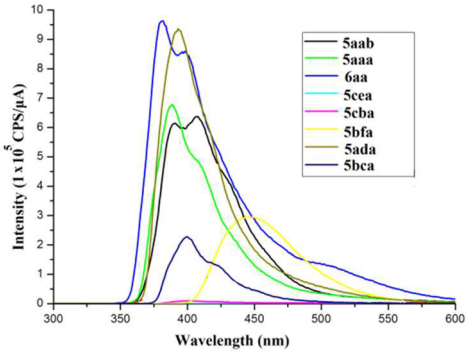

Figure 3. Fluorescence spectra of the compounds **5** recorded in DCM.

The compounds **3aa**–**ad** are already known in the literature, and compounds **3ca**–**bf** are newly synthesized according to general procedure 1.

Spectral Data for the 2-Aminophenylbenzimidazole Compounds 3ca–bf. *2-(1H-Benzo[d]imidazol-2-yl)-4-bromoaniline (**3ca**).* Following general procedure 1, **3ca** was isolated as a colorless solid: yield 207 mg (72%); mp 184–186 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3ae** was isolated as a yellow solid: yield 168 mg (65%); mp 138–140 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3be** was isolated as a orange solid: yield 176 mg (60%); mp 144–146 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3ce** was isolated as a yellow solid: yield 222 mg (66%); mp 184–186 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3cb** was isolated as a colorless solid: yield 198 mg (63%); mp 236–238 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3cc** was isolated as a colorless solid: yield 195 mg (65%); mp 158–160 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3cf** was isolated as a light yellow solid: yield 226 mg (58%); mp 236–238 °C; IR (MIR-ATR, 4000–600 cm^{-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 general procedure 1, **3cd** was isolated as a colorless solid: yield 173 mg (54%); mp 198–200 °C; IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} 3302, 3198, 2925, 1603, 1482, 1406, 1233, 864, 817, 745 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 6.83 (d, 8.8 Hz,

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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 general procedure 1, **3bf** was isolated as a light yellow solid: yield 201 mg (58%); mp 222−224 °C; IR (MIR-ATR, 4000−600 cm^{-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.

General Procedure 2: Synthesis of Quinazolines 5 via Ni-Catalyzed Isocyanide Insertion. To a mixture of 2-aminophenylbenzimidazole **3** (0.2 mmol), isocyanide **4** (0.2 mmol), and Ni(acac)$_2$ (15 mol %) in a 10 mL Schlenk tube was added 2 mL of DMF, and the mixture was stirred at 100 °C for 2−4 h (monitored by TLC) underan oxygen balloon. After the completion of the reaction, the reaction mixture was cooled and was quenched with ice-cold water. Then the reaction mixture was extracted with ethyl acetate (3 × 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 quinazoline products **5**.

General Procedure 3: One-Pot SDAC Synthesis of Quinazolines 5 via Isatoic Anhydride Opening/Ring Closing to 2-Aminophenylbenzimidazole/Ni-Catalyzed Isocyanide Insertion. To a 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 the mixture was stirred at 90 °C for 2−3 h and monitored by TLC. After completion of the reaction the acetic acid was evaporated using a rotary evaporator and dried under vacuum. To this residue was added isocyanide **4** (0.25 mmol), Ni(acac)$_2$ (15 mol %), and 2 mL of DMF, and the mixture was stirred at 100 °C for 2−3 h (monitored by TLC) under an oxygen balloon. After the completion of the reaction, the reaction mixture was cooled and was quenched with ice-cold water. Then the reaction mixture was extracted with ethyl acetate (3 × 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 quinazoline products **5**.

Spectral Data for the Quinazoline Compounds 5aaa−bfa. *N-Cyclohexylbenzo[4,5]imidazo[1,2-c]quinazolin-6-amine (**5aaa**).* Following general procedure 2, **5aaa** was isolated as a colorless solid: yield 54 mg (68%); mp 158−160 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3446, 3054, 2925, 2852, 1626, 1598, 1527, 1446, 1339, 758, 732 cm^{-1}; ^{1}H 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, 8 Hz, 1H), 8.02 (d, 8 Hz 1H), 8.54 (d, 8 Hz 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 general procedure 2, **5baa** was isolated as a colorless solid: yield 56 mg (64%); mp 178−180 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3449, 3054, 2928, 2852, 1625, 1598, 1528, 1208, 823, 731 cm^{-1}; ^{1}H 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 general procedure 2, **5caa** was isolated as a colorless solid: yield 61 mg (62%); mp 140−142 °C; IR (MIR-ATR, 4000−600 cm^{-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, found395.0860.

*N-(tert-Butyl)benzo[4,5]imidazo[1,2-c]quinazolin-6-amine (**5aab**).* Following general procedure 2, **5aab** was isolated as a colorless solid: yield 54 mg (75%); mp 134−136 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5bab** was isolated as a colorless solid: yield 61 mg (75%); mp 168−170 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5cab** was isolated as a colorless solid: yield 60 mg (65%); mp 188−190 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5aba** was isolated as a light yellow solid: yield 56 mg (65%); mp 208−210 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 3, **5aea** was isolated as a yellow solid: yield 44 mg (48%); mp 178−180 °C; IR (MIR-ATR, 4000−600 cm^{-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),

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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 general procedure 2, **5bea** was isolated as a yellow solid: yield 45 mg (45%); mp 136−138 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5cea** was isolated as a yellow solid: yield 52 mg (47%); mp 204−206 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5cba** was isolated as a colorless solid: yield 68 mg (65%); mp 216−218 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5abb** was isolated as a colorless solid: yield 59 mg (74%); mp 228−230 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5aac** was isolated as a colorless solid: yield 48 mg (60%); mp 152−154 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5aad** was isolated as a colorless solid: yield 47 mg (58%); mp 168−170 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5cca** was isolated as a colorless solid: yield 66 mg (65%); mp 208−210 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5bca** was isolated as a colorless solid: yield 65 mg (72%); mp 184−186 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5bcb** was isolated as a colorless solid: yield 62 mg (73%); mp 210−212 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5bda** was isolated as a colorless inseparable solid mixture: yield 60 mg (62%); mp 178−180 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 2, **5cfa** was isolated as a yellow inseparable solid mixture: yield 82 mg (66%); mp 210−212 °C; IR (MIR-ATR, 4000−600 cm^{-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,

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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 general procedure 2, **5cda** was isolated as a inseparable colorless solid mixture: yield 74 mg (69%); mp 190−192 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3445, 2927, 2853, 1626, 1597, 1522, 1466, 1422, 1207, 821, 737 cm^{-1}; ^{1}H 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 general procedure 2, **5aha** was isolated as a colorless inseparable solid mixture: yield 54 mg (65%); mp 174−176 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3408, 2920, 1607, 1482, 834, 735 cm^{-1}; ^{1}H 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 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, 4000−600 cm^{-1}) ν_{max} 3444, 3062, 2927, 2853, 1627, 1599, 1525, 1428, 1208, 1068, 865, 761; ^{1}H 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, 4000−600 cm^{-1}) ν_{max} 3431, 2927, 2852, 1625, 1598, 1528, 1450, 1340, 814, 759 cm^{-1}; ^{1}H 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 2 Hz, 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 general procedure 2, **5bdb** was isolated as a colorless inseparable solid mixture: yield 58 mg (65%); mp 206−208 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3450, 2967, 2928, 1631, 1600, 1526, 1198, 822, 776 cm^{-1}; ^{1}H 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 general procedure 2, 5bfa was isolated as a a yellow inseparable solid mixture: yield 68 mg (60%); mp 192−194 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3338, 3056, 2928, 2853, 1628, 1598, 1275, 824, 718 cm^{-1}; ^{1}H 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.

General Procedure 4: Synthesis of Free Amine 6-Amino-benzimidazoquinazolines 6aa and 6ba from 5aab and 5bab by *tert*-Butyl Deprotection. In an 10 mL sealed tube was placed compound **5aab** or **5bab** (0.5 mmol) and 2 mL of nitromethane was added, followed by addition of $Sc(OTf)_2$ (0.75 mmol). The tube was heated to 150 °C for 6 h. Then the solvent was evaporated using a rotary evaporator. The crude product was dissolved in ethyl acetate and filtered through a pad of Celite, and the crude product was purified through a silica gel (100−200 mesh) column using hexane and ethyl acetate (4/1) as eluents to yield the desired product **6aa** or **6ba** as a free amine.

Spectral Data for the Compounds 6aa and 6ba. *Benzo[4,5]-imidazo[1,2-c]quinazolin-6-amine (**6aa**).* Following general procedure 4, **6aa** was isolated as a colorless solid: yield 76 mg (65%); mp >300 °C; IR (MIR-ATR, 4000−600 cm^{-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 general procedure 4, **6ba** was isolated as a colorless solid: yield 90 mg (67%); mp 268−270 °C; IR (MIR-ATR, 4000−600 cm^{-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.

General Procedure 5: Synthesis of Compounds 8a,b via a Groebke−Blackburn−Bienayme (GBB) Type Reaction. To a mixture of amine (**6**, 0.2 mmol), 4-chlorobenzaldehyde (**7**, 0.2 mmol), and *tert*-butyl isocyanide (**4b**; 0.2 mmol) were added scandium triflate (20 mol %) and 2 mL of DMSO, and the mixture was heated to 110 °C for 8 h. After completion of the reaction (checked by TLC), ice-cold water was added, the mixture was extracted with ethyl acetate (3 × 15 mL), and the extract was dried over anhydrous Na_2SO_4 and

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concentrated under reduced pressure. The crude extract was purified by filtration through a short pad of silica gel (60−120 mesh) column using hexane/EtOAc (5/1) to give compound **8a** or **8b**.

Spectral Data for the Compounds 8a,b. *N-Cyclohexyl-2-(2-fluorophenyl)benzo[4,5]imidazo[1,2-c]imidazo[1,2-a]quinazolin-3-amine (**8a**).* Following general procedure 5, **8a** was isolated as a yellow solid: yield 58 mg (65%); mp 188−190 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3334, 2960, 1609, 1478, 1374, 823, 732 cm^{-1}; ^1H 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, $^1J_{C-F}$ = 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 general procedure 5, **8b** was isolated as a yellow solid: yield 53 mg (60%); mp 236−238 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} 3369, 2968, 1603, 1474, 1365, 1203, 835, 746 cm^{-1}; ^1H 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 at DOI: 10.1021/acs.joc.6b02423.

Experimental procedures and characterization data for all new compounds, NMR spectra, and X-ray data for **5abb** (PDF)

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for D.S.S.: sharada@iith.ac.in.

ORCID

Duddu S. Sharada: 0000-0001-5861-4126

Notes

The authors declare no competing financial interest.

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