An Efficient Three-component, One-pot Synthesis of Quinazolines under Solvent-free and Catalyst-free Condition

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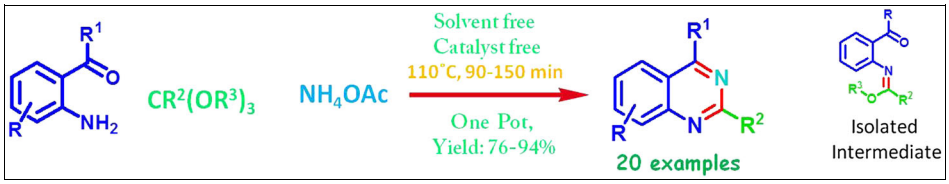

An efficient green protocol for the synthesis of quinazolines in the absence of solvent and catalyst has been developed. 2,4-Disubstituted quinazolines have been synthesized from three-component one-pot reactions of 2-aminoaryl ketones, orthoesters, and ammonium acetate. The present method has advantages of operational simplicity, substrate generality, clean reaction, high yields (76–94%), and moderate reaction time. The plausible mechanism of the reaction has been proposed based on the spectral characterization and single crystal X-ray analysis of isolated intermediate.

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INTRODUCTION

The concept of green chemistry and its principles [1] spread worldwide with the aim to develop environmental consciousness in chemical synthesis. As a result, the mindset of researchers has been diverted from the traditional chemistry processes, and scientists are adopting green chemistry, which not only is advantageous to the environment but also makes economic sense for the industry and academia [2]. The reduction of waste, lowering of energy costs, and avoidance of toxic organic solvents and other auxiliaries in chemical transformations have become the major concerns in industry and academia to develop an environmentally benign synthetic protocol.

Quinazoline is one of the most important nitrogen-containing fused heterocycles present in a wide variety of natural products and synthetic pharmaceutical ingredients [3–6]. They are known to show diverse biological and therapeutic properties [7–22]. Several drugs have been developed based on quinazoline motif and marketed by various pharmaceutical companies [23]. In addition, quinazoline scaffolds have also been found important in other relevant fields such as material science [24], agrochemicals [25–27], and explosives [28].

A variety of conventional procedures have been reported for the synthesis of quinazolines [29–36], but most of them suffer from multistep synthesis, lower yield, harsh conditions, and use of toxic solvents, expensive catalyst, and additives. Quite recently, practical protocols in the absence of solvents [37] and catalysts [38] have been reported. However, these methods suffer from drawbacks such as requirement of additives and much effort to recycle the materials. Moghadam et al. [39] reported one-pot, three-component synthesis of 4-aminoquinazolines under microwave condition; however, it suffers from limitation of substrate generality. The group of Mahajan [40] reported the synthesis of quinazolines under solvent-free and catalyst-free conditions using conventional microwave oven. However, this method requires tedious synthesis of starting materials. Recently, Bandaru et al. [41] synthesized 2,4-disubstituted quinazolines in aqueous medium using 2-aminocarbonyl compounds, aldehydes, and ammonium acetate; however, this method has limitations such as its low product yield, the requirement of excess ammonium acetate (10 equiv), and failure to yield the required product with aliphatic aldehydes. The three-component synthesis of quinazolines using molecular iodine catalyst under neat/EtOH condition [42] and copper-catalyzed traditional solvent-assisted synthesis [43] were reported during the course of the present work. Owing to their widespread applications, the quest for new, simple, and efficient method for the synthesis of quinazolines from readily available precursors under green reaction condition is of continuing interest among the chemists.

Among various chemical approaches, multicomponent reactions [44] have gained significant importance because of their highly flexible, (chemo)selective, convergent, and atom-efficient nature [45–48] and hence become current area of interest in organic, medicinal, and combinatorial chemistry research [49–51]. Being one-pot reactions, multicomponent reactions are practically single-step conversions, and they are easier to carry out than classical

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multistep approach to synthesize complex organic molecules. If such reactions with near quantitative yield could be carried out under solvent-free and catalyst-free conditions from readily available starting materials, they would comply with most of the green chemistry principles [1] and closely approach the concept of ideal synthesis [52].

As a part of our ongoing research program on the development of efficient and green approaches in organic synthesis [53,54], herein we report a one-pot three-component protocol for the synthesis of quinazolines. This method involves the reaction of 2-aminoarylketones, orthoesters, and ammonium acetate under solvent-free and catalyst-free conditions in one pot (Scheme 1). The present protocol has several advantages such as it involves neat reaction condition, uses readily available starting materials that are well known in several green transformations, achieves high yield, and has moderate reaction time and hence can be considered as green or sustainable synthetic protocol.

RESULTS AND DISCUSSION

Initially, the three-component reaction of 2-aminobenzophenone (**1a**) with 1 equiv of triethyl orthoformate (**2a**) and 1 equiv of ammonium acetate were investigated under solvent-free and catalyst-free conditions at 110°C. The reaction was monitored with TLC (petroleum ether/ethyl acetate, 9:1). Partial conversion was observed after 1 h, but the complete conversion was not observed even after prolonged reaction time (Table 1, entry 1). However, quinazoline (**4a**) was isolated in 52% yield, and unconsumed starting material **1a** was recovered. These results encouraged us to optimize the reaction conditions, and hence, excess amounts of triethyl orthoformate and ammonium acetate have been used in order to improve the product yield (Table 1, entries 2–4). The optimized ratio of **1a**/**2a**/NH_4OAc 1:1.5:1.5 was determined to be the more suitable combination for better conversion and to obtain the desired product with good yield, without

Scheme 1. Synthesis of quinazolines under solvent-free and catalyst-free conditions.

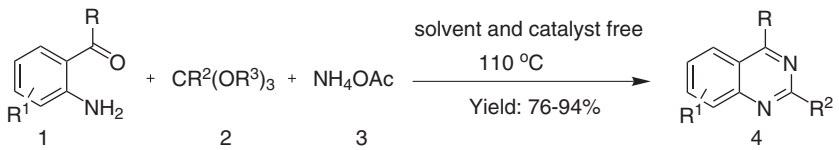
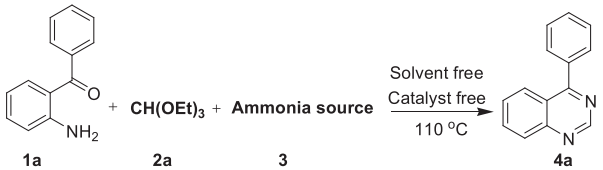


Table 1

Optimization of the one-pot three-component synthesis of quinazolines.



Entry	Ammonia source	Molar ratio **1a**:**2a**:**3**	Time (min)[a]	Yield (%)[b]
1		1:1:1	240	52
2		1:1.2:1.2	240	66
3	Ammonium acetate	1:1.2:1.5	240	70
4		**1**:**1.5**:**1.5**	**120**	**93**
5	Urea	1: 1.5:1.5	180	32
6	Ammonium sulfate	1: 1.5:1.5	180	46
7	Ammonium chloride	1: 1.5:1.5	180	trace
8	Ammonium fluoride	1: 1.5:1.5	180	trace
9	Ammonium phosphate	1: 1.5:1.5	180	67
10	Ammonium oxalate	1: 1.5:1.5	180	43
11	Ammonium hydroxide	1: 1.5:1.5	180	52
12	Ammonium carbonate	1: 1.5:1.5	180	81

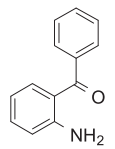
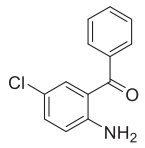
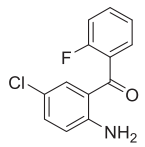
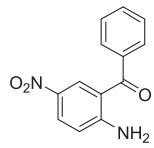
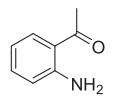
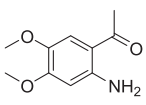
[a]The reactions were monitored by TLC.
[b]Isolated yield.
To highlight the optimized conditions.

any impurity formation, and in moderate reaction time (Table 1, entry 4). Further, decrease of temperature to 90°C resulted in poor reactant conversion even after prolonged reaction time. Subsequently, a series of solvent-free reaction of 2-aminobenzophenone and triethyl orthoformate have been carried out with various other ammonia sources under identical conditions in order to compare the efficiency (Table 1, entries 5–12) of the current green protocol. Decreased yields, a small amount of unidentified impurities along with unconsumed starting materials were observed when urea, ammonium chloride, ammonium fluoride, ammonium phosphate, ammonium oxalate, ammonium hydroxide, and ammonium sulfate were used as ammonia source. Comparative conversion was observed when ammonium carbonate was used as ammonia source; however, it requires longer reaction time. Hence, ammonium acetate was found to be the most efficient ammonia source for the present three-component synthesis, and further reactions were carried out using ammonium acetate as a source of ammonia.

In order to evaluate the scope and limitations of the present protocol, the reaction was further performed using various substituted 2-aminoaryl ketones and trialkyl orthoesters, and the results are summarized in Table 2. To evaluate the generality of the reaction, the reaction was performed with both 2-aminobenzophenones and 2′-aminoacetophenones. The reaction with 2′-aminoacetophenones proceeds faster than 2-aminobenzophenones to yield corresponding quinazolines. This may be attributed

Table 2

Three-component synthesis of quinazolines under solvent-free and catalyst-free conditions.

Entry	2-Aminoarylketone	Trialkyl orthoester	Time (min)	Product[a]	Yield (%)[b]	Lit. ref.[c]
1		$H–C(OC_2H_5)_3$	120	**4a**	93	59,60
2		$H_3C–C(OC_2H_5)_3$	120	**4b**	89	59,60
3		$H_5C_2–C(OC_2H_5)_3$	120	**4c**	90	59
4		$H_9C_4–C(OCH_3)_3$	120	**4d**	86	59
5		$H_5C_6–C(OCH_3)_3$	150	**4e**	90	
6		$H–C(OC_2H_5)_3$	120	**4f**	94	60,61
7		$H_3C–C(OC_2H_5)_3$	120	**4g**	88	62
8		$H_5C_2–C(OC_2H_5)_3$	120	**4h**	88	59
9		$H_5C_6–C(OCH_3)_3$	150	**4i**	87	
10		$H–C(OC_2H_5)_3$	120	**4j**	93	63
11		$H_3C–C(OC_2H_5)_3$	120	**4k**	86	
12		$H_5C_6–C(OCH_3)_3$	150	**4l**	84	36
13		$H–C(OC_2H_5)_3$	120	**4m**	88	
14		$H_5C_2–C(OC_2H_5)_3$	120	**4n**	76	
15		$H_9C_4–C(OCH_3)_3$	120	**4o**	79	
16		$H_5C_6–C(OCH_3)_3$	150	**4p**	Trace	
17		$H–C(OC_2H_5)_3$	90	**4q**	88	64,65
18		$H_3C–C(OC_2H_5)_3$	120	**4r**	79	59
19		$H_5C_6–C(OCH_3)_3$	120	**4s**	81	
20		$H–C(OC_2H_5)_3$	90	**4t**	Trace	
21		$H_3C–C(OC_2H_5)_3$	120	**4u**	82	
22		$H_5C_6–C(OCH_3)_3$	120	**4v**	84	41

[a]Reaction conditions: 2-aminoaryl ketone (1 mmol), trialkyl orthoester (1.5 mmol), and ammonium acetate (1.5 mmol) at 110°C.
[b]Isolated yield.
[c]The spectral data are consistent with reported literature.

to the steric factor induced by the aryl substitution, which reduces the reactivity of carbonyl group. The reaction worked well with both electron-withdrawing and electron-donating substituents on the aniline ring of 2-amino-benzophenones. However, poor conversion was observed with strong electron-donating group on the aniline ring of 2′-aminoacetophenone, and unexpectedly, only trace amount of product was observed when 2-amino-4′,5′-dimethoxy-acetophenone reacted with triethyl orthoformate, even after prolonged reaction time as shown in Table 2, entry 20.

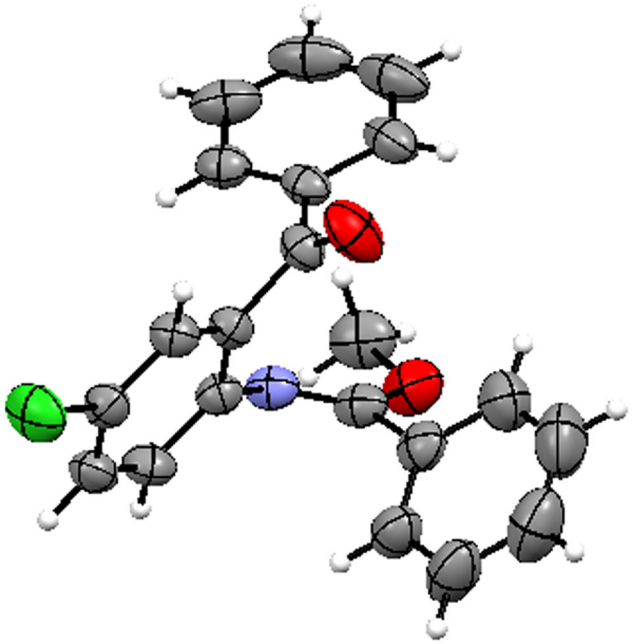


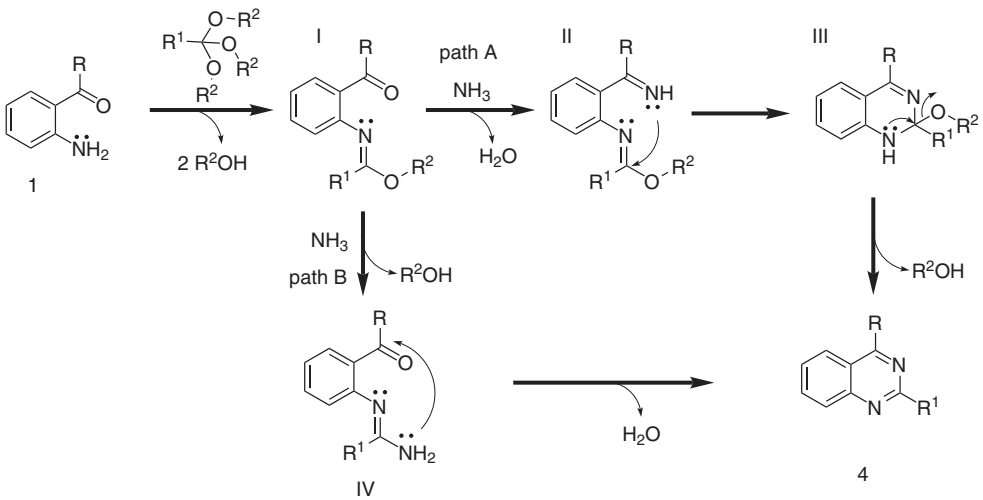
Figure 1. ORTEP (50% probability) diagram of the crystal structure of *N*-2-benzoyl-4-chlorophenylbenzimidate (**4ii**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com].

Furthermore, the reaction feasibility was also examined with different substituted trialkyl orthoesters. The reactivity of aliphatic orthoesters was found to be better than orthobenzoate, and their order of reactivity is orthoformate > orthoalkylate (orthoacetate ≈ orthopropionate ≈ orthovalerate) > orthobenzoate. This may be attributed to the steric effect induced by the substituent on the orthoester functionality. It was found that there was no remarkable effect of chain length of orthoalkylates on the present reaction. For instance, the reaction of 2-aminobenzophenone with orthoacetate, orthopropionate, and orthovalerate underwent smoothly to obtain corresponding quinazolines in good yields. The reactions of 2-aminobenzophenones with trimethyl orthobenzoate found to be very slow and took longer time to complete. This may be attributed to the formation of stabilized imidate intermediate (**I**, scheme 2) as a result of the presence of phenyl group at 2-position, and this phenomenon helps us to isolate the intermediate in order to predict the mechanistic pathway.

To elucidate the reaction mechanism, the reaction of 2-aminobenzophenone with ammonium acetate and trimethylorthobenzoate was quenched after 60 min. It was found that the reaction was incomplete and methyl *N*-2-benzoylphenylbenzimidate (**4ei**) was formed as a major product with trace amount of aromatized quinazoline **4e**. Further, a similar observation was found when the three-component reaction was performed using (2-amino-5-chlorophenyl)(phenyl)methanone and (2-amino-5-chlorophenyl)(2-fluorophenyl)methanone. The isolated intermediates **4ei**, **4ii**, and **4li** were confirmed by spectral analysis, and in addition, *N*-2-benzoyl-4-chlorophenylbenzimidate (**4ii**) was confirmed by single crystal X-ray diffraction analysis (CCDC no. 912138) (Figure 1).

Based on our studies and literature references, two plausible mechanistic pathways are proposed as shown in Scheme 2. It

Scheme 2. Proposed mechanism for the formation of quinazolines **4** in the current protocol.



was unambiguously confirmed that the initial reaction of 2-aminoketone and orthoester leads to the formation of imidate intermediate [**I**] with the elimination of alcohol. The imidate intermediate [**I**] can undergo two different pathways to obtain the final quinazoline (**4**). According to Panja et al., the ketone group can form a ketimine [**II**] by condensation with the ammonia generated [42], which on simultaneous intramolecular cyclization and aromatization with the elimination of alcohol yields quinazoline (**4**). Alternatively, the imidate can react with ammonia generated to form vinylamidine intermediate [**IV**] [55], which can lead to formation of the final quinazoline (**4**) product through intramolecular cyclization with the elimination of water.

CONCLUSION

In conclusion, herein we report a three-component, one-pot synthesis of quinazolines using 2-aminoaryl ketones, orthoesters, and ammonium acetate as building blocks under solvent-free and catalyst-free conditions. The mechanism has been investigated scientifically with the confirmation of the intermediate using spectral and single crystal X-ray analysis. It was clearly found that the first step of the reaction involves the formation of imidate intermediate. Notably, this single flask protocol offers easier method to synthesize both aliphatic and aromatic substitutions at 2-position and 4- position of quinazolines. The current protocol circumvents some of the problems and limitations associated with the earlier procedures, is advantageous in terms of operational simplicity, ready availability of starting materials, simple work up procedure, and high product yield, and it is conceivable that it offers a facile and environmental friendly approach toward the development of biologically potent quinazolines.

EXPERIMENTAL

General methods. Melting points were determined with Stuart SMP3 (Stuart Scientific, UK) melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo scientific Nicolet Avatar 330 (Thermo Scientific, USA) FT-IR spectrometer as neat sample. NMR spectra were recorded as a solution in CDCl3/DMSO-d_6 500 MHz (^{1}H) and 400 MHz (^{13}C) instrument. Chemical shifts (δ) are reported in parts per million (ppm) with TMS as an internal standard. NMR raw data were analyzed with the program MestReNova (Mestrelab Research) 7.0.0-8331. Mass spectra were performed on Waters Micromass Q-Tof mass spectrometer with an ESI source. Elemental analysis was performed using Perkin Elmer, Series II, 2400 (Perkin Elmer, USA) analyzer. The X-ray single-crystal diffraction was performed on the Bruker AXS APEX II system (Bruker, Germany). All experiments were monitored by TLC, performed on pre-coated silica gel 60 F254 plates (Merck). Column chromatography was performed on silica gel (60–120 mesh, Merck) using ethyl acetate/petroleum ether (boiling range 60–80°C) as eluent.

General procedure for the synthesis of quinazoline derivatives. 2-Aminoaryl ketone 1 (1 mmol), orthoester 2 (1.5 mmol), and ammonium acetate 3 (1.5 mmol) were charged into a 10-mL round-bottom flask, and the mixture was heated to 110°C using conventional oil bath. The reaction mixture was stirred for 90–150 min until the starting material **1** was consumed to maximum extent. The mixture was diluted with EtOAc (10 mL × 2) and quenched with water (10 mL). The organic layer was separated and directly column chromatographed using 1:9 ethyl acetate/petroleum ether (boiling range 60–80°C) as the eluent to obtain pure quinazoline **4**. The structures of the products were unequivocally confirmed by spectral data and elemental analysis. All spectra of previously reported compounds were consistent with literature [36,41,59–65].

2,4-Diphenylquinazoline (4e). White solid; yield: 90%; mp: 119–121°C (lit. 118–120°C) [56]; IR (neat, cm^{-1}): 3056, 1610, 1562, 1535, 1482, 1380, 1336, 1165, 1073; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.48–7.55 (m, 4H), 7.59–7.62 (m, 3H), 7.87–7.90 (m, 3H), 8.13(d, 1H, J = 8.5 Hz), 8.16 (d, 1H, J = 8.5 Hz), 8.7 (dd, 2H, J_1 = 8 Hz, J_2 = 1.5 Hz); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 121.7, 126.9, 128.4, 128.6, 128.7, 129.2, 129.9, 130.2, 130.5, 133.5, 137.7, 138.2, 152.0, 160.3, 168.3; ESI MS (m/z) = 283.1 $(M+H)^+$; *Anal*. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92, Found: C, 84.94; H, 5.14; N, 9.82.

6-Chloro-2,4-diphenylquinazoline (4i). White solid; yield: 87%; mp: 196–198°C (lit. 190–192°C) [57]; IR (neat, cm^{-1}): 3051, 1556, 1530, 1473, 1381, 1301, 1157, 1071; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.49–7.55 (m, 3H), 7.60–7.64 (m, 3H), 7.81(dd, 1H, J_1 = 2 Hz, J_2 = 9 Hz), 7.85–7.88 (m, 2H), 8.09–8.11 (m, 2H), 8.66–8.68 (m, 2H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 122.2, 125.8, 128.6, 128.7, 128.8, 130.1, 130.2, 130.8, 130.9, 132.6, 134.5, 137.1, 137.8, 150.5, 160.5, 167.6; ESI MS (m/z) = 317.1 $(M+H)^+$; *Anal*. Calcd for $C_{20}H_{13}ClN_2$: C, 75.83; H, 4.14; N, 8.84, Found: C, 75.67; H, 4.28; N, 8.71.

6-Chloro-4-(2-fluorophenyl)-2-methylquinazoline (4k). White solid; yield: 86%; mp: 139–141°C; IR (neat, cm^{-1}): 3059, 2913, 1614, 1548, 1484, 1385, 1215; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.95 (s, 3H), 7.27–7.31 (m, 1H), 7.38 (td, 1H, J_1 = 1 Hz, J_2 = 7.5 Hz); 7.56–7.59 (m, 2H), 7.72 (t, 1H, J = 2.5 Hz), 7.81 (dd, 1H, J_1 = 2.5 Hz, J_2 = 9 Hz), 7.96 (d, 1H, J = 9 Hz); ^{13}C-NMR(100.6 MHz, $CDCl_3$) δ: 26.5, 116.2, 116.4, 124.9, 125.6, 129.9, 131.5, 132.0, 132.1, 132.7, 135.0, 149.5, 161.0, 163.9; ESI MS (m/z) = 273.1 $(M+H)^+$; *Anal*. Calcd for $C_{15}H_{10}ClFN_2$: C, 66.06; H, 3.70; N, 10.27, Found: C, 65.90; H, 3.81; N, 10.13.

2-Ethyl-6-nitro-4-phenylquinazoline (4n). Pale yellow solid; yield: 76%; mp: 127–129°C; IR (neat, cm^{-1}): 3090, 2975, 2917, 2850, 1611, 1578, 1542, 1474, 1326, 1079; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.43 (t, 3H, J = 7.5 Hz), 3.16 (q, 2H, J = 7.5 Hz), 7.68–7.73 (m, 3H), 7.88 (dt, 2H, J_1 = 2 Hz, J_2 = 5.5 Hz), 8.22 (d, 1H, J = 9 Hz), 8.68 (dd, 1H, J_1 = 2 Hz, J_2 = 9 Hz), 8.82 (d, 1H, J = 2.5 Hz); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 12.1, 32.9, 119.6, 123.7, 126.3, 128.6, 129.5, 129.9, 130.4, 135.6, 144.9, 153.5, 170.0, 170.9; ESI MS (m/z) = 280.2 $(M+H)^+$; *Anal*. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05, Found: C, 68.94; H, 4.78; N, 14.91.

2-Butyl-6-nitro-4-phenylquinazoline (4o). White solid; yield: 79%; mp: 104–107°C; IR (neat, cm^{-1}): 3059, 2953, 2925, 2860, 1615, 1543, 1491, 1336, 1251, 1086; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.95 (t, 3H, J = 7.5 Hz), 1.39–1.46 (sextet, J = 7.5 Hz, 2H), 1.86–1.92 (m, 2H), 3.13 (t, 2H, J = 7.5 Hz), 7.68–7.73 (m, 3H), 7.86–7.88 (m, 2H),

8.21 (d, 1H, $J = 9.5$ Hz), 8.67 (dd, 1H, $J_1 = 2.5$ Hz, $J_2 = 9.5$ Hz), 8.81 (d, 1H, $J = 2.5$ Hz); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 22.7, 30.8, 40.0, 120.1, 124.2, 126.9, 129.1, 130.1, 130.4, 130.9, 136.2, 145.4, 153.9, 170.5, 170.8; ESI MS (m/z) = 308.2 $(M + H)^+$; *Anal*. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67, Found: C, 70.50; H, 5.41; N, 13.49.

4-Methyl-2-phenylquinazoline (4s). White solid; yield: 81%; mp: 71–74°C (lit. 72–76°C) [58]; IR (neat, cm^{-1}): 3058, 3007, 2920, 1611, 1540, 1489, 1432, 1387, 1335, 1226, 1023; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.03 (s, 3H), 7.49–7.55 (m, 3H), 7.57–7.60 (m, 1H), 7.85–7.88 (m, 1H), 8.07–8.11 (m, 2H), 8.61–8.63 (m, 2H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 22.03, 123.05, 125.0, 126.9, 128.6, 129.3, 130.4, 133.5, 138.4, 150.5, 160.2, 168.2; ESI MS (m/z) = 221.1 $(M + H)^+$; *Anal*. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72, Found: C, 81.90; H, 5.33; N, 12.65.

6,7-Dimethoxy-2,4-dimethylquinazoline (4u). Light brownish solid; yield: 82%; mp: 87–89°C; IR (neat, cm^{-1}): 2944, 2838, 1655, 1614, 1568, 1500, 1461, 1410, 1234, 1014; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.8 (s, 3H), 2.85 (s, 3H), 4.04 (s, 6H), 7.18 (s, 1H), 7.25 (s, 1H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 21.7, 26.2, 56.2, 56.3, 102.3, 106.7, 155.7, 164.7; ESI MS (m/z) = 219.1 $(M + H)^+$; *Anal*. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84, Found: C, 65.93; H, 6.55; N, 12.77.

Methyl N-2-benzoylphenylbenzimidate (intermediate of 4e) (4ei). Pale yellow viscous liquid; IR (neat, cm^{-1}): 3059, 2947, 1648, 1594, 1446, 1284, 1109; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.52 (s, 3H), 6.76 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 8$ Hz), 7.05(td, 1H, $J_1 = 1$ Hz, $J_2 = 7.5$ Hz), 7.16–7.23 (m, 4H), 7.28–7.41 (m, 5H), 7.50–7.53 (m, 1H), 7.67–7.69 (m, 2H); ^{13}C-NMR(100.6 MHz, $CDCl_3$) δ: 53.9, 115.5, 117.0, 122.3, 122.5, 128.0, 128.1, 129.1, 129.1, 129.8, 130.1, 131.5, 132.5, 147.3, 159.4, 197.3; ESI MS (m/z) = 338.2 $(M + Na)^+$, 316.2 $(M + H)^+$, 284.2 $(M–OMe)^+$; *Anal*. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44, Found: C, 79.92; H, 5.51; N, 4.38.

Methyl N-2-benzoyl-4-chlorophenylbenzimidate (intermediate of 4i) (4ii). White solid; mp: 96–98°C; IR (neat, cm^{-1}): 3059, 2949, 1651, 1590, 1441, 1396, 1280, 1108; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 6.70 (d, 1H, $J = 8.5$ Hz), 7.2 (d, 2H, $J = 4$ Hz), 7.28–7.33 (m, 4H), 7.40–7.43 (m, 2H), 7.53–7.56 (m, 1H), 7.7 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 54.0, 123.9, 127.8, 128.2, 128.3, 129.0, 129.3, 129.8, 130.4, 130.7, 131.3, 132.6, 132.9, 137.3, 145.8, 160.1, 195.8; ESI MS (m/z) = 372.2 $(M + Na)^+$, 350.2 $(M + H)^+$, 318.2$(M–OMe)^+$; *Anal*. Calcd for $C_{21}H_{16}ClNO_2$: C, 72.10; H, 4.61; N, 4.00, Found: C, 71.98; H, 4.56; N, 4.11.

Methyl N-4-chloro-2-(2-fluorobenzoyl)phenylbenzimidate (intermediate of 4l) (4li). White solid; mp: 93–96°C; IR (neat, cm^{-1}): 3061, 2933, 2921, 1645, 1597, 1477, 1442, 1278, 1223, 1105; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.43 (s, 3H), 6.60 (d, 1H, $J = 9$ Hz), 7.06–7.10 (m, 1H), 7.19–7.25 (m, 6H), 7.31–7.34 (m, 1H), 7.46–7.50 (m, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 53.9, 116.1, 116.3, 123.8, 124.2, 128.2, 129.0, 129.5, 130.4, 130.5, 130.9, 132.2, 133.7, 133.8, 146.1, 159.8, 160.0, 162.3, 192.4; ESI MS (m/z) = 390.2 $(M + Na)^+$, 368.2 $(M + H)^+$, 336.2 $(M–OMe)^+$; *Anal*. Calcd for $C_{21}H_{15}ClFNO_2$: C, 68.58; H, 4.11; N, 3.81, Found: C, 68.47; H, 4.18; N, 3.78.

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