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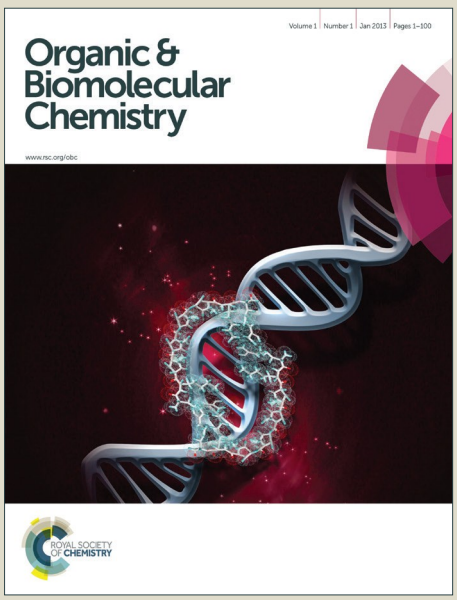

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Copper-catalyzed Tandem Ullmann type C–N Coupling and Dehydrative Cyclization: Synthesis of Imidazo[1,2-c]quinazolines

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A simple and efficient one-pot protocol has been demonstrated for the synthesis of imidazo[1,2-c]quinazoline derivatives through copper catalyzed tandem reaction between substituted 2-(2-bromophenyl)-1H-imidazoles and formamide. The synthetic protocol involves initial Ullmann-type C–N coupling followed by intramolecular dehydrative cyclization. The method uses readily available 2-(2-bromophenyl)-1H-imidazoles as the starting materials to afford imidazo[1,2-c]quinazolines in moderate to good yields and provided 610 mg (71%) yield of **3a** from a gram scale reaction.

Introduction

Nitrogen containing polyheterocyclic compounds have received much attention from synthetic as well as medicinal chemists, because of the diverse range of their pharmacological properties. Among them quinazoline fused molecules such as indolo-, imidazo- and benzimidazo-quinazolines are found to exhibit a wide range of therapeutic activities such as PI3-kinase inhibition,[1] tumor necrosis factor alpha (TNF-α) production inhibitors,[2] antimicrobial agents (BMCL)[3] etc. (Figure 1). The hybrid structures of benzimidazole and quinazoline derivatives also show interesting properties in organic light–emitting devices (OLEDs). Dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline derivatives have been reported to behave as selective ratiometric fluorescent chemosensor for iron and aluminum ions (Figure 1).[4, 5] Despite high importance of these molecules in pharmaceuticals and materials science, synthetic methods for the preparation of quinazoline fused heterocyclic frameworks are limited.[6-9] Moreover, these methods generally require multistep synthesis, strict reaction conditions and inaccessible starting materials. Therefore, alternative synthetic approaches for quinazoline fused heterocyclic frameworks are desired.

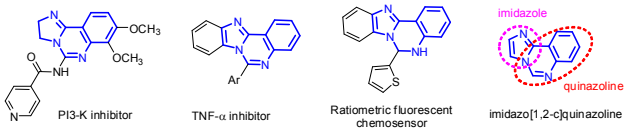
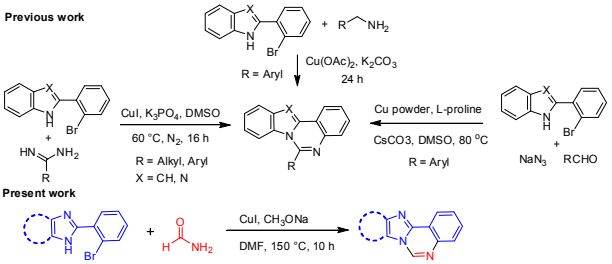


Figure 1: Structure of some important quinazoline fused heterocyclic compounds

In recent years, copper salts have been proven to be highly efficient catalysts in cross coupling reactions including Ullmann-type couplings reactions due to their less toxicity and high functional group tolerance and economical attractiveness.[10-14]

Copper-catalyzed tandem reactions have emerged as powerful tools for the synthesis of polyheterocycles,[15-24] and some quinazoline fused heterocycles have been synthesized *via* copper-catalyzed tandem reactions.[25-29] Fu and co–workers synthesized benzo[4,5]imidazo[1,2-*c*]quinazolineand indolo[1,2-*c*]quinazoline derivatives using copper-catalyzed cascade reaction of amidines or amino acids with 2-(2-bromophenyl)-1H-benzo[*d*]imidazolesand 2-(2-halophenyl)indoles, respectively (Scheme 1).[25, 26] Wang *et. al* have demonstrated a copper-catalyzed cascade approach of fused quinazoline from *N*-(2-benzimidazolyl)-2-aminobenzamide and 2-halobenzaldehyde *via* C–N coupling.[27] Indolo[1,2-*c*]quinazolines have been synthesized from 2-(2-halophenyl)-1H-indoles and (aryl)methanamines by copper-catalyzed sequential Ullmann N-arylation and aerobic oxidative C–H amination.[28] Synthesis of benzimidazo[1,2-*c*]quinazolines was reported through copper-catalyzed cross-coupling reactions of 2-(2-halophenyl)-benzoimidazoles with aldehydes using sodium azide as nitrogen source.[29] We reported synthesis of azole-fused quinazolines *via* copper catalyzed one-pot, sequential Ullmann–type coupling and Pd/Cu co-catalyzed intramolecular dehydrative C–N bonding.[30] In the pursuit of our continuous efforts for the synthesis of fused heterocycles,[31-37] herein we report a convenient and efficient ligand free copper-catalyzed synthesis of imidazo[1,2-*c*]quinazoline derivatives *via* sequential Ullmann type C–N coupling and dehydrative cyclization between 2-(2-bromophenyl)-1H-imidazoles and formamide (Scheme 1).



Scheme 1.Copper-catalyzedsynthesis of quinazolinefused heterocycles.

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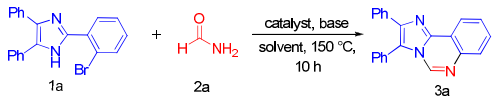
Electronic Supplementary Information (ESI) available: [Copies of NMR (1H & 13C) spectra for synthesized compounds **3a-q** and **4a-c**]. See DOI: 10.1039/x0xx00000x

Results and discussion

Our initial study commenced with the model reaction of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**1a)** with formamide (**2a)** in the presence of $CuCl_2$ (10 mol %), K_2CO_3 (2.0 equiv) in dimethylformamide (DMF) at 150 °C under air atmosphere for 10 h. To our delight 2,3-diphenylimidazo[1,2-*c*]quinazoline (**3a**) was isolated in 30% yield (Table 1, entry 1).

Table 1: Optimization of reaction conditions for the synthesis of 3a.[a]



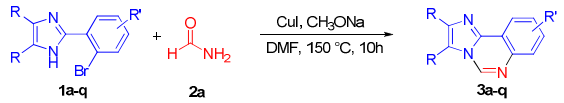
Entry	Catalyst (mol %)	Base	Solvent	% Yield[b]
1	$CuCl_2$ (10)	K_2CO_3	DMF	30
2	CuBr (10)	K_2CO_3	DMF	34
3	$Cu(OAc)_2$ (10)	K_2CO_3	DMF	39
4	$Cu(OTf)_2$ (10)	K_2CO_3	DMF	33
5	CuI (10)	K_2CO_3	DMF	45
6	CuI (20)	K_2CO_3	DMF	52
7	CuI (30)	K_2CO_3	DMF	60
8	CuI (40)	K_2CO_3	DMF	61
9	-	K_2CO_3	DMF	NR[c]
10	CuI(30)	K_3PO_4	DMF	45
11	CuI(30)	KOH	DMF	56
12	CuI(30)	*t*-BuOK	DMF	48
13	**CuI (30)**	**CH_3ONa**	**DMF**	**70**
14	CuI(30)	CH_3ONa	DMA	62
15	CuI(30)	CH_3ONa	DMSO	60
16	CuI(30)	CH_3ONa	Toluene	NR
17	CuI(30)	CH_3ONa	Dioxane	NR
18	CuI (30)	CH_3ONa	DMF	trace[d]
19	CuI (30)	CH_3ONa	DMF	62[e]
20	CuI (30)	CH_3ONa	DMF	58[f]
21	CuI (30)	CH_3ONa	DMF	63[g]
22	CuI (30)	CH_3ONa	DMF	65[h]
23	CuI (30)	CH_3ONa	DMF	63[i]

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (10 mmol), catalyst (0.3 mmol), base (2.0 mmol), solvent (2.0 mL), 150 °C, 10 h. [b]Isolated yields. [c]NR = No reaction. [d]Under N_2 atm. [e]Zinc iodide (30 mol %) used as additive. [f]Potassium per sulphate (50 mol %) used as additive. [g]Pivolic acid (30 mol %) used as additive. [h]1,10-phenonthroline (40 mol %) used as ligand. [i]L-proline (40 mol %) used as ligand.

Encouraged by the results of model reaction, task of reaction optimization for improved yield of **3a** was undertaken by varying bases, catalysts and solvents. The results for various optimization experiments are summarized in table 1. Screening of various copper catalyst such as $CuCl_2$, CuBr, $Cu(OAc)_2$, $Cu(OTf)_2$ and CuI revealed that among all the screened copper salt, CuI was found to give highest yield (45%) of **3a** using 10 mol % catalyst loading (Table 1, entries 1-5). Subsequently, effect of catalyst loading was investigated. Initially significant increment in the yield of **3a** was observed by increasing loading of CuI from 10 mol % to 30 mol %, however, further increase in loading of CuI did not improve yield of **3a** (Table 1, entries 4-8). Formation of **3a** was not observed in the absence of the catalysts even after keeping the reaction for longer time (Table 1, entry 9). Next, we evaluated effect of different bases such as K_3PO_4, KOH, KO^{t}Bu, and CH_3ONa on the yield of **3a** in the presence of CuI as catalyst (Table 1, entries 10-13). Among these bases, use of CH_3ONa gave highest yield of **3a** (Table 1, entries 13). Variation of solvents for the model reaction revealed that polar aprotic solvents such as DMF, DMA and DMSO were suitable for this transformation (Table 1, entries 13-15). Formation of **3a** was not observed when non-polar aprotic solvents such as toluene and 1,4-dioxane were used (Table 1, entries 16, 17). It is also important to mention that use of different additive such as zinc iodide, potassium per sulphate, pivolic acid and ligands such as 1,10-phenonthroline, and L-proline did not improve the yield of **3a**.

After having the optimized reaction conditions in hand (Table 1, entry 4), the generality of the tandem process was investigated by employing various substituted 2-(2-bromophenyl)-1*H*-imidazoles (Table 2). Reactions of 2-(2-bromophenyl)-4,5-diaryl-1*H*-imidazoles having substituted aryl rings at C4- and C5-positions of imidazole with formamide gave corresponding imidazo[1,2-*c*]quinazolines (**3a-f**) in 35-70% yields. Similarly, reaction of 2-(2-bromophenyl)-1*H*-imidazoles with different substituents such as fluoro, methyl, methoxy on both aryl rings at C4- and C5-positions as well as on C2-position of imidazole with formamide gave corresponding imidazo[1,2-*c*]quinazolines**(3g-q)** in 45-58% yields. Structure of all the synthesized imidazo[1,2-*c*]quinazolines was elucidated by NMR and HRMS data (Supporting information).

Table 2: Substrate scope for synthesis of imidazo[1,2-*c*]quinazoline (3)[a]

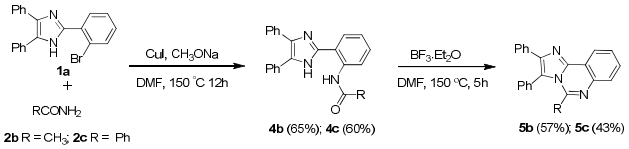


Sr. No.	R	R′	Product	Yield[b]
1	C_6H_5	H	**3b**	70
2	4-$CH_3C_6H_4$	H	**3c**	35
3	3-$OCH_3C_6H_4$	H	**3d**	42
4	4-$OCH_3C_6H_4$	H	**3e**	61
5	4-FC_6H_4	H	**3f**	55
6	CH_3	H	**3a**	55
7	CH_3	5-F	**3g**	58
8	C_6H_5	4-CH_3	**3h**	48
9	C_6H_5	5-F	**3i**	51
10	C_6H_5	5-OCH_3	**3j**	51
11	4-$CH_3C_6H_4$	5-F	**3k**	46
12	C_6H_5	4,5-$(OCH_3)_2$	**3l**	57
13	4-$CH_3C_6H_4$	4,5-$(OCH_3)_2$	**3m**	52
14	4-$OCH_3C_6H_4$	4,5-$(OCH_3)_2$	**3n**	45
15	4-FC_6H_4	4,5-$(OCH_3)_2$	**3o**	53
16	4-FC_6H_4	5-F	**3p**	31
17	4-$OCH_3C_6H_4$	5-F	**3q**	56

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (10.0 mmol), catalyst (0.3 mmol), base (2.0 mmol), solvent (2.0 mL), 150 °C, 10 h. [b]Isolated yields.

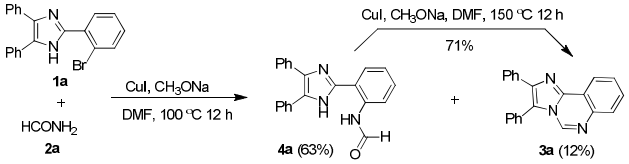
Reaction of 2-(2-bromophenyl)-4,5-diphenyl-1H-imidazole (1a) with acetamide (**2b**) and benzamide (**2c**) under the optimized reaction condition gave C-N coupled product N-(2-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)acetamide (**4b**) and N-(2-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)benzamide (**4c**) in 65% and 60% yields, respectively (Scheme 2). The expected imidazo[1,2-*c*]quinazolines were not observed from these reactions even after longer reaction time. This might be due to relatively low electrophilicity of amide carbonyl group in these amides as compared to formamide.

However, on treating **4b** and **4c** with $BF_3.OEt_2$ in DMF at 150 °C for 5 h corresponding imidazo[1,2-*c*]quinazolines **5b** and **5c** were obtained in 57% and 43%, respectively.



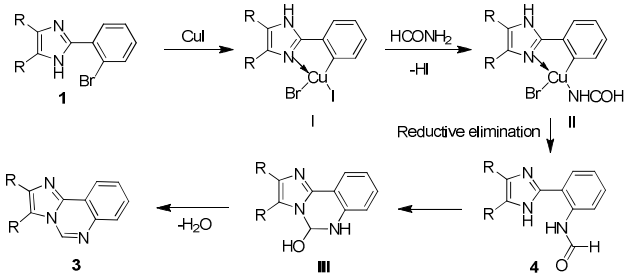
Scheme 2. Reaction of **1a** with acetamide (**2b**) and benzamide (**2c**).

To investigate the possible reaction pathway for this tandem approach, we performed some control experiment (Scheme 3). Temperature dependent study was performed for the reaction of **1a** with **2a** in the presence of CuI, CH_3ONa in DMF. No product formation was observed up to 50 °C, but when reaction mixture was heated at 100 °C for 24 h along with expected imidazo[1,2-*c*]quinazoline (**3a**), C-N coupled product, *N*-(2-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)formamide (**4a**) was also observed in 63% yield. Further, imidazo[1,2-*c*]quinazoline (**3a**) was obtained in 71% yield when isolated **4a** was allowed to react under optimized reaction condition.



Scheme 3: Control experiments

On the basis of literature reports[38-40] and our own results, a plausible mechanism for the synthesis of imidazo[1,2-*c*]quinazolines is outlined in scheme 4. It is believed that oxidative addition of CuI with 2-(2-bromophenyl)-4,5-diphenyl-*1H*-imidazole leads to formation of copper(III) intermediate **I**. This step is assisted by the presence of internal directing group from imidazole which also acts as ligand for this reaction. Further, substitution of iodide from **I** by formamide in the presence of CH_3ONa affords intermediate **II** which then undergoes reductive elimination to give *N*-arylated amide **4**. Finally, copper catalyst assisted intramolecular dehydrative cyclization of **4** *via* intermediate **III** results in the formation of fused quinazoline derivative **3**. Formation of imidazo[1,2-*c*]quinazolines **5b** and **5c** by adding Lewis acid BF_3-OEt_2 to **4b** and **4c** is also in agreement with involvement of intermediate III *via* nucleophilic addition to amidic carbonyl group.



Scheme 4: Probable reaction mechanism

Finally, to evaluate the scalability of the protocol, model reaction was performed at gram scale and **3a** was isolated in 610 mg (71%) from the reaction of 1 g of **1a** under the optimized reaction condition.

Conclusions

In summary, we have successfully developed a novel and efficient copper catalyzed one-pot tandem approach for the synthesis of imidazo[1,2-*c*]quinazolines from 2-(2-bromoaryl)-1H-imidazoles and formamide. The protocol involves sequential copper-catalyzed Ullmann type coupling of formamide followed by dehydrative cyclization to give target compounds in moderate to good yields.

Experimental Section

General information

Melting points were determined in open capillary tubes on a EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were determined by their NMR spectra (^{1}H and ^{13}C NMR) using Bruker AV 400 MHz spectrometer. ^{13}C NMR spectra are fully decoupled. High resolution mass spectra (HRMS) were carried out using a quadrupole time of-flight (Q-TOF) mass spectrometer (Applied Biosystem). 2-(2-Bromoaryl)-1H-imidazoles (**1a-q**) were synthesized throughone-pot, three-component condensation of benzils, 2-bromoarylaldehydes and ammonium acetate using $Yb(OTf)_3$ as catalyst.[41]All other chemicals were obtained from the commercial suppliers and used without further purification.

Representative procedure for 2,3-diphenylimidazo[1,2-c]quinazoline derivatives

A clean oven dried 10 mL round bottom flask was charged with **1a** (1.0 mmol), **2a** (10 mmol), CH_3ONa (2 mmol), CuI (0.25 mmol) in DMF (2.0 mL) was stirred at 150 °C for 10 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool to ambient temperature, diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography to get the desired imidazo[1,2-*c*]quinazoline**3a** in 70% yield (90 mg).

2,3-Diphenylimidazo[1,2-*c*]quinazoline (3a). Brown solid (90 mg, 70%), mp 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.69 – 8.66 (m, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.69 (m, 4H), 7.61 – 7.52 (m, 5H), 7.36 – 7.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.8, 141.1, 135.6, 133.4, 130.7, 130.0, 129.7, 129.4, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 123.0, 121.5, 119.4; HRMS (ESI) calcd for $C_{22}H_{16}N_3[M+H]^+$ 322.1339 found 322.1344.

2,3-Di-*p*-tolylimidazo[1,2-*c*]quinazoline (3b). Off-white solid (46 mg, 35%), mp 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.69 – 8.68 (m, 1H), 7.97 – 7.95 (m, 1H), 7.72 – 7.69 (m, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.50 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.7, 141.1, 139.4, 137.6, 135.7, 130.6, 130.6, 130.4, 129.9, 129.1, 128.5,

128.3, 127.9, 125.5, 122.9, 121.2, 119.4, 21.5, 21.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3$ $[M+H]^+$ 350.1652 found 350.1655.

2,3-Bis(3-methoxyphenyl)imidazo[1,2-*c*]quinazoline (3c). Off-white solid (55 mg, 42%), mp 160-162 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.75 (s, 1H), 8.54 (m, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.79 – 7.76 (m, 2H), 7.56 – 7.52 (m, 1H), 7.27 – 7.17 (m, 4H), 7.19 – 7.15 (m, 2H), 6.88 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 160.4, 159.6, 141.6, 141.1, 140.4, 137.0, 135.1, 131.2, 130.8, 130.0, 129.8, 129.2, 128.6, 123.5, 122.8, 122.2, 120.3, 119.1, 116.5, 115.8, 113.9, 113.3, 55.8, 55.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$[M+H]$^+$ 382.1550 found 382.1543.

2,3-Bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline (3d). Off-white solid (81 mg, 61%), mp 195-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.67 – 8.66 (m, 1H), 7.96 – 7.94 (m, 1H), 7.72 – 7.66 (m, 4H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 159.3, 142.0, 141.4, 141.1, 135.7, 132.1, 129.9, 129.2, 128.5, 128.3, 126.1, 122.9, 120.5, 120.4, 119.3, 115.2, 113.9, 55.4, 55.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$[M+H$^+$] 382.1550 found 382.1556.

2,3-Bis(4-fluorophenyl)imidazo[1,2-*c*]quinazoline (3e). Off white solid (72 mg, 55%), mp 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.66 – 8.64 (m, 1H), 7.98 – 7.96 (m, 1H), 7.76 – 7.67 (m, 4H), 7.54 – 7.50 (m, 2H), 7.33 – 7.28 (m, 2H), 7.04 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (d, *J* = 250.8 Hz), 162.6 (d, *J* = 247.8 Hz), 142.4, 141.1, 135.2, 132.7 (d, *J* = 8.4 Hz), 130.3, 129.8 (d, *J* = 8.1 Hz), 129.4 (d, *J* = 3.2 Hz), 128.7, 128.4, 124.3 (d, *J* = 3.5 Hz), 122.9, 120.1, 119.2, 117.1 (d, *J* = 21.8 Hz), 115.5 (d, *J* = 21.5 Hz); HRMS (ESI) calcd for $C_{22}H_{14}F_2N_3$ [M+H$^+$] 358.1150 found 358.1153.

2,3-Dimethylimidazo[1,2-*c*]quinazoline (3f). Off-white solid (65 mg, 55%), mp 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.52 (m, 1H), 7.96 – 7.93 (m, 1H), 7.69 – 7.62 (m, 2H), 2.53 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.5, 138.7, 135.1, 129.5, 128.4, 128.2, 122.3, 119.0, 116.1, 13, 8.1; HRMS (ESI) calcd for $C_{12}H_{12}N_3$ $[M+H]^+$ 198.1026 found 198.1032.

9-Fluoro-2,3-dimethylimidazo[1,2-*c*]quinazoline (3g). Brown solid (70 mg, 58%), mp 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.10 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.92 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.36 (td, *J* = 8.6, 2.9 Hz, 1H), 2.52 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.83 (d, *J* = 249.2 Hz), 140.75 (d, *J* = 4.4 Hz), 139.08, 137.12, 134.37 (d, *J* = 2.5 Hz), 130.67 (d, *J* = 9.2 Hz), 120.34 (d, *J* = 10.5 Hz), 118.03 (d, *J* = 24.4 Hz), 116.55, 107.32 (d, *J* = 24.6 Hz), 12.96, 8.13; HRMS (ESI) calcd for $C_{12}H_{11}FN_3$[M+H$^+$] 216.0932 found 216.0926.

8-Methyl-2,3-diphenylimidazo[1,2-*c*]quinazoline(3h). Brown solid (62 mg, 48%), mp 210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.73 (m, 3H), 7.58 – 7.53 (m, 5H), 7.36 – 7.28 (m, 4H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.6, 141.3, 140.6, 135.61, 133.5, 130.7, 130.2, 129.6, 129.4, 128.6, 128.4, 128.1, 128.1, 127.8, 122.7, 121.2, 116.9, 21.6; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ $[M+H]^+$ 336.1495 found 336.1499.

9-Fluoro-2,3-diphenylimidazo[1,2-*c*]quinazoline (3i). Brown solid (66 mg, 51%): mp 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.32 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.97 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.74 – 7.72 (m, 2H), 7.60 – 7.53 (m, 5H), 7.46 – 7.41 (m, 1H), 7.36 – 7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, *J* = 249.7 Hz), 141.7 (d, *J* = 4.4 Hz), 137.74 (d, *J* = 1.9 Hz), 134.87 (d, *J* = 2.5 Hz) 133.2, 130.8 (d, *J* = 9.2 Hz), 130.7, 129.7, 129.6, 128.6, 128.5, 128.3, 128.11, 127.99, 127.9, 121.8, 120.8, 120.7, 118.6 (d, *J* = 24.3 Hz), 108.1 (d, *J* = 24.6 Hz); HRMS (ESI) calcd for $C_{22}H_{15}FN_3$ $[M+H]^+$ 340.1245 found 340.1248.

9-Methoxy-2,3-diphenylimidazo[1,2-*c*]quinazoline (3j). Off white solid (66 mg, 51%), mp 220-222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.03 (d, *J* = 2.7 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.61 – 7.53 (m, 5H), 7.37 – 7.29 (m, 4H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 142.3, 141.7, 135.8, 133.5, 133.4, 130.7, 130.0, 129.7, 129.4, 128.58, 128.5, 128.2, 127.8, 121.5, 120.6, 120.4, 102.7, 56.0; HRMS (ESI) calcd for $C_{23}H_{18}N_3O$ $[M+H]^+$ 352.1444 found 352.1420.

9-Fluoro-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (3k). Brown solid (60 mg, 46%), mp 235-240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.31 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.96 (dd, *J* = 8.9, 5.1 Hz, 1H), 7.63 (d, 2H), 7.46 – 7.36 (m, *J* = 8.1 Hz, 5H), 7.16 (d, *J* = 7.9 Hz, 2H), 2.51 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, *J* = 249.4 Hz), 141.5 (d, *J* = 4.2 Hz), 139.6, 137.8, 137.7, 135, 135.0, 130.7 (d, *J* = 9.1 Hz), 130.5, 130.4, 129.2, 127.9, 125.3, 121.5, 120.7 (d, *J* = 10.5 Hz), 118.5 (d, *J* = 24.3 Hz), 108.1 (d, *J* = 24.6 Hz), 21.5, 21.3; HRMS (ESI) calcd for $C_{24}H_{19}FN_3$ $[M+H]^+$ 368.1558 found 368.1561.

8,9-Dimethoxy-2,3-diphenylimidazo[1,2-*c*]quinazoline (3l). Off-white solid (75 mg, 57%), mp 207-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.00 (s, 1H), 7.73 – 7.71 (m, 2H), 7.60 – 7.52 (m, 5H), 7.38 – 7.29 (m, 4H), 4.13 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 150.5, 142.5, 141.7, 136.8, 134.1, 133.6, 130.7, 129.6, 129.3, 128.7, 128.5, 128.2, 127.8, 120.9, 113.3, 108.9, 102.5, 56.6, 56.2; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$[M+H]$^+$ 382.1550 found 381.1553.

8,9-Dimethoxy-2,3-di-p-tolylimidazo[1,2-*c*]quinazoline (3m). Greyish solid(69 mg,52%), mp 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.99 (s, 1H), 7.66 – 7.62 (m, 2H), 7.40 – 7.37 (m, 5H), 7.15 – 7.11 (m, 2H), 4.14 (s, 3H), 4.04 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 150.4, 142.3, 141.5, 139.2, 137.5, 136.7, 134.2, 130.8, 130.6, 130.3, 129.1, 127.0, 125.8, 120.5, 113.3, 108.9, 102.5, 56.6, 56.2, 21.5, 21.3; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1863 found 410.1867.

8,9-Dimethoxy-2,3-bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline (3n). Brown solid (60 mg, 45%), mp 170– 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.99 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 3H), 7.37 (s, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.12 (s, 3H), 4.04 (s, 3H), 3.93 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.2, 158.9, 151.6, 150.4, 136.7, 134.2, 132.1, 129.3, 129.1, 126.3, 120.8, 119.8, 115.1, 114.0, 113.2, 109.0, 102.4, 56.5, 56.2, 55.4, 55.3; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761 found 442.1765

2,3-Bis(4-fluorophenyl)-8,9-dimethoxyimidazo[1,2-*c*]quinazoline (3o). Light brown solid (60 mg, 53%): mp 255-257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.96 (s, 1H), 7.67 (s, 2H), 7.50 (s, 2H), 7.37 (s, 1H), 7.28 (s, 2H), 7.03 (s, 2H), 4.13 (s, 3H), 4.05 (s, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (d, *J* = 250.6 Hz), 162.6 (d, *J* = 248.0 Hz), 151.9, 150.6, 142.5, 141.01, 136.83, 133.78, 132.7 (d, *J* = 8.3

Hz), 129.8 (d, *J* = 8.1 Hz), 129.6, 124.5, 119.4, 117.1 (d, *J* = 21.8 Hz), 115.5 (d, *J* = 21.5 Hz), 113.1, 108.9, 102.4, 56.5, 56.2; HRMS (ESI) calcd for $C_{24}H_{18}F_2N_3O_2$ $[M+H]^+$ 418.1362 found 418.1365.

8-Fluoro-2,3-bis(4-fluorophenyl)imidazo[1,2-*c*]quinazoline (3p). White off solid (41 mg, 31%), mp 261-263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.29 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.97 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.51– 7.49 (m, 2H), 7.47 – 7.42 (m, 1H), 7.33 – 7.28 (m, 2H), 7.07 – 7.03 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 251.0 Hz), 162.6 (d, *J* = 248.1 Hz), 162.0 (d, *J* = 250.1 Hz), 141.8 (d, *J* = 4.4 Hz), 141.3, 137.7, 134.5 (d, *J* = 2.5 Hz), 132.7 (d, *J* = 8.4 Hz), 130.8 (d, *J* = 9.2 Hz), 129.8 (d, *J* = 8.2 Hz), 129.1 (d, *J* = 3.3 Hz), 124.0 (d, *J* = 3.6 Hz), 120.5 (d, *J* = 10.5 Hz) , 120.3, 118.8 (d, *J* = 24.4 Hz), 117.2 (d, *J* = 21.9 Hz), 115.6 (d, *J* = 21.6 Hz), 108.1 (d, *J* = 24.6 Hz); HRMS (ESI) calcd for $C_{22}H_{13}F_3N_3$ $[M+H]^+$ 376.1056 found 376.1062.

9-Fluoro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c]quinazoline (3q). Off white solid (74 mg, 56%), mp 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.30 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.95 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.46 – 7.30 (m, 3H), 7.13 – 7.09 (m, 2H), 6.91 – 6.87 (m, 2H), 3.94 (s, 3H), 3.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 249.3 Hz), 160.4, 159.4, 141.7, 141.4 (d, *J* = 3.9 Hz), 137.7 (d, *J* = 1.8 Hz), 135.0 (d, *J* = 2.5 Hz), 132.1, 130.7 (d, *J* = 9.2 Hz), 129.2, 125.9, 120.7, 120.7 (d, *J* = 10.3 Hz), 118.4 (d, *J* = 24.3 Hz), 120.3, 115.2, 113.9, 108.0 (d, *J* = 24.5 Hz), 55.4, 55.3; HRMS (ESI) calcd for $C_{24}H_{19}FN_3O_2$ $[M+H]^+$ 400.1456 found 400.1461.

N-(2-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)formamide (3a). White solid (88 mg, 63%), mp 218-220 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.99 (s, 1H), 12.66 (s, 1H), 8.65 (d, *J* = 5.8 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.52 (m, 4H), 7.51 – 7.31 (m, 7H), 7.27 – 7.21 (M 2H); ^{13}C NMR (101 MHz, DMSO) δ 162.88, 160.81, 145.19, 136.46, 136.17, 134.50, 130.86, 129.93, 129.59, 129.34, 129.23, 128.90, 128.78, 127.45, 126.85, 123.69, 120.99, 116.39; HRMS (ESI) calcd for $C_{22}H_{13}F_3N_3$ $[M+H]^+$ 340.1444 found 340.1447.

N-(2-(4,5-Diphenyl-*1H*-imidazol-2-yl)phenyl)acetamide (4b). Off white solid (82 mg, 65%), mp 248-250 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.00 – 12.99 (m, 2H), 8.63 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 1H), 7.58 – 7.54 (m, 4H), 7.51 – 7.43 (m, 3H), 7.39 – 7.32 (m, 3H), 7.30 – 7.25 (m, 1H), 7.19 – 7.15 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 168.7, 145.5, 137.5, 135.7, 134.6, 130.8, 129.6, 129.4, 129.2, 128.9, 128.8, 128.4, 127.4, 127.1, 126.5, 123.0, 119.9, 115.8, 25.7; HRMS (ESI) calcd for $C_{23}H_{20}N_3O$ $[M+H]^+$ 354.1601found 354.1604.

N-(2-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)benzamide (4c). Off white solid (100 mg, 60%), mp 242-245 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.68 (s, 1H), 13.05 (s, 1H), 8.88 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.57 – 7.34 (m, 13H), 7.25 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 165.5, 145.6, 137.5, 136.4, 135.4, 134.5, 132.3, 130.6, 129.6, 129.2, 128.9, 128.7, 128.5, 128.01, 127.9, 127.6, 126.7, 123.5, 120.4, 116.6; HRMS (ESI) calcd for $C_{28}H_{22}N_3O$ $[M+H]^+$ 416.1757 found 416.1761.

5-Methyl-2,3-diphenylimidazo[1,2-*c*]quinazoline (5b): White solid (77 mg, 57%), mp 138-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.65 (m, 2H), 7.63 (d, *J* = 6.7 Hz, 2H), 7.60 – 7.47 (m, 5H), 7.35-7.24 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 143.5, 142.1, 140.5, 133.7, 132.5, 131.9, 130.0, 129.63, 128.7, 128.3, 127.9, 127.7, 127.5, 127.2, 122.9, 122.7, 118.8, 24.4; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ 336.1495 found 336.1492 $[M+H^+]$.

2,3,5-Triphenylimidazo[1,2-c]quinazoline (5c): White solid (68 mg, 43%), mp 230-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 7.7, 1.5 Hz, 1H), 8.0 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.57 – 7.52 (m, 2H), 7.29 – 7.24 (m, 5H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.97 – 6.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.64, 144.42, 142.72, 140.60, 133.89, 133.82, 131.26, 130.48, 130.13, 129.33, 128.72, 128.71, 128.22, 128.20, 128.04, 127.78, 127.60, 127.56, 123.35, 122.99, 118.68; HRMS (ESI) calcd for $C_{28}H_{20}N_3$ 398.1652 found 398.1657 $[M+H^+]$.

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