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FULL PAPER

Copper-Catalyzed Synthesis of Trinuclear N-Fused Hybrid Scaffolds by Double C(sp^2)-N Bond Formation between 2-(2-Bromoaryl)indoles and 2-Aminoazoles

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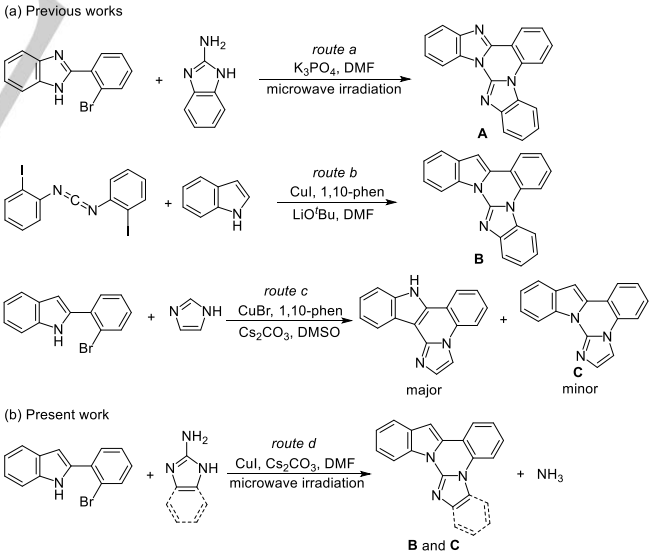
Abstract: 2-(2-Bromoaryl)indoles react with 2-aminoazoles by microwave irradiation in DMF in the presence of a catalytic amount of CuI and a base to produce trinuclear N-fused hybrid scaffolds, benzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazolines and imidazo[1,2-*a*]indolo[1,2-*c*]quinazolines in moderate to good yields. The reaction seems to proceed via copper-catalyzed C(sp^2)-N coupling and subsequent intramolecular cyclocondensation accompanied by ammonia evolution. Complete regioselective C-N cyclization is observed with the reaction of 2-(2-bromophenyl)indole with 2-aminoazoles.

Introduction

Many challenges on the synthesis of polynuclear N-fused hybrid scaffolds have been attempted due to their intrinsic biological activities and optical properties that are not exhibited in each homonuclear scaffolds.[1] During the course of our continuous efforts directed toward developing new synthetic methods for polynuclear N-fused hybrid scaffolds under transition metal-catalyzed and transition metal-free conditions,[2] we reported on the synthesis of trinuclear N-fused hybrid scaffold **A** by base-promoted double C(sp^2)-N coupling between 2-(2-bromoaryl)benzimidazoles and 2-aminobenzimidazole under transition metal-free condition (Scheme 1, route a).[3,4] The present work started during the course of application of such a protocol to the reaction with indole analogues to form trinuclear N-fused hybrid scaffolds, benzo[4,5]imidazo[1,2-*c*]indolo[1,2-*a*]quinazolines **B** (Scheme 1, route d). In contrast to widely known synthetic methods and biological activities of each homonuclear scaffold (indole, quinazoline, and benzimidazole) of scaffold **B** and binuclear scaffolds by the combination of such a homonuclear scaffold, only one report is found for the synthetic method of their trinuclear N-fused hybrid scaffold **B**.[5] Lv and coworkers reported that bis(*o*-iodophenyl) carbodiimide reacted with indoles in the presence of CuI and 1,10-phenanthroline to produce scaffold **B** via sequential processes such as nucleophilic addition, tautomerization, Ullmann-type C-N coupling, and intramolecular C(sp^2)-H arylation (Scheme 1, route b).[5] Herein this report shows another example for the synthesis of trinuclear N-fused hybrid scaffold **B** by CuI-catalyzed double C(sp^2)-N coupling between 2-(2-bromoaryl)indoles and 2-aminobenzimidazole with broad substrate scope under microwave irradiation (Scheme 1, route d). The present reaction can also be extended to the reaction of 2-(2-bromoaryl)indoles with 2-aminoimidazole to produce trinuclear N-fused hybrid scaffold **C** (Scheme 1, route d). To the best of our knowledge, there are no reports on synthetic method and biological activity of scaffold **C** except for one report. It is known that Hu and coworkers obtained scaffold **C** as side minor product in copper-catalyzed coupling and cyclization of 2-(2-bromophenyl)indole with imidazole (Scheme 1, route c).[6]

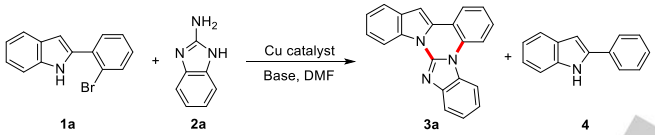


Scheme 1. Synthetic routes for trinuclear N-fused hybrid scaffolds.

Results and Discussion

In contrast to the case for the reaction of 2-(2-bromophenyl)benzoimidazole with 2-aminobenzimidazole **2a** shown in route a of Scheme 1,[3] performing the reaction of 2-(2-

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



Entry	[**2a**]/ [**1a**]	Catalyst	Base	Temp (ºC)	Time (h)	Conv of **1a** (%)	Yield of **3a** (%)	Yield of **4** (%)
1	1	CuI	K_3PO_4	110	1	100	47	26
2	1	CuI	K_3PO_4	130	1	100	56	21
3	1	CuI	K_3PO_4	150	1	100	70	18
4	1	CuI	K_3PO_4	150	2	100	74	18
5	1.2	CuI	K_3PO_4	150	1	100	72	10
6	1	CuI	Cs_2CO_3	150	1	100	72	14
7	1	CuI	K_2CO_3	150	1	100	65	12
8	1	CuI	KO^{t}Bu	150	1	100	47	30
9	1	CuI	NaO^{t}Bu	150	1	100	41	28
10	1	CuI	NaOAc	150	1	92	62	27
11	1	CuI	CsF	150	1	76	53	18
12[b]	1	CuI	Cs_2CO_3	150	1	100	57	9
13[c]	1	CuI	Cs_2CO_3	150	1	100	73	6
14	1	Cu_2O	K_3PO_4	150	1	100	69	10
15	1	CuBr	K_3PO_4	150	1	89	69	15
16	1	Cu powder	K_3PO_4	150	1	83	66	15
17	1	CuCl	K_3PO_4	150	1	81	57	13
18[d]	1	CuI	Cs_2CO_3	150	1	51	36	0
19[e]	1	CuI	Cs_2CO_3	150	1	42	21	0
20[f]	1	CuI	K_3PO_4	150	20	91	73	13

[a] Reaction condition: **1a** (0.3 mmol), catalyst (0.03 mmol), base (0.6 mmol), DMF (3 mL), under microwave irradiation (100 W of initial power). [b] In the presence of L-proline (0.06 mmol). [c] In the presence of 1,10-phenanthroline (0.06 mmol). [d] In HMPA in place of DMF. [e] In xylene in place of DMF. [f] Usual heating (screw-capped vial).

bromophenyl)indole **1a** with **2a** under similar catalyst-free conditions scarcely afforded trinuclear N-fused hybrid scaffold **3a** and both substrates were recovered intact. The results of several attempted cyclizations between **1a** and **2a** in the presence of a copper catalyst for the optimization of conditions are listed in Table 1. Treatment of equimolar amounts of **1a** and **2a** in DMF in the presence of a catalytic amount of CuI (10 mol% based on **1a**) and K_3PO_4 (2 equiv. to **1a**) at 110 ºC for 1 h under microwave irradiation afforded **3a** in 47% isolated yield along with concomitant formation of 2-phenyl-1*H*-indole (**4**) (26% yield) by a debromination of **1a** (Table 1, entry 1). It is known that aryl halides are readily hydrodebydrogenated in the presence of a copper catalyst.[7] The yield of **3a** increased with elevating temperature up to 150 ºC (Table 1, entries 1-3). No significant change of the yield of **3a** was observed with prolonging the reaction time and higher molar ratio of [**2a**]/[**1a**] (Table 1, entries 4 and 5). Performing the reaction using other bases such as Cs_2CO_3, K_2CO_3, KO^{t}Bu, NaO^{t}Bu, NaOAc, and CsF under the employed conditions resulted in lower yields of **3a** with incomplete conversion of **1a** in some cases except for Cs_2CO_3, which showed an activity similar to that of K_3PO_4 (Table 1, entries 6-11). Further addition of ligands such as L-proline and 1,10-phenanthroline resulted in no significant change of **3a** yield (Table 1, entries 12 and 13). The reaction also proceeded with other copper catalysts such as Cu_2O, CuBr, and copper powder with similar catalytic activities to that of CuI (Table 1, entries 14-16). However, lower yield of **3a** and incomplete conversion of **1a** were observed with CuCl (Table 1, entry 17). Among solvents examined under the employed conditions, DMF was shown to be the solvent of choice (Table 1, entries 18 and 19). Usual heating conditions for 20 h also can be used alternatively for the effective formation of **3a** (Table 1, entry 20).

On the other hand, similar treatment of **1a** with benzimidazole **5** in place of **2a** under the employed conditions afforded C-N/C-C coupling product **6** (34% yield) in preference to C-N/C-N coupling product **3a** (11% yield) (eq 1). As shown in route c of Scheme 1, it is known that such a similar competition reaction also occurs in one-pot two-step treatment of 2-(2-bromophenyl)indole with imidazole under a copper catalytic system.[6] This result indicates that the present reaction is superior to the reaction of **1a** with benzimidazole in terms of the completely selective formation of trinuclear N-fused hybrid scaffold **3a**.

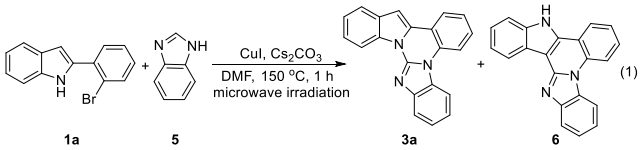
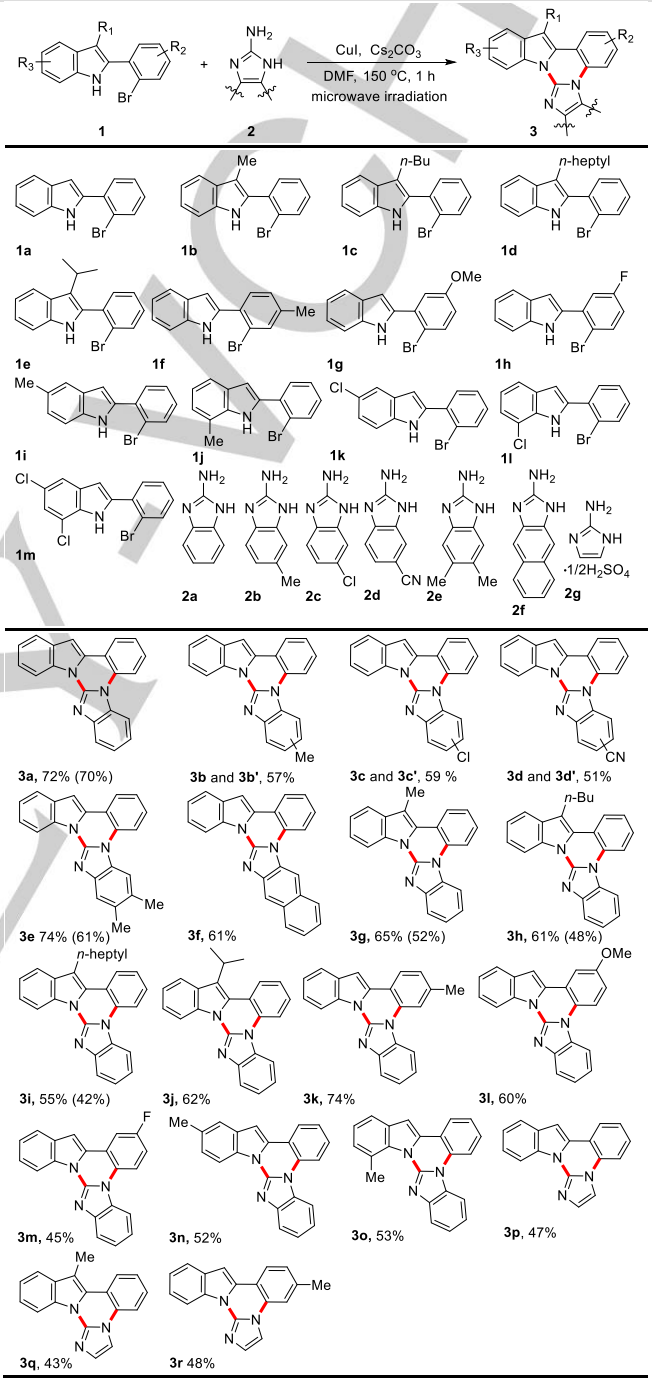


Table 2 shows the representative results for the coupling/cyclization reactions between various 2-(2-bromoaryl)indoles **1**[8] and 2-aminobenzimidazoles **2**[9] under the optimized conditions (Table 1, entries 3 and 6). 2-(2-Bromophenyl)indole **1a** was readily cyclized with 2-aminobenzimidazoles **2b**-**2e** having electron-donating and withdrawing substituents and benzo-fused 2-aminobenzimidazole **2f** to give the corresponding trinuclear N-fused hybrid scaffolds **3b**-**3f** in 51-72% yields. In the cases of **2b**-**2d**, the products were produced as isomeric mixtures (1:1.7 for **3b** and **3b'**; 1:0.9 for **3c** and **3c'**; 1:1 for **3d** and **3d'**).[10] The isomeric ratios were calculated by the intensity of the clearly separated protons in ^{1}H NMR spectra (see Supporting Information for ^{1}H and ^{13}C NMR spectra). The reaction of readily available 2-(2-bromophenyl)indoles **1b**-**1e** having straight and branched alkyl chains at indole moiety (R_1) with **2a** also produced the corresponding trinuclear N-fused hybrid scaffolds **3g**-**3j** irrespective of the identity of such alkyl substituents. From the reaction of 2-(2-bromoaryl)indoles **1f**-**1h** having methyl, methoxy, and fluoro substituents on bromoaryl moiety (R_2) with **2a**, the corresponding trinuclear N-fused hybrid scaffolds **3k**-**3m** were also formed in 45-74% yields. 2-(2-Bromophenyl)indoles (**1i** and **1j**) containing methyl substituent on indole moiety (R_3) also reacted with **2a** to give the cyclized products (**3n** and **3o**) in similar yields irrespective of the position of methyl substituent, whereas the present reaction is not tolerant of chloro functional group on indole moiety (R_3). When 2-(2-bromophenyl)indoles **1k**-**1m** were treated with **2a** under the optimized conditions, all afforded dechlorinated trinuclear N-fused hybrid scaffold **3a** in 50-55% yields. As shown in Table 2, higher product yields were obtained with Cs_2CO_3 in several cases. Similar treatment of 2-(2-bromoaryl)indoles (**1a**, **1b**, and **1f**) with commercially available 2-aminoimidazole sulfate **2g** also afforded the corresponding trinuclear N-fused hybrid scaffolds **3p**-**3r** without the formation of C-N/C-C coupling products in cases of **1a** and **1f** as shown in route c of Scheme 1. The product yields were generally lower than that obtained with 2-aminobenzimidazoles **2a**-**2f**, and debromination products along with several identifiable compounds were formed with complete conversion of 2-(2-bromoaryl)indoles.

The reaction pathway seems to proceed via an initial formation of Ullmann-type product **7** by copper-catalyzed C-N coupling between **1a** and **2a** (Scheme 2).[11] In contrast to transition metal-free formation of trinuclear N-fused hybrid scaffolds from 2-(2-bromoaryl)benzimidazoles and **2a**, the present reaction needs a

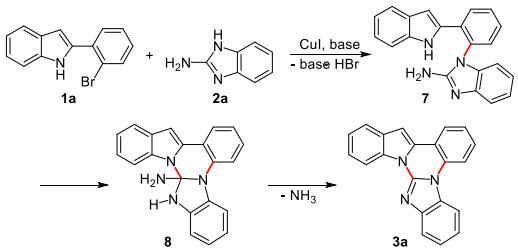
Table 2. Scope of reaction[a]



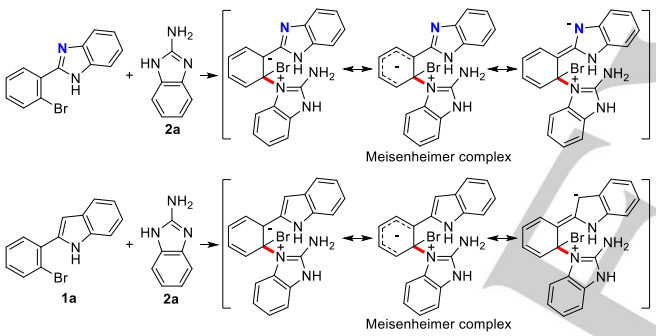
[a] All reactions were carried out with **1** (0.3 mmol), **2** (0.3 mmol), CuI (0.03 mmol), Cs_2CO_3 (0.6 mmol), and DMF (3 mL) at 150 °C for 1 h under microwave irradiation (100 W of initial power) unless otherwise stated. Yields using K_3PO_4 in place of Cs_2CO_3 are shown in parentheses.

copper catalyst to form such a C-N bond. It appears that this is attributed to the stability difference of a resonance-stabilized negatively charged intermediate called a Meisenheimer complex formed by the nucleophilic attack of the ring nitrogen of **2a** to the carbon attached to Br in **1a** (Scheme 3).[12] Because nitrogen is

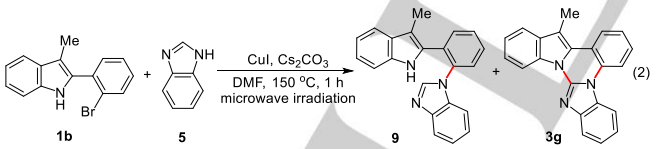
more electronegative than carbon, the negative intermediate from **1a** and **2a** is less stable than the one from 2-(2-bromophenyl)benzimidazole and **2a**. We confirmed in a separate experiment that similar treatment of **1b** with benzimidazole **5** under the employed conditions afforded C-N coupled product **9** in 63% yield along with **3g** (8% yield) (eq 2). Subsequent intramolecular nucleophilic addition of indole N-H to C=N of neighboring guanidine moiety to form an intermediate **8** is followed by β-elimination to produce **3a** along with NH_3.[13] Like the reaction between 2-(2-bromophenyl)benzimidazole and **2a**, the evolution of NH_3 was confirmed by both the color change of Nessler's reagent[14] and the measurement with LSE-NH_3 Monitor (see supporting information).



Scheme 2. A plausible reaction pathway.



Scheme 3. Stability difference of Meisenheimer complexes.



Conclusion

In summary, the coupling/cyclization reactions of 2-(2-bromoaryl)indoles with 2-aminoazoles under microwave irradiation in the presence of CuI and a base conveniently afforded the corresponding trinuclear N-fused hybrid scaffolds. Complete regioselective cyclization in the reaction of 2-(2-bromophenyl)indole with aminoazoles especially renders this process remarkable. Further studies on mechanistic aspects and challenges on the construction of polynuclear N-fused hybrid scaffolds by the present protocol using 2-aminoazoles under transition metal-catalyzed or transition metal-free conditions are in progress.

Experimental Section

General information: ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance Digital 500 spectrometer using TMS as an internal standard. Melting point were measured by a microscopic melting point apparatus (Standford Research Inc. MPA100 automatic melting point apparatus). IR spectra were recorded on Shimadzu FTIR-8400S infrared spectrophotometer. High-resolution mass data were obtained using electronic ionization or fast atom bombardment (HRMS-EI or FAB, magnetic sector-electric sector double focusing mass analyzer) at the Korea Basis Science Center (Deagu). The pure products were isolated by TLC (a glass plate coated with Kieselgel 60 GF_{254}, Merck). The starting 2-(2-bromoaryl)indoles[8] and 2-aminobenzimidazoles[9] were synthesized by known methods. Other commercially available organic and inorganic compounds were used without further purification.

General procedure for the synthesis of 3: To a 5 mL microwave reaction tube was added 2-(2-bromoaryl)indole **1** (0.3 mmol), 2-aminoazole **2** (0.3 mmol), CuI (0.006 g, 0.03 mmol), Cs_2CO_3 (0.195 g, 0.6 mmol), and DMF (3 mL). After stirring the reaction mixture at room temperature for 10 min, it was heated at 150 °C for 1-2 h under microwave irradiation (100 W of initial power). The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate inorganic precipitates. Removal of the solvent left a crude mixture, which was purified by thin layer chromatography (dichloromethane/hexane = 1/1) to give **3**. Except for known compounds, **3a**[5] and **3p**,[6] all new products were characterized spectroscopically as shown below.

Benzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3a)[5]: Pale yellow solid (66 mg, 72%); R_f = 0.34; M.p. 235-237 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (s, 1H), 7.34-7.37 (m , 2H), 7.38-7.43 (m, 2H), 7.48-7.54 (m, 2H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.87-7.89 (m, 1H), 8.04-8.06 (m , 2H), 8.21 (d, *J* = 8.4 Hz, 1H), 9.05 (dd, *J* = 8.3 and 0.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 98.6, 112.4, 115.1, 115.8, 117.2, 119.5, 120.4, 122.4, 123.4, 123.7, 123.8, 124.7, 125.0, 129.1, 129.5, 130.4, 131.2, 131.7, 133.4, 143.0, 143.4; HRMS (FAB) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{13}N_3$ 308.1188, found 308.1185.

Isomeric mixture of 2-methylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline and 3-methylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3b and 3b'): Pale yellow solid (55 mg, 57%); R_f = 0.31; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (s, 3H), 2.55 (s, 3H), 7.09-7.12 (m, two isomers, 3H), 7.18 (dd, *J* = 8.1 and 0.6 Hz, 1H), 7.27-7.31 (m, two isomers, 2H), 7.36-7.40 (m, two isomers, 2H), 7.44-7.50 (m, two isomers, 4H), 7.62 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, two isomers, 2H), 7.77 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.99 (dd, *J* = 7.8 and 1.4 Hz, 1H), 8.00 (dd, *J* = 7.9 and 1.4 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 9.00 (dd, *J* = 8.3 and 0.7 Hz, 1H), 9.01 (dd, *J* = 8.3 and 0.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 22.3, 98.5, 112.0, 112.8, 115.0, 115.1, 116.0, 117.1, 117.2, 119.1, 119.7, 120.4, 123.4, 123.6, 123.8, 124.7, 124.8, 125.0, 128.5, 129.1, 129.6, 130.7, 131.4, 131.87, 131.93, 132.3, 133.5, 133.6, 143.2, 143.4, 143.5; IR (KBr): $\tilde{\nu}$ = 694, 741, 777, 928, 1049, 1148, 1258, 1412, 1450, 1557, 1629, 2851, 2918, 3051 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{15}N_3$ 321.1266, found 321.1263.

Isomeric mixture of 2-chlorobenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline and 3-chlorobenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3c and 3c'): White solid (60 mg, 59%); R_f = 0.37; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.03 (s, 1H), 7.04 (s, 1H), 7.21 (dd, *J* = 8.7 and 2.1 Hz, 1H), 7.25-7.29 (m, two isomers, 2H), 7.31 (dd, *J* = 8.5 and 1.9 Hz, 1H), 7.35-7.38 (m, two isomers, 2H), 7.40-7.46 (m, two isomers, 4H), 7.66-7.69 (m, two isomers, 3H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H), 7.91-7.93 (m, two isomers, 3H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.86 (s, 1H), 8.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 98.9, 99.0, 112.7, 112.9, 114.8, 114.9, 115.7, 115.8, 117.16, 117.20, 119.3, 120.0, 120.46, 120.49, 122.4, 123.57, 123.60, 124.0, 124.1, 124.8, 125.2, 125.3, 127.7, 129.0, 129.1, 129.15, 129.21, 129.5, 130.8, 130.9, 131.0, 131.19, 131.25, 133.30, 133.33, 141.6, 143.8, 144.1, 144.2; IR (KBr): $\tilde{\nu}$ =

696, 741, 777, 928, 1047, 1146, 1261, 1449, 1557, 1632, 3051 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{21}H_{12}ClN_3$ 341.0720, found 341.0720.

Isomeric mixture of benzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline-2-carbonitrile and benzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline-3-carbonitrile (3d and 3d'): Pale yellow solid (51 mg, 51%); R_f = 0.41; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15 (s, two isomers**,** 2H), 7.38-7.43 (m, two isomers, 4H), 7.47-7.50 (m, two isomers**,** 2H), 7.51-7.57 (m, two isomers**,** 3H), 7.61 (dd, *J* = 8.3 and 1.4 Hz, 1H), 7.73-7.75 (m, two isomers**,** 2H), 7.80 (d, *J* = 8.3 Hz, 1H), 8.00-8.05 (m, two isomers**,** 5H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 8.86-8.89 (m, two isomers**,** 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 99.7, 99.8, 105.0, 107.0, 113.0, 115.0, 115.1, 115.7, 115.8, 116.5, 117.5, 119.4, 119.86, 119.94, 120.7, 123.4, 124.0, 124.1, 124.3, 124.4, 124.9, 125.0, 125.9, 125.95, 125.99, 127.7, 129.3, 129.5, 129.57, 129.64, 130.67, 130.73, 130.9, 133.1, 133.3, 133.4, 143.0, 144.8, 146.4; IR (KBr): $\tilde{\nu}$ = 700, 735, 785, 935, 1053, 1140, 1267, 1346, 1472, 1555, 1634, 2220, 2851, 2918, 3051 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{12}N_4$ 333.1140, found 333.1138.

2,3-Dimethylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3e): Pale yellow solid (74 mg, 74%); R_f = 0.37; M.p. 248-249 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.41 (s, 3H), 7.14 (s, 1H), 7.29-7.32 (m, 1H), 7.37-7.40 (m, 1H), 7.47-7.50 (m, 2H), 7.57 (s, 1H), 7.72 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 8.03 (dd, *J* = 7.9 and 1.4 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 9.01 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2, 20.8, 98.1, 113.0, 114.9, 115.8, 117.0, 119.8, 120.3, 123.2, 123.6, 124.59, 124.61, 128.7, 129.0, 129.4, 131.1, 131.3, 131.9, 132.3, 133.3, 141.3, 142.9; IR (KBr): $\tilde{\nu}$ = 704, 739, 795, 858, 1001, 1140, 1279, 1352, 1472, 1599, 1636, 2918, 3049 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{23}H_{17}N_3$ 335.1422, found 335.1419.

Indolo[1,2-*c*]naptho[2',3':4,5]imidazo[1,2-*a*]quinazoline (3f): Pale yellow solid (65 mg, 61%); R_f = 0.34; M.p. 264-266 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.12 (s, 1H), 7.31-7.34 (m, 1H), 7.38-7.41 (m, 1H), 7.42-7.47 (m, 2H), 7.48-7.51 (m, 1H), 7.54-7.57 (m, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.94-7.97 (m, 2H), 8.00 (d, *J* = 7.8 Hz, 1H), 8.19 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.31 (s, 1H), 9.04 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 99.3, 109.2, 114.9, 115.8, 116.1, 116.9, 120.5, 123.7, 124.0, 124.4, 124.6, 124.70, 124.74, 127.8, 128.0, 129.3, 129.8, 130.2, 130.9, 131.3, 131.4, 131.8, 133.7, 142.8, 145.8; IR (KBr): $\tilde{\nu}$ = 704, 743, 795, 844, 1024, 1148, 1256, 1410, 1472, 1599, 1645, 3047, 3113 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{25}H_{15}N_3$ 357.1266, found 357.1263.

10-Methylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3g): White solid (63 mg, 65%); R_f = 0.31; M.p. 192-194 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.57 (s, 3H), 7.19-7.22 (m, 1H), 7.26-7.29 (m, 1H), 7.32-7.38 (m, 3H), 7.44-7.47 (m, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 8.02-8.04 (m, 2H), 8.98 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.1, 109.9, 112.4, 114.6, 115.7, 118.1, 118.6, 119.2, 122.0, 122.7, 123.5, 124.0, 124.5, 125.2, 125.6, 127.7, 130.3, 130.7, 131.6, 132.1, 143.2, 143.5; IR (KBr): $\tilde{\nu}$ = 685, 739, 1084, 1258, 1342, 1460, 1557, 1628, 1680, 2857, 2920, 3053 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{15}N_3$ 321.1266, found 321.1263.

10-Butylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3h): White solid (67 mg, 61%); R_f = 0.34; M.p. 161-163 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3H), 1.50-1.57 (m, 2H), 1.72-1.78 (m, 2H), 3.13 (t, *J* = 7.9 Hz, 2H), 7.27-7.45 (m, 5H), 7.48-7.51 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 8.09-8.11 (m, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 9.05 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 23.0, 24.9, 31.4, 112.4, 114.9, 115.7, 115.8, 118.2, 118.5, 119.2, 122.0, 122.8, 123.5, 124.1, 124.7, 125.1, 125.2, 127.9, 130.3, 130.6, 131.8, 132.2, 143.2, 143.7; IR (KBr): $\tilde{\nu}$ = 731, 853, 1013, 1207, 1261, 1381, 1460, 1560, 1628, 2864, 2951, 3045 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{25}H_{21}N_3$ 363.1735, found 363.1738.

10-Heptylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3i): White solid (67 mg, 55%); R_f = 0.31; M.p. 271-274 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3H), 1.30-1.32 (m, 4H), 1.38-1.44 (m, 2H), 1.51-1.57 (m, 2H), 1.78-1.84 (m ,2H), 3.21 (t, *J* = 8.0 Hz, 2H), 7.33-7.36 (m, 1H), 7.38-7.44 (m, 3H), 7.51-7.55 (m, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.86-7.88 (m, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 8.21 (dd, *J* = 8.1 and 1.2 Hz, 1H), 8.28 (dd, *J* = 8.3 and 0.8 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.3, 29.2, 29.3, 29.9, 31.8, 112.4, 115.1, 115.9, 116.0, 118.3, 118.7, 119.3, 122.1, 122.9, 123.6, 124.2, 124.9, 125.3, 125.4, 128.1, 130.4, 130.7, 132.0, 132.4, 143.3, 143.9; IR (KBr): $\tilde{\nu}$ = 729, 849, 1013, 1179, 1261, 1358, 1462, 1560, 1628, 2849, 2922, 3053 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{28}H_{27}N_3$ 405.2205, found 405.2203.

10-Isopropylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3j): White solid (65 mg, 62%); R_f = 0.31; M.p. 261-262 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 7.1 Hz, 6H), 4.08 (sept, *J* = 7.1 Hz, 1H), 7.33-7.44 (m, 4H), 7.51-7.54 (m, 1H), 7.55-7.58 (m, 1H), 7.86-7.87 (m, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1 H), 8.28-8.31 (m, 2H), 9.18 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 26.9, 112.5, 115.2, 116.3, 118.8, 119.3, 121.0, 122.07, 122.12, 122.5, 123.7, 123.9, 124.8, 126.1, 128.3, 128.9, 130.3, 132.3, 133.4, 143.4, 144.0; IR (KBr): $\tilde{\nu}$ = 710, 743, 935, 1018, 1148, 1258, 1362, 1452, 1558, 1630, 2850, 2961, 3053 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{24}H_{19}N_3$ 349.1579, found 349.1581.

7-Methylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3k): White solid (71 mg, 74%); R_f = 0.31; M.p. 214-215 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 6.96 (s, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.30-7.32 (m, 1H), 7.36-7.39 (m, 2H), 7.45-7.48 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 8.99 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 97.7, 112.6, 114.5, 115.3, 115.9, 119.5, 120.3, 122.3, 123.4, 123.5, 123.7, 124.5, 126.0, 129.7, 130.5, 131.5, 131.7, 133.3, 139.7, 143.1, 143.6; IR (KBr): $\tilde{\nu}$ = 729, 791, 914, 1059, 1161, 1252, 1319, 1412, 1450, 1587, 1632, 2922, 3051, 3115 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{15}N_3$ 321.1266, found 321.1263.

8-Methoxybenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3l): White solid (61 mg, 60%); R_f = 0.28; M.p. 243-244 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 3H), 7.02 (dd, *J* = 9.1 and 2.8 Hz, 1H), 7.09 (s, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.38-7.43 (m, 3H), 7.49-7.52 (m, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 9.1 Hz, 1H), 9.05 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.8, 98.78, 98.79, 108.18, 108.19, 112.2, 115.97, 116.00, 116.37, 116.41, 119.6, 120.5, 122.3, 123.5, 123.6, 124.0, 129.5, 130.4, 131.3, 133.6, 143.0, 156.7; IR (KBr): $\tilde{\nu}$ = 581, 600, 729, 786, 872, 1033, 1170, 1249, 1348, 1449, 1560, 1622, 2831, 2935, 3008; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{15}N_3O$ 337.1215, found 337.1214.

8-Fluorobenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3m): Pale yellow solid (44 mg, 45%); R_f = 0.28; M.p. 271-272 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.07 (s, 1H), 7.16-7.20 (m, 1H), 7.31-7.34 (m, 1H), 7.37-7.40 (m, 2H), 7.47-7.51 (m, 1H), 7.63-7.65 (m, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 8.09-8.11 (m, 1H), 8.98 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 99.7, 110.9 (d, *J* = 24.5 Hz), 112.1, 116.0, 116.3 (d, *J* = 23.4 Hz), 116.8 (d, *J* = 8.4 Hz), 119.0 (d, *J* = 9.1 Hz), 119.8, 120.7, 122.6, 123.7, 123.9, 124.4, 128.2, 129.4, 130.3, 133.6, 143.0 (d, *J* = 15.4 Hz), 159.5 (d, *J* = 243.9 Hz); IR (KBr): $\tilde{\nu}$ = 690, 727, 793, 858, 1043, 1165, 1260, 1418, 1454, 1566, 1630, 2847, 2914, 3064 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{21}H_{12}FN_3$ 325.1015, found 325.1015.

12-Methylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3n): Pale yellow solid (50 mg, 52%); R_f = 0.31; M.p. 248-250 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.55 (s, 3H), 7.14 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.36-7.44 (m, 3H), 7.55-7.58 (m ,2H), 7.90 (d, *J* = 7.9 Hz, 1H), 8.09-811 (m, 2H), 8.28 (d, *J* = 8.3 Hz, 1H), 8.91 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 98.4, 112.6, 115.2, 115.5, 117.5, 119.6, 120.3, 122.5, 123.9, 124.9, 125.1, 125.6, 129.1, 130.0, 130.7, 131.4, 131.88, 131.91, 133.2, 143.2, 143.7; IR (KBr): $\tilde{\nu}$ = 692, 723, 748, 802, 910, 1055, 1144, 1260,

1418, 1464, 1562, 1628, 2853, 2916, 3055 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{15}N_3$ 321.1266, found 321.1264.

14-Methylbenzo[4,5]imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3o): White solid (51 mg, 53%); R_f = 0.32; M.p. 205-207 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.19 (s, 3H), 7.17 (s, 1H), 7.25-7.27 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.31-7.38 (m, 3H), 7.50-7.56 (m, 2H), 7.78-7.80 (m, 1H), 7.99 (dd, *J* = 7.8 and 1,3 Hz, 1H), 8.01-8.03 (m, 1H), 8.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4, 101.0, 112.1, 115.4, 118.3, 118.6, 119.6, 122.5, 123.7, 124.2, 125.0, 125.1, 126.8, 128.0, 129.1, 131.4, 131.5, 132.0, 133.4, 134.4, 142.4, 144.2; IR (KBr): $\tilde{\nu}$ = 671, 729, 797, 914, 1020, 1184, 1275, 1404, 1553, 1626, 2923, 3046 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{15}N_3$ 321.1266, found 321.1264.

Imidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3p)[6]**:** Yellow solid (36 mg, 47%); R_f = 0.30; mp 212-213 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 0.7 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.36-7.41 (m, 2H), 7.44-7.50 (m, 2H), 7.57-7.59 (m, 2H), 7.77-7.79 (m, 1H), 8.08 (dd, *J* = 7.9 and 1.1 Hz, 1H), 8.82 (dd, *J* = 8.3 and 0.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 97.6, 109.5, 115.0, 115.1, 117.5, 120.5, 122.9, 123.6, 124.8, 125.8, 128.4, 128.96, 129.01, 129.8, 130.9, 132.6, 139.5; HRMS (FAB) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{11}N_3$ 258.1031, found 258.1028.

9-Methylimidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3q): Yellow solid (35 mg, 43%); R_f = 0.32; M.p. 219-221 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (s, 3H), 7.28 (d, *J* = 1.7 Hz, 1H), 7.37-7.41 (m, 2H), 7.43-7.48 (m, 2H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.56 (dd, *J* = 8.0 and 1.2 Hz, 1H) 7.74-7.76 (m, 1H), 8.23 (dd, *J* = 7.9 and 1.2 Hz, 1H), 8.81-8.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3, 109.1, 109.2, 114.9, 118.4, 119.2, 122.3, 123.8, 125.49, 125.53, 125.7, 127.9, 128.5, 130.0, 130.1, 131.4, 139.7; IR (KBr): $\tilde{\nu}$ = 692, 745, 812, 864, 957, 1020, 1084, 1128, 1256, 1325, 1377, 1468, 1641, 2729, 2804, 3075 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{18}H_{13}N_3$ 271.1109, found. 271.1107.

6-Methylimidazo[1,2-*a*]indolo[1,2-*c*]quinazoline (3r): Pale yellow solid (39 mg, 48%); R_f = 0.32; M.p. 221-223 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 7.12 (s, 1H), 7.19 (dd, *J* = 8.1 and 0.8 Hz, 1H), 7.30 (d, *J* = 1.7 Hz, 1H), 7.35-7.38 (m, 2H), 7.43-7.46 (m, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.75-7.77 (m, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 8.81 (dd, *J* = 8.3 and 0.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 96.6, 109.3, 114.7, 114.8, 115.2, 120.2, 122.7, 123.1, 124.5, 126.8, 128.2, 128.9, 129.7, 131.1, 132.4, 139.4, 139.5; IR (KBr): $\tilde{\nu}$ = 693, 746, 813, 865, 958, 1021, 1046, 1129, 1257, 1326, 1380, 1469, 1605, 1645, 2732, 2799, 3074 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{18}H_{13}N_3$ 271.1109, found. 271.1110.

Experimental procedure for mechanism study: To a 5 mL microwave reaction tube was added 2-(2-bromophenyl)-3-methyl-1*H*-indole (**1b**) (0.086 g, 0.3 mmol), benzimidazole **5** (0.035 g, 0.3 mmol), CuI (0.006 g, 0.03 mmol), Cs_2CO_3 (0.195 g, 0.6 mmol), and DMF (3 mL). The work-up procedure was similar to that described above.

1-(2-(3-Methyl-1*H*-indol-2-yl)phenyl)-1*H*-benzo[*d*]imidazole (9): Pale yellow solid (61 mg, 63%); R_f = 0.14; M.p. 186-187 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (s, 3H), 6.89-6.93 (m, 1H), 7.02-7.05 (m, 1H), 7.11-7.17 (m, 2H), 7.24-7.26 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.61-7.63 (m, 1H), 7.67-7.69 (m, 3H), 7.71-7.73 (m, 1H), 8.01(s, 1H), 11.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.6, 108.4, 110.2, 111.0, 118.4, 119.5, 121.4, 122.0, 123.0, 127.1, 128.1, 128.5, 129.5, 129.7, 130.7, 132.7, 133.6, 134.4, 136.0, 142.9, 143.7; IR (KBr): $\tilde{\nu}$ = 741, 899, 1009, 1225, 1310, 1458, 1499, 1560, 1686, 2856, 2922, 3055 cm^{-1}; HRMS (EI) *m/z*: (M^+) calcd for $C_{22}H_{17}N_3$ 323.1422, found. 323.1425.

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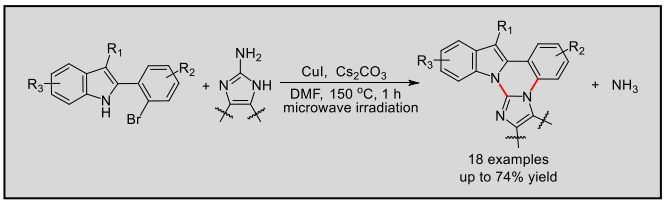
Cyclization



A promising synthetic method of indole-quinazoline-benzimidazole and indole-quinazoline-imidazole trinuclear N-fused hybrid scaffolds has been developed by copper-catalyzed C(sp^2)-N coupling and cyclization of 2-(2-bromoaryl)indoles with 2-aminoazoles as new building blocks. Further challenges on the construction of polynuclear N-fused hybrid scaffolds using 2-aminoazoles are expected.