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Facile Assembly of Fused Isoquinolines by Gold(I)-Catalyzed Coupling–Cyclization Reactions between *o*-Alkynylbenzaldehydes and Aromatic Amines Containing Tethered Nucleophiles

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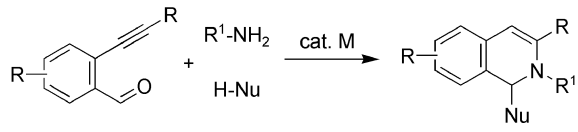
A gold(I)-catalyzed, operationally simple coupling–cyclization technique was developed for the synthesis of isoquinoline-fused polycyclic compounds. The reaction makes use of two coupling partners such as *o*-alkynylbenzaldehydes and aromatic amines having tethered nucleophiles. The reaction is easy to perform, broad in scope, and allows the generation of a number of biologically important heterocyclic motifs from readily accessible starting materials. A mechanism for the reaction is discussed.

Introduction

Metal-catalyzed tandem cyclization reactions provide an efficient way to build heterocycles from readily accessible organic compounds.[1] In the past few years, π-acids (complexes of Au, Cu, Ag, Pd, Ru, etc.) have emerged as powerful catalysts for this purpose. The feasibility of activating C–C bonds by coordination to those catalysts have led to the development of a variety of catalytic reactions involving carbon–carbon and carbon–heteroatom bond formation[2] with high atom economy.[3] Recently, a concise synthesis of 1,2-dihydroisoquinolines was established by tandem nucleophilic addition and cyclization of 2-(1-alkynyl)arylaldimines (preformed or generated in situ from *o*-alkynylbenzaldehydes and amines) and various nucleophiles in the absence of a catalyst[4] or in the presence of carbophilic Lewis acid catalysts such as AgOTf,[5] $In(OTf)_3$, or $AuClPPh_3$/$AgNTf_2$[6] and Cu^{I} or Pd^{II} salts[7] $CuSO_4$/$C_{12}H_{25}SO_3Na$[8] and $Mg(ClO_4)_2$/$Cu(OTf)_2$[9] (Scheme 1). Wu et al. reported the combination of AgOTf with proline[10]/triphenylphosphane[11] as catalysts for the synthesis of 1,2-dihydroisoquinolines from *o*-alkynylbenzaldehydes.



Scheme 1. Concept of metal-catalyzed cyclization reactions.

Fused isoquinolines are ubiquitous structural motif in a numerous biologically active natural products[12] and pharmaceutically important compounds.[13] Numerous approaches have been reported for the synthesis of such compounds; however, most of them are either limited in scope or require more than one step.[14] Therefore, the development of a new general process for the synthesis of fused isoquinolines would be very useful to synthetic organic chemists. Recently, Porco and Su reported an elegant synthesis of pyrroloisoquinolines involving domino cyclization/[3+2] dipolar cycloaddition catalyzed by silver(I) catalysts.[15] As a part of our continued interest in alkyne activation,[16] we hypothesized that coupling reactions of *o*-alkynylbenzaldehydes **1** and anilines **2** through intermolecular condensation would provide the corresponding imines, which in the presence of appropriate alkyne activators would afford fused isoquinolines in an apparently very simple way (Scheme 2). Herein, we report the successful realization of this concept by utilizing AuCl as a catalyst. The cascade[17] transformation shows very broad substrate scope towards diversely substituted *o*-alkynylbenzaldehydes and aromatic amines having tethered nucleophiles. During the preparation of this manuscript, a paper by Ohno and coworkers detailing the preparation of fused isoquinolines through a copper-catalyzed multicomponent reaction was published.[18]

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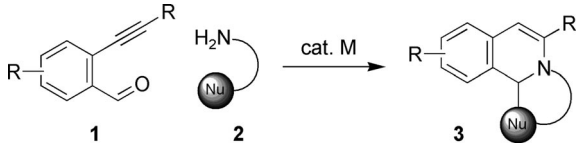


Scheme 2. Concept of metal-catalyzed coupling–cyclization reactions for the synthesis of fused isoquinolines.

Results and Discussion

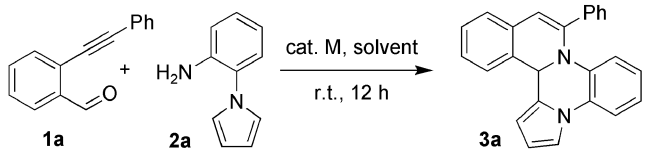
At the outset of this study, our efforts were directed at discovering the appropriate catalyst and reaction conditions to perform the proposed reaction (**1a** + **2a** → **3a**). The results of this study are summarized in Table 1. When **1a** was treated with one equivalent of **2a** in the presence of 5 mol-% $PtCl_2$ and 4 Å MS in dichloroethane (DCE) at room temperature, product **3a** was obtained in 50% yield (Table 1, Entry 1). The use of $Cu(OTf)_2$ as a catalyst gave **3a** in 80% yield (Table 1, Entry 2). When AgOTf and $Au(PPh_3)Cl$ were employed as catalysts, **3a** was obtained in 70 and 30% yield, respectively (Table 1, Entries 3 and 4). A marginal increase in yield was observed with a combination of $Au(PPh_3)Cl$ (5 mol-%) and AgOTf (10 mol-%; Table 1, Entry 5). Desired product **3a** was obtained in 95% yield when AuCl alone was used as the catalyst (Table 1, Entry 6). It is evident that the yield of **3a** was not significantly affected by the presence of water, as no molecular sieves were used to trap the in situ generated water (Table 1, Entry 7). Other solvents such as MeOH, toluene, and THF were examined; however, they proved not to be satisfactory (Table 1, Entries 8–10). It should be noted that the presence of a catalyst is essential. The reaction between **1a** and **2a** in the absence of a catalyst led to recovery of starting materials **1a** and **2a** in quantitative yields (Table 1, Entry 11). It should be noted that a Brønsted acid such as HCl does not catalyze this reaction.

With the optimal conditions in hand, we examined the scope of the gold(I)-catalyzed coupling–cyclization strategy (Table 2). 2-Aminophenylpyrrole derivatives **2b**, **2c**, and **2d** were treated with **1a** in DCE at room temperature to give cyclofused isoquinolines **3b**, **3c**,[19] and **3d** in 97, 81, and 78% yield, respectively (Table 2, Entries 1, 2, and 3). A wide range of substituted *o*-alkynylbenzaldehydes **1b**–**k** reacted well to furnish **3e**–**n** in moderate to high yields (62–98%; Table 2, Entries 4–13) regardless of the electronic nature of the aromatic ring. When *N*-(2-aminophenyl)indoles **2e** and **2f** were treated with **1a**, expected products **3o** and **3p** were obtained in 85 and 87% yield, respectively (Table 2, Entries 14 and 15).

Surprisingly, when 2-(2-aminophenyl)indole **2g** was treated with **1a** in the presence of AuCl (5 mol-%) at 80 °C for 12 h, cyclic aminal **3q**[20] was obtained exclusively in 85% yield (Table 2, Entry 16) instead of its regioisomer **3q′** (Scheme 3). Interestingly, when **2g** was treated with **1a** at 100 °C for 48 h, **3q′** was obtained in quantitative yield (Scheme 3). This shows that **3q′** was generated through the intermediacy of **3q**, and this was confirmed by treating **3q** with AuCl (5 mol-%) at 100 °C for 36 h, which gave **3q′** in quantitative yield. Thus, it is established that **3q** is the kinetically controlled product, whereas **3q′** is the thermodynamically controlled product. In contrast to **1a**, reaction of **1l** with **2g** under the same reaction conditions exclusively gave single regioisomer **3r** (Table 2, Entry 17). Because the main structural feature distinguishing **1a** from **1l** is the R group, we believe that the electronic nature of the R group might have contributed to this selectivity. As depicted in Figure 1. the nitrogen atom of the isoquinoline moiety in **3q** (R = C_6H_5, sp^2 carbon, electronegative) is less available than the lone pair of electrons on the nitrogen atom of the isoquinoline moiety present in **3r′** (R = nC_6H_{13}, sp^3 carbon, electropositive). Hence, for the conversion of **3q** into **3q′**, a higher temperature and a longer reaction time (100 °C, 48 h) were required to surmount the activation barrier to the corresponding iminium ion.[21] On the other hand, such an activation barrier is low for the formation of **3r** from **3r′**; therefore, a low temperature (80 °C) and a shorter reaction time (12 h) were found to be adequate for obtaining **3r**. An alternative explanation based on electrocyclization would be the torsional effect of the phenyl group.[22] An iminium ion derived from **3q** would be in a twisted confirmation to avoid steric interaction between the two phenyl groups. This will lead to a higher activation energy for electrocyclization. The alkyl group in **3r** is much smaller than the phenyl group. Thus, the electrocyclization of the imine derived from **3r** should be faster.

As anticipated, 2-(2-aminophenyl)-1*H*-benzimidazole (**2h**) gave **3s** in 83% yield under the standard conditions (Table 2, Entry 18). Substituted 2-aminobenzamides were also found to be viable substrates for this reaction. Thus, the reaction of **2i**–**m** with either **1a** or **1l** led to formation of **3t**–**z** in 65–90% yield (Table 2, Entries 19–25).[23] Aromatic amines having additional nucleophiles at the *ortho* position,

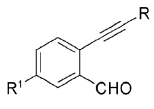
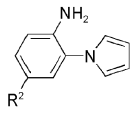
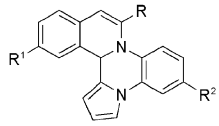
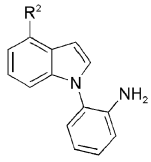
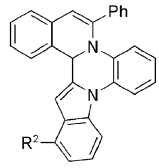
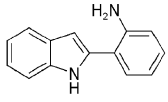
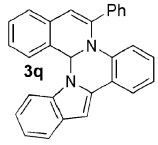
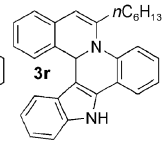
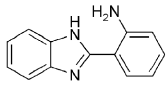
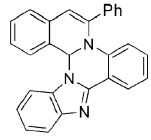
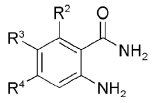
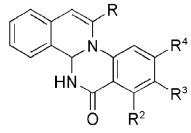
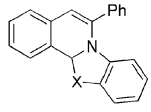
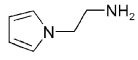
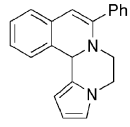
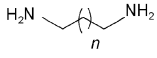
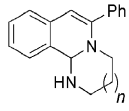
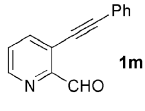
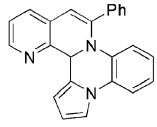
Table 1. Selected optimization studies.[a]



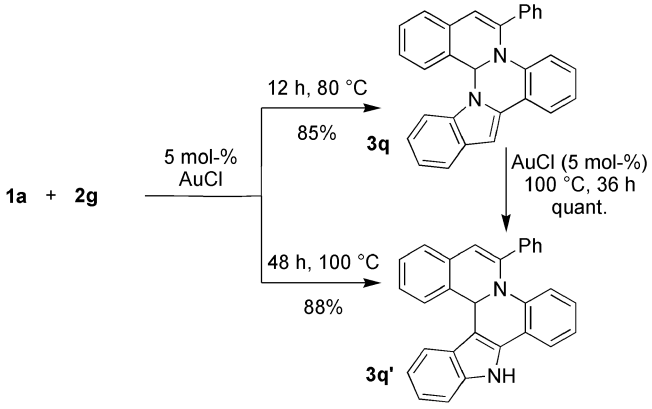
Entry	Catalyst[a]	Additive	Solvent	% Yield[b]
1	$PtCl_2$	4Å MS	DCE	50
2	$Cu(OTf)_2$	4Å MS	DCE	80
3	AgOTf	4Å MS	DCE	70
4	$Au(PPh_3)Cl$	4Å MS	DCE	30
5	$Au(PPh_3)Cl$/AgOTf	4Å MS	DCE	85[c]
6	AuCl	4Å MS	DCE	95
7	AuCl	–	DCE	96
8	AuCl	–	MeOH	85
9	AuCl	–	toluene	60
10	AuCl	–	THF	65
11	–	–	DCE	–[d]

[a] Reaction conditions: **1a** (0.19 mmol), **2a** (0.19 mmol), catalyst (5 mol-%), solvent (0.2 M), r.t., 12 h. [b] Isolated yield. [c] 5 mol-% $Au(PPh_3)Cl$ and 10 mol-% AgOTf were used. [d] Quantitative recovery of **1a** and **2a**.

Table 2. Coupling–cyclization strategy for the synthesis of isoquinoline-fused polycyclic compounds.[a]

Entry	1	2	3	% Yield[b]
1	 **1a** R = Ph, R^1 = H	 **2b** R^2 = Me	 **3b**	97
2	**1a** R = Ph, R^1 = H	**2c** R^2 = COOMe	**3c**	81
3	**1a** R = Ph, R^1 = H	**2d** R^2 = Cl	**3d**	78
4	**1b** R = *m*-Cl-C_6H_4, R^1 = H	**2a**	**3e**	76
5	**1c** R = *m*-F-C_6H_4, R^1 = H	**2a**	**3f**	92
6	**1d** R = *p*-Me-C_6H_4, R^1 = H	**2a**	**3g**	98
7	**1e** R = *m*-OH-C_6H_4, R^1 = H	**2a**	**3h**	92
8	**1f** R = *m*-OMe-C_6H_4, R^1 = H	**2a**	**3i**	90
9	**1g** R = *p*-CF_3-C_6H_4, R^1 = H	**2a**	**3j**	75
10	**1h** R = *p*-CN-C_6H_4, R^1 = H	**2a**	**3k**	78
11	**1i** R = *p*-NO_2-C_6H_4, R^1 = H	**2a**	**3l**	62
12	**1j** R = Ph, R^1 = F	**2a**	**3m**	69
13	**1k** R = Ph, R^1 = CF_3	**2a**	**3n**	64
14	**1a** R = Ph, R^1 = H	 **2e** R^2 = H	 **3o**	85
15	**1a** R = Ph, R^1 = H	**2f** R^2 = OMe	**3p**	87
16	**1a** R = Ph, R^1 = H	 **2g**	 **3q**	85[c]
17	**1l** R = nC_6H_{13}, R^1 = H	**2g**	 **3r**	89[c]
18	**1a** R = Ph, R^1 = H	 **2h**	 **3s**	83[c]
19	**1a** R = Ph, R^1 = H	**2i** R^2 = R^3 = R^4 = H	**3t**	85[c]
20	**1a** R = Ph, R^1 = H	**2j** R^3 = Me, R^2 = R^4 = H	**3u**	89[c]
21	**1a** R = Ph, R^1 = H	 **2k** R^2 = F, R^3 = R^4 = H	 **3v**	78[c]
22	**1a** R = Ph, R^1 = H	**2l** R^2 = R^4 = H, R^3 = Br	**3w**	90[c]
23	**1a** R = Ph, R^1 = H	**2m** R^2 = R^3 = H, R^4 = Cl	**3x**	88[c]
24	**1l** R = nC_6H_{13}, R^1 = H	**2k** R^2 = F, R^3 = R^4 = H	**3y**	65[c]
25	**1l** R = nC_6H_{13}, R^1 = H	**2l** R^2 = R^4 = H, R^3 = Br	**3z**	70[c]
26	**1a** R = Ph, R^1 = H	 **2n** X = SO_2NH_2	 **3aa**	75[d]
27	**1a** R = Ph, R^1 = H	**2o** X = CH_2NH_2	**3ab**	95[c]
28	**1a** R = Ph, R^1 = H	**2p** X = CH_2OH	**3ac**	76[c]
29	**1a** R = Ph, R^1 = H	**2q** X = NH_2	**3ad**	94[c]
30	**1a** R = Ph, R^1 = H	 **2r**	 **3ae**	55
31	**1a** R = Ph, R^1 = H	 **2s** *n* = 1	 **3af**	– [e]
32	**1a** R = Ph, R^1 = H	**2t** *n* = 0	**3ag**	– [e]
33	 **1m**	**2a**	 **3ah**	96[c]

[a] Reaction conditions: *o*-alkynylbenzaldehyde **1** (0.19 mmol) was treated with aniline **2** (0.19 mmol) in DCE (0.2 M) in the presence of AuCl (5 mol-%) at room temperature for 12 h, unless otherwise noted. [b] Isolated yield. [c] Stirred at 80 °C for 12 h. [d] Stirred at 80 °C for 48 h. [e] A complex mixture of unidentified products was obtained.



Scheme 3. Reaction of **1a** with **2g** at various temperatures.

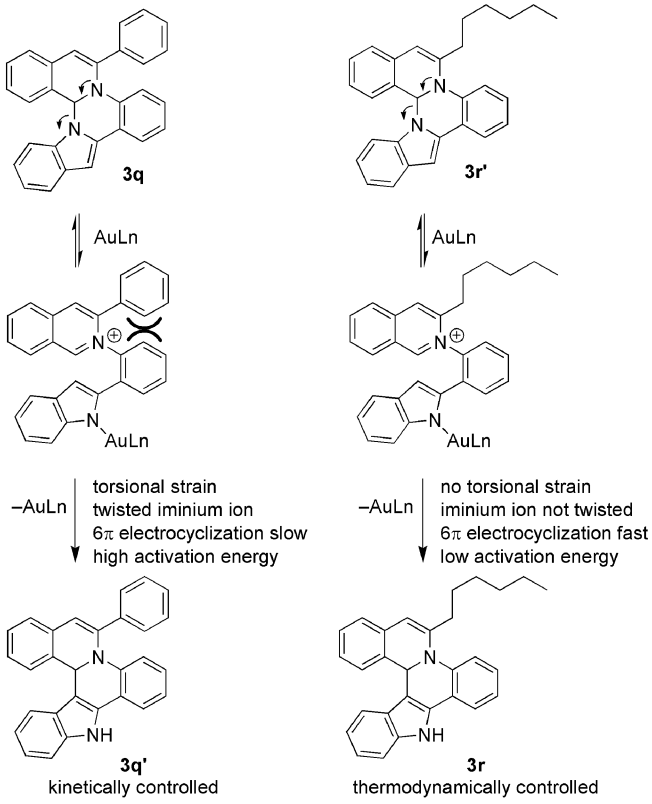


Figure 1. Plausible reason for the switch in regioselectivity.

such as 2-aminobenzenesulfonamide (**2n**), 2-aminobenzylamine (**2o**), 2-aminobenzylalcohol (**2p**), and 1,2-diaminobenzene (**2q**) gave substituted heterocycles **3aa**, **3ab**, **3ac**, and **3ad** in 75, 95, 76, and 94% yield, respectively (Table 2, Entries 26–29). The present reaction has proven to be excellent only for aromatic amines. The aliphatic amine containing substrates such as 2-pyrrolylethylamine (**2r**) gave **3ae** in only 55% yield (Table 2, Entry 30). Similarly, 1,3-diaminopropane (**2s**) and 1,2-diaminoethane (**2t**) did not afford **3af** and **3ag** (Table 2, Entries 31 and 32). It is of interest to note that the catalyst system tolerates the pyridine ring. The reaction between **1m** and **2a** under the standard reaction conditions afforded polycyclic heteroaromatic compound **3ah** in 96% yield (Table 2, Entry 33). It should be noted that the present reaction is limited only to internal alkynes; terminal alkynes are not viable substrates.

A proposed mechanism of the tandem reaction, by taking the reaction of **1a** and **2a** as an example, is shown in Figure 2. At first, condensation between **1a** and **2a** would occur to provide imine **4**. Imine **4**, thus formed, can be converted into final product **3a** through a cascade process proposed in catalytic cycle A or B. In cycle A, intermediate **6** is formed through a Mannich-type reaction of iminoalkyne gold complex **5**.[24] The AuCl-assisted regiospecific intramolecular hydroamination reaction of **6** would lead to the formation of **7**.[25] Subsequent protonation produces **3a**, with regeneration of AuCl. A conceivable alternative pathway is given in cycle B. Gold-coordinated isoquinolinium ion **9**, formed by nucleophilic attack of the imine nitrogen atom at the gold-coordinated alkyne (cf. **8**), would be trapped by the pyrrole to form **10**. Aromatization and protonation might then occur to give product **3a** with regeneration of AuCl.

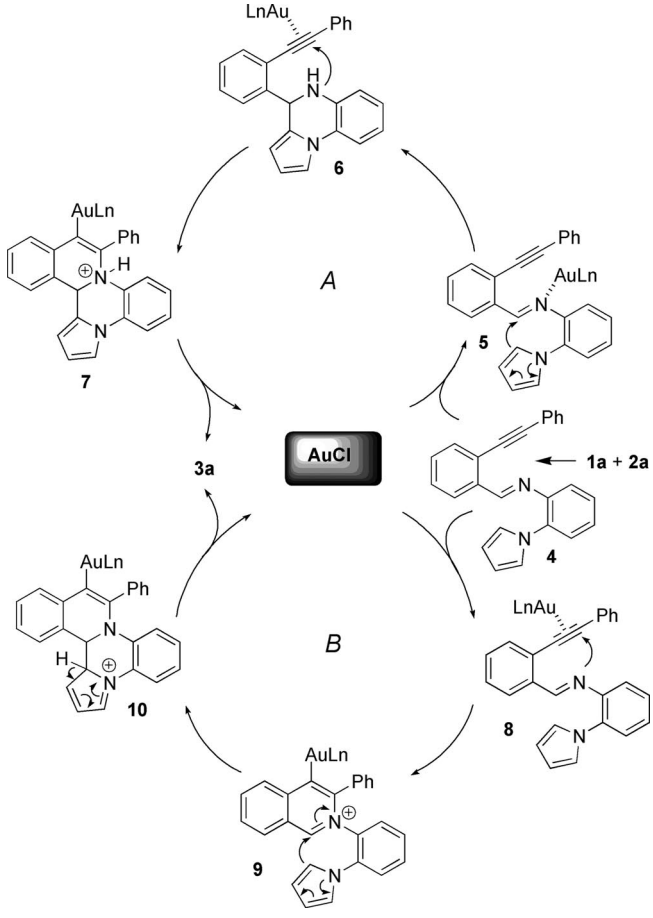
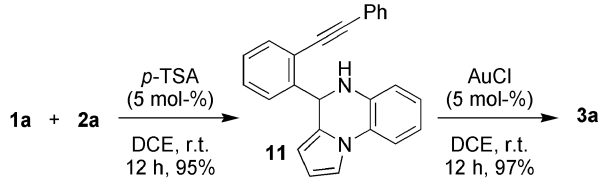


Figure 2. Plausible mechanism for the AuCl-catalyzed cascade cyclization by taking the reaction of **1a** with **2a** as an example.

To gain insight into the mechanism we have conducted the experiment presented in Scheme 4. The *p*-toluenesulfonic acid (*p*-TSA) catalyzed reaction of **1a** with **2a** gave aminoalkyne **11** in 95% yield. The intramolecular hydroamination occurred when **11** was subjected to gold catalysis

under the standard conditions to give **3a** in 97% yield. This result unambiguously suggests that the mechanism explained in cycle A is operative. To further support this mechanism, we carefully monitored the progress of the reaction between **1a** and **2a**. After 2 h, TLC and ^{1}H NMR analysis indicated the presence of anticipated intermediate **11**, product **3a**, and starting materials **1a** and **2a**. In short, AuCl acts as a dual-role catalyst[26] and catalyzes both the reactions mentioned in catalytic cycle A (condensation to form **6** and hydroamination) and therefore addition of external additives such as Brønsted acids and Lewis acid catalysts in the reaction mixture is not necessary. Although we have proven that the mechanism explained in cycle A is operating, we cannot completely eliminate the possibility of cycle B; both of the two proposed mechanism may be operating concurrently.



Scheme 4. Mechanistic studies.

Conclusions

In summary, we have developed a gold-catalyzed cascade cyclization that allows rapid preparation of biologically important isoquinoline-fused polycyclic compounds. The method appeared to be very general with respect to starting materials with different electronic properties. It is likely that the efficiency and novelty of this method combined with its operational simplicity will make it attractive for library construction. Application of this strategy for the synthesis of related fused polycyclic heteroaromatics and evaluation of their biological activities is in progress.

Experimental Section

Preparation of 3a as a Representative Example: To a DCE (1.0 mL, 0.2 M) solution of **1a** (0.040 g, 0.19 mmol) and **2a** (0.030 g, 0.19 mmol) in a 2.0-mL vial was added AuCl (2.5 mg, 5 mol-%) under a nitrogen atmosphere. The mixture was stirred at room temperature for 12 h. Then, the reaction mixture was filtered through a pad of silica gel (ethyl acetate), and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate, 99:01) to obtain **3a** (0.064 g, 96%) as a pure compound.

10-Phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3a): 96% yield; yellow solid; m.p. 149–150 °C; R_f = 0.60 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 6.7 Hz, 2 H), 7.37–7.09 (m, 9 H), 6.91 (d, J = 7.3 Hz, 1 H), 6.69 (td, J = 7.6, 1.0 Hz, 1 H), 6.61 (td, J = 8.1, 1.5 Hz, 1 H), 6.44 (t, J = 3.0 Hz, 1 H), 6.28–6.27 (m, 2 H), 5.61 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 135.6, 133.6, 132.7, 132.4, 128.9, 128.7, 127.8, 127.5, 126.2, 124.8, 124.5, 124.2, 123.4, 119.9, 118.8, 116.7, 114.5, 114.4, 110.4, 107.9, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3019, 1526, 1423, 1215, 1046, 928, 755, 669 cm^{-1}. HRMS: calcd. for $C_{25}H_{17}N_2$ [M – H]$^+$ 345.1391; found 345.1400.

6-Methyl-10-phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3b): 97% yield; yellow solid; m.p. 141–142 °C; R_f = 0.83 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, J = 6.8 Hz, 2 H), 7.33–7.03 (m, 9 H), 6.85 (d, J = 7.4 Hz, 1 H), 6.43 (t, J = 3.0, Hz, 1 H), 6.38 (d, J = 8.1 Hz, 1 H), 6.26 (d, J = 2.3 Hz, 1 H), 6.13 (d, J = 8.3 Hz, 1 H), 5.53 (s, 1 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 135.7, 132.7, 129.9, 128.9, 128.7, 128.3, 127.7, 127.4, 126.2, 125.8, 124.7, 124.5, 123.5, 119.9, 118.7, 116.4, 115.1, 114.4, 110.2, 107.8, 56.9, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 3154, 3058, 2923, 2856, 1713, 1618, 1510, 1337, 805, 756, 697 cm^{-1}. HRMS: calcd. for $C_{26}H_{19}N_2$ [M – H]$^+$ 359.1548; found 359.1542.

Methyl 10-Phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline-6-carboxylate (3c): 81% yield; white solid; m.p. 208–209 °C; R_f = 0.81 (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.74 (d, J = 6.7 Hz, 2 H), 7.42–7.12 (m, 9 H), 6.92 (d, J = 7.5 Hz, 1 H), 6.48 (t, J = 3.0 Hz, 1 H), 6.32–6.27 (m, 2 H), 5.65 (s, 1 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 142.6, 134.9, 133.7, 132.3, 129.1, 128.9, 128.1, 127.7, 126.0, 125.9, 125.1, 124.4, 122.7, 121.4, 118.1, 117.4, 115.6, 114.9, 110.9, 108.3, 56.9, 51.8 ppm. IR (KBr): $\tilde{\nu}$ = 3137, 3070, 2955, 1702, 1610, 1512, 1400, 1337, 1029, 761, 718, 691 cm^{-1}. HRMS: calcd. for $C_{27}H_{19}N_2O_2$ [M – H]$^+$ 403.1446; found 403.1443.

6-Chloro-10-phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3d): 78% yield; yellow solid; m.p. 154–155 °C; R_f = 0.74 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 7.8 Hz, 2 H), 7.34–7.27 (m, 4 H), 7.17 (t, J = 7.3, Hz, 1 H), 7.11–7.07 (m, 4 H), 6.85 (d, J = 7.3, Hz, 1 H), 6.61 (dd, J = 8.2, 1.9 Hz, 1 H), 6.44 (t, J = 3.2 Hz, 1 H), 6.28 (s, 1 H), 6.22 (d, J = 1.9 Hz, 1 H), 5.55 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 134.9, 133.6, 133.4, 132.5, 129.4, 129.1, 127.9, 127.7, 126.8, 126.1, 125.1, 124.5, 123.1, 118.9, 118.7, 117.3, 115.3, 114.6, 110.7, 108.2, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3065, 2915, 2843, 1716, 1600, 1500, 1449, 1339, 1298, 1102, 1022, 765, 695 cm^{-1}. HRMS: calcd. for $C_{25}H_{16}ClN_2$ [M – H]$^+$ 379.1002; found 379.0989.

10-(3-Chlorophenyl)-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3e): 76% yield; yellow solid; m.p. 166–167 °C; R_f = 0.88 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 7.60 (t, J = 5.1 Hz, 1 H), 7.28–7.07 (m, 8 H), 6.87 (d, J = 7.4 Hz, 1 H), 6.68 (td, J = 7.6, 1.0 Hz, 1 H), 6.59 (td, J = 8.2, 1.3 Hz, 1 H), 6.44 (t, J = 3.2 Hz, 1 H), 6.27 (d, J = 2.1 Hz, 1 H), 6.21 (d, J = 7.9 Hz, 1 H), 5.54 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9, 137.7, 133.6, 132.2, 132.1, 130.5, 130.2, 128.7, 128.2, 127.6, 125.9, 125.0, 124.6, 124.3, 123.2, 120.2, 118.6, 117.9, 114.6, 114.5, 110.4, 107.9, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3063, 2924, 2856, 1597, 1509, 1478, 1089, 753 cm^{-1}. HRMS: calcd. for $C_{25}H_{16}ClN_2$ [M – H]$^+$ 379.1002; found 379.1015.

10-(3-Fluorophenyl)-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3f): 92% yield; yellow solid; m.p. 126–127 °C; R_f = 0.73 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.7 Hz, 1 H), 7.41 (d, J = 10.2 Hz, 1 H), 7.30–7.07 (m, 7 H), 6.96 (dt, J = 8.3, 1.8 Hz, 1 H), 6.87 (d, J = 7.4 Hz, 1 H), 6.86 (t, J = 7.5 Hz, 1 H), 6.60 (t, J = 7.9 Hz, 1 H), 6.45 (t, J = 3.2 Hz, 1 H), 6.28 (d, J = 2.1 Hz, 1 H), 6.23 (d, J = 7.9 Hz, 1 H), 5.55 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 142.1, 138.2, 133.6, 132.3, 130.5, 128.2, 127.6, 126.2, 125.0, 124.6, 124.3, 123.2, 121.7, 120.2, 118.6, 117.7, 115.7, 115.4, 114.6, 113.9, 112.8, 110.4, 107.9, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3132, 3028, 2921, 2846, 1704, 1602, 1501, 1410, 1318, 1100, 1069, 892, 748, 702 cm^{-1}. HRMS: calcd. for $C_{25}H_{16}FN_2$ [M – H]$^+$ 363.1297; found 363.1299.

10-(4-Methylphenyl)-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3g): 98% yield; yellow solid; m.p. 110–112 °C; R_f = 0.51 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.1 Hz, 2 H), 7.27–7.04 (m, 8 H), 6.86 (d, J = 7.4 Hz, 1 H), 6.64 (t, J = 7.6 Hz, 1 H), 6.56 (td, J = 7.6, 1.3 Hz, 1 H), 6.43 (t, J = 3.2 Hz, 1 H), 6.27 (m, 2 H), 5.54 (s, 1 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 135.5, 134.1, 133.6, 132.9, 132.5, 129.8, 127.6, 127.5, 126.2, 124.8, 124.5, 124.3, 123.6, 119.9, 118.9, 115.9, 114.5, 110.4, 107.9, 56.9, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 3180, 3060, 2923, 2854, 1713, 1607, 1507, 1434, 875, 747 cm^{-1}. HRMS: calcd. for $C_{26}H_{19}N_2$ $[M - H]^+$ 359.1548; found 359.1539.

3-(15b*H*-Isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-10-yl)phenol (3h): 92% yield; yellow solid; m.p. 128–129 °C; R_f = 0.19 (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.04 (m, 9 H), 6.85 (d, J = 7.4 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.65 (t, J = 7.4 Hz, 1 H), 6.57 (td, J = 7.6, 1.3 Hz, 1 H), 6.44 (t, J = 3.0 Hz, 1 H), 6.26 (d, J = 6.0 Hz, *2* H), 5.50 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 143.0, 137.2, 133.5, 130.0, 127.8, 127.5, 125.1, 124.9, 124.5, 124.3, 119.9, 118.8, 118.1, 116.9, 116.1, 114.5, 114.3, 113.0, 110.4, 109.3, 107.9, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3512, 3050, 2914, 2848, 1716, 1590, 1500, 1475, 1435, 1333, 1289, 886, 745, 695 cm^{-1}. HRMS: calcd. for $C_{25}H_{17}N_2O$ $[M - H]^+$ 361.1340; found 361.1327.

10-(3-Methoxyphenyl)-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3i): 90% yield; white solid; m.p. 166–167 °C; R_f = 0.28 (hexane/EtOAc, 97.5:2.5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.04 (m, 9 H), 6.86 (d, J = 7.3 Hz, 1 H), 6.81 (dd, J = 8.1, 2.0 Hz, 1 H), 6.65 (td, J = 7.4, 1.1 Hz, 1 H), 6.57 (td, J = 7.9, 1.3 Hz, 1 H), 6.43 (t, J = 8.1 Hz, 1 H), 6.27 (dd, J = 4.0, 1.1 Hz, 1 H), 6.26 (s, 1 H), 5.55 (s, 1 H), 3.72 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 143.2, 137.3, 133.6, 132.6, 132.4, 129.9, 127.8, 127.5, 126.0, 124.8, 124.5, 124.3, 123.4, 119.9, 118.7, 117.0, 114.5, 114.4, 114.3, 111.6, 110.3, 107.9, 56.9, 55.4 ppm. IR (KBr): $\tilde{\nu}$ = 3182, 3058, 3007, 2927, 1721, 1600, 1509, 1475, 1046, 888, 750 cm^{-1}. HRMS: calcd. for $C_{26}H_{19}N_2O$ $[M - H]^+$ 375.1748; found 375.1754.

10-[4-(Trifluoromethyl)phenyl]-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3j): 75% yield; yellow solid; m.p. 128–129 °C; R_f = 0.67 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.5 Hz, 2 H), 7.61 (d, J = 8.3 Hz, 2 H), 7.31–7.13 (m, 6 H), 6.93 (d, J = 6.8 Hz, 1 H), 6.74 (t, J = 7.5 Hz, 1 H), 6.64 (t, J = 7.5 Hz, 1 H), 6.46 (t, J = 3.0 Hz, 1 H), 6.30 (d, J = 2.3 Hz, 1 H), 6.19 (d, J = 8.3 Hz, 1 H), 5.60 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 139.1, 137.6, 133.6, 132.1, 131.9, 131.3, 129.1, 128.8, 128.5, 127.7, 126.3, 126.0, 125.9, 125.8, 125.2, 124.6, 124.3, 123.1, 122.7, 121.8, 121.6, 120.4, 118.7, 118.6, 114.7, 114.6, 110.5, 108.1, 106.2, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3019, 2922, 2852, 1701, 1610, 1509, 1323, 839, 747 cm^{-1}. HRMS: calcd. for $C_{26}H_{16}F_3N_2$ $[M - H]^+$ 413.1265; found 413.1249.

4-[15b*H*-Isoquino(2,1-*a*)pyrrolo(2,1-*c*)quinoxalin-10-yl]benzonitrile (3k): 78% yield; yellow solid; m.p. 156–157 °C; R_f = 0.43 (hexane/EtOAc, 97.5:2.5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.3 Hz, 2 H), 7.65 (d, J = 9.1 Hz, 2 H), 7.31–7.18 (m, 6 H), 6.94 (d, J = 6.0 Hz, 1 H), 6.75 (t, J = 7.6 Hz, 1 H), 6.63 (t, J = 7.6 Hz, 1 H), 6.46 (t, J = 3.0 Hz, 1 H), 6.30 (d, J = 2.3 Hz, 1 H), 6.14 (d, J = 7.6 Hz, 1 H), 5.59 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 140.0, 133.7, 132.7, 131.9, 131.8, 128.8, 127.7, 126.5, 126.3, 125.4, 124.7, 124.3, 122.9, 120.6, 119.7, 118.7, 118.4, 114.7, 111.8, 110.6, 108.2, 56.8 ppm. IR (KBr): $\tilde{\nu}$ = 3108, 2920, 2886, 2284, 1698, 1589, 1505, 1302, 1105, 849, 752, 685 cm^{-1}. HRMS: calcd. for $C_{26}H_{16}N_3$ $[M - H]^+$ 370.1344; found 370.1348.

10-(4-Nitrophenyl)-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3l): 62% yield; dark-yellow, thick liquid; R_f = 0.49 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, J = 9.1 Hz, 2 H), 7.95 (d, J = 9.1 Hz, 2 H), 7.32–7.19 (m, 6 H), 6.96–6.94 (d, J = 6.8 Hz, 1 H), 6.77 (t, J = 7.6 Hz, 1 H), 6.63 (t, J = 7.6 Hz, 1 H), 6.47 (t, J = 3.8 Hz, 1 H), 6.31 (t, J = 2.3 Hz, 1 H), 6.14 (d, J = 6.8 Hz, 1 H), 5.62 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 141.9, 140.9, 133.7, 133.4, 131.8, 129.0, 127.8, 126.6, 126.3, 125.5, 124.7, 124.3, 122.8, 120.7, 120.4, 118.4, 114.7, 110.6, 109.3, 108.2, 56.8 ppm. IR (film): $\tilde{\nu}$ = 3062, 2923, 2848, 1716, 1591, 1510, 1334, 1102, 851, 760, 690 cm^{-1}. HRMS: calcd. for $C_{25}H_{16}N_3O_2$ $[M - H]^+$ 390.1242; found 390.1250.

14-Fluoro-10-phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (3m): 69% yield; brown solid; m.p. 204–205 °C; R_f = 0.70 (hexane/EtOAc, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 7.6 Hz, 2 H), 7.33–7.14 (m, 7 H), 6.84 (td, J = 8.5, 2.3 Hz, 1 H), 6.69 (td, J = 8.5, 1.3 Hz, 1 H), 6.63–6.56 (m, 2 H), 6.44 (t, J = 3.2 Hz, 1 H), 6.28–6.24 (m, 2 H), 5.54 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 161.1, 142.6, 136.0, 135.9, 135.4, 132.2, 128.9, 128.8, 127.9, 126.4, 126.3, 126.0, 124.3, 122.7, 120.1, 118.7, 115.8, 114.7, 114.5, 114.2, 112.3, 112.0, 110.5, 107.9, 56.6 ppm. IR (KBr): $\tilde{\nu}$ = 3162, 3048, 2926, 1708, 1632, 1524, 1470, 1380, 1122, 1029, 864, 752, 695 cm^{-1}. HRMS: calcd. for $C_{25}H_{16}FN_2$ $[M - H]^+$ 363.1297; found 363.1299.

10-Phenyl-14-(trifluoromethyl)-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]-quinoxaline (3n): 64% yield; yellow solid; m.p. 187–188 °C; R_f = 0.69 (hexane/EtOAc, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.73 (m, 2 H), 7.42–7.24 (m, 7 H), 7.10–7.09 (m, 2 H), 6.71 (t, J = 7.7 Hz, 1 H), 6.59 (t, J = 7.6 Hz, 1 H), 6.47 (t, J = 3.2 Hz, 1 H), 6.31 (d, J = 2.3 Hz, 1 H), 6.24 (d, J = 7.7 Hz, 1 H), 5.57 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6, 135.9, 135.2, 133.9, 131.7, 129.5, 129.1, 126.6, 125.9, 124.8, 124.6, 124.3, 122.2, 121.6, 120.5, 119.1, 115.4, 114.9, 114.7, 110.8, 108.4, 56.8 ppm. IR (KBr): $\tilde{\nu}$ = 3138, 3054, 2923, 2853, 1720, 1607, 1513, 1422, 1325, 1118, 1069, 892, 752, 704 cm^{-1}. HRMS: calcd. for $C_{26}H_{16}F_3N_2$ $[M - H]^+$ 413.1265; found 413.1273.

6-Phenyl-17b*H*-indolo[1,2-*a*]isoquino[1,2-*c*]quinoxaline (3o): 85% yield; red, thick liquid; R_f = 0.42 (hexane/EtOAc, 97:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.1 Hz, 1 H), 7.77 (t, J = 7.9 Hz, 3 H), 7.69 (d, J = 7.6 Hz, 1 H), 7.34–7.13 (m, 8 H), 7.05 (t, J = 7.4 Hz, 1 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.78 (t, J = 7.6 Hz, 1 H), 6.64–6.60 (m, 2 H), 6.36 (d, J = 8.1 Hz, 1 H), 5.68 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.6, 135.5, 132.8, 132.5, 132.0, 130.7, 129.9, 129.0, 127.9, 127.7, 126.1, 125.1, 124.6, 123.9, 122.7, 121.2, 121.1, 120.5, 119.2, 116.8, 116.3, 112.3, 102.3, 57.9 ppm. IR (film): $\tilde{\nu}$ = 3054, 2922, 2853, 1666, 1597, 1452, 1062, 1024, 743, 693 cm^{-1}. HRMS: calcd. for $C_{29}H_{19}N_2$ $[M - H]^+$ 395.1548; found 395.1550.

16-Methoxy-6-phenyl-17b*H*-indolo[1,2-*a*]isoquino[1,2-*c*]quinoxaline (3p): 87% yield; white solid; m.p. 189–190 °C; R_f = 0.50 (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.3 Hz, 2 H), 7.67 (d, J = 8.3 Hz, 1 H), 7.38–7.01 (m, 10 H), 6.84–6.78 (m, 2 H), 6.69–6.62 (m, 2 H), 6.37 (d, J = 8.3 Hz, 1 H), 5.71 (s, 1 H), 4.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 148.7, 143.6, 132.6, 130.4, 129.0, 128.9, 127.9, 127.7, 126.1, 125.0, 124.7, 124.0, 123.6, 120.5, 120.4, 119.2, 116.8, 116.5, 105.7, 101.3, 99.5, 57.9, 55.5 ppm. IR (KBr): $\tilde{\nu}$ = 3051, 2925, 1599, 1508, 1482, 1083, 1049, 953, 749, 698 cm^{-1}. HRMS: calcd. for $C_{30}H_{21}N_2O$ $[M - H]^+$ 425.1654; found 425.1649.

6-Phenyl-17a*H*-indolo[1,2-*c*]isoquino[2,1-*a*]quinazoline (3q): 85% yield; white solid; m.p. 196–197 °C; R_f = 0.51 (hexane/EtOAc, 90:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, J = 7.3 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 1 H), 7.74 (d, J = 7.3 Hz, 2 H), 7.41–7.32 (m, 6 H), 7.29–7.25 (m, 4 H), 7.09 (t, J = 8.3 Hz, 1 H), 6.95 (t, J =

8.3 Hz, 1 H), 6.89 (t, J = 7.3 Hz, 1 H), 6.70 (s, 1 H), 6.47 (d, J = 8.3 Hz, 1 H), 6.30 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.2, 143.9, 142.1, 139.8, 134.7, 133.9, 132.1, 131.0, 130.4, 129.3, 129.2, 128.8, 128.3, 126.2, 125.5, 125.4, 123.2, 123.1, 122.8, 121.0, 119.8, 109.1, 69.5 ppm. IR (KBr): $\tilde{\nu}$ = 3053, 2922, 2853, 1590, 1491, 1443, 1359, 1102, 1021, 749, 690 cm^{-1}. HRMS: calcd. for $C_{29}H_{19}N_2$ [M – H]$^+$ 395.1548; found 395.1544.

6-Phenyl-12,16c-dihydroindolo[3,2-*c*]isoquino[2,1-*a*]quinoline (3q′): 88% yield; yellow solid; m.p. 206–207 °C; R_f = 0.51 (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (br. s, 1 H), 7.72 (dd, J = 8.3, 1.5 Hz, 2 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.36–7.28 (m, 3 H), 7.22–7.04 (m, 7 H), 6.89 (d, J = 7.6 Hz, 1 H), 6.71–6.64 (m, 2 H), 6.19 (dd, J = 8.3, 1.5 Hz, 1 H), 6.00 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 142.6, 139.6, 137.3, 135.5, 133.9, 132.2, 130.7, 129.0, 128.6, 127.4, 127.2, 126.5, 126.0, 124.6, 123.7, 122.1, 121.4, 119.8, 119.2, 118.2, 117.8, 117.5, 116.9, 111.6, 105.6, 56.9 ppm. IR (KBr): $\tilde{\nu}$ = 3406, 3055, 2922, 2853, 1661, 1606, 1578, 1456, 1347, 1204, 1027, 746, 694 cm^{-1}. HRMS: calcd. for $C_{29}H_{19}N_2$ [M – H]$^+$ 395.1548; found 395.1541.

6-Hexyl-12,16c-dihydroindolo[3,2-*c*]isoquino[2,1-*a*]quinoline (3r): 89% yield; yellow oil; R_f = 0.68 (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 7.41 (d, J = 8.3 Hz, 2 H), 7.22–7.14 (m, 2 H), 7.08 (t, J = 7.6 Hz, 3 H), 7.01–6.91 (m, 2 H), 6.82 (d, J = 7.6 Hz, 1 H), 6.69 (t, J = 7.6 Hz, 1 H), 6.54 (s, 1 H), 6.50 (d, J = 7.6 Hz, 1 H), 5.8 (s, 1 H), 2.73–2.63 (m, 1 H), 2.54–2.44 (m, 1 H), 1.79–1.62 (m, 2 H), 1.48–1.35 (m, 2 H), 1.35–1.25 (m, 4 H), 0.86 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.7, 140.1, 137.1, 132.8, 132.2, 130.9, 127.9, 127.0, 126.7, 124.2, 123.6, 122.5, 120.4, 120.3, 119.8, 118.8, 118.7, 117.8, 117.0, 116.5, 111.2, 107.3, 57.9, 32.9, 31.6, 30.1, 29.2, 22.6, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3521, 3202, 2895, 2924, 1647, 1624, 1585, 1512, 1472, 1386, 1326, 1124, 886, 824, 758, 695, 682 cm^{-1}. HRMS: calcd. for $C_{29}H_{27}N_2$ [M – H]$^+$ 403.2174; found 403.2177.

6-Phenyl-17a*H*-benzo[4,5]imidazo[1,2-*c*]isoquino[2,1-*a*]quinazoline (3s): 83% yield; yellow solid; m.p. 220–221 °C; R_f = 0.41 (hexane/EtOAc, 95:5). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 7.78 (d, J = 7.2 Hz, 2 H), 7.39–7.31 (m, 6 H), 7.27–7.24 (m, 3 H), 7.06 (t, J = 8.2 Hz, 1 H), 6.93 (t, J = 7.2 Hz, 1 H), 6.88 (t, J = 7.2 Hz, 1 H), 6.69 (s, 1 H), 6.46 (d, J = 7.2 Hz, 1 H), 6.29 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.9, 142.1, 139.8, 134.7, 133.9, 132.2, 131.0, 130.5, 129.3, 129.1, 128.8, 128.3, 126.2, 125.5, 125.4, 123.2, 123.1, 122.8, 121.0, 119.8, 117.9, 116.9, 115.2, 109.1, 69.6 ppm. IR (KBr): $\tilde{\nu}$ = 3062, 2964, 2852, 1596, 1496, 1482, 1372, 1108, 1085, 752, 692, 684 cm^{-1}. HRMS: calcd. for $C_{28}H_{18}N_3$ [M – H]$^+$ 396.1501; found 396.1504.

12-Phenyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3t): 85% yield; yellow solid; m.p. 192–193 °C; R_f = 0.52 (hexane/EtOAc, 70:30). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.76 (s, 1 H), 7.78–7.75 (m, 3 H), 7.39–7.22 (m, 7 H), 6.98–6.93 (m, 2 H), 6.74 (t, J = 7.4 Hz, 1 H), 6.13 (d, J = 8.4 Hz, 1 H), 5.73 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 161.8, 143.9, 141.9, 134.8, 132.9, 129.1, 128.9, 128.7, 128.2, 128.0, 127.4, 127.3, 126.7, 126.5, 125.8, 125.6, 123.4, 122.3, 119.7, 116.5, 67.2 ppm. IR (KBr): $\tilde{\nu}$ = 3498, 3164, 2987, 1710, 1622, 1432, 1082, 752, 685, 672 cm^{-1}. HRMS: calcd. for $C_{22}H_{17}N_2O$ [M + H]$^+$ 325.1340; found 325.1331.

8-Methyl-12-phenyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3u): 89% yield; white solid; m.p. 194–195 °C; R_f = 0.30 (hexane/EtOAc, 90:10). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.00 (d, J = 4.9 Hz, 1 H), 7.78 (d, J = 6.8 Hz, 2 H), 7.49–7.30 (m, 9 H), 6.85 (t, J = 6.8 Hz, 1 H), 6.01 (d, J = 7.8 Hz, 1 H), 5.67 (d, J = 2.9 Hz, 1 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 161.9, 141.9, 141.5, 134.9, 133.4, 132.1, 130.2, 129.0, 128.8, 128.1, 127.9, 127.3, 125.8, 125.5, 123.4, 122.1, 121.3, 117.1, 67.1, 19.8 ppm. IR (KBr): $\tilde{\nu}$ = 3502, 3158, 2987, 2962, 1709, 1624, 1534, 1484, 1362, 1086, 812, 745, 642, 630 cm^{-1}. HRMS: calcd. for $C_{23}H_{19}N_2O$ [M + H]$^+$ 339.1497; found 339.1509.

7-Fluoro-12-phenyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3v): 78% yield; white solid; m.p. 231–232 °C; R_f = 0.21 (hexane/EtOAc, 90:10). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.03 (d, J = 4.8 Hz, 1 H), 7.79 (s, 2 H), 7.48–7.35 (m, 8 H), 7.07–7.05 (m, 1 H), 6.56 (t, J = 8.8 Hz, 1 H), 5.97 (d, J = 8.8 Hz, 1 H), 5.68 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1, 159.7, 158.9, 146.0, 141.7, 138.3, 136.4, 133.7, 131.9, 131.1, 129.1, 128.9, 128.7, 128.3, 128.1, 127.3, 127.0, 126.5, 125.7, 123.4, 118.5, 116.9, 112.8, 111.5, 108.3, 101.7, 66.9 ppm. IR (KBr): $\tilde{\nu}$ = 3480, 3187, 3059, 2936, 1697, 1615, 1471, 1360, 1288, 1240, 1116, 1073, 802, 754, 689 cm^{-1}. HRMS: calcd. for $C_{22}H_{16}FN_2O$ [M + H]$^+$ 343.1246; found 343.1244.

8-Bromo-12-phenyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3w): 90% yield; yellow solid; m.p. 259–269 °C; R_f = 0.34 (hexane/EtOAc, 90:10). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.21 (d, J = 5.1 Hz, 1 H), 7.80 (d, J = 6.9 Hz, 2 H), 7.76 (d, J = 2.5 Hz, 1 H), 7.47–7.28 (m, 8 H), 7.11 (dd, J = 8.9, 2.5 Hz, 1 H), 6.05 (d, J = 8.7 Hz, 1 H), 5.69 (d, J = 4.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 160.4, 142.8, 141.3, 134.9, 134.2, 133.7, 132.6, 131.7, 129.4, 128.9, 128.0, 127.9, 127.1, 125.5, 125.4, 123.2, 119.5, 118.4, 116.7, 111.3, 67.2 ppm. IR (KBr): $\tilde{\nu}$ = 3520, 3167, 3051, 2920, 1684, 1597, 1473, 1364, 1025, 814, 758, 698 cm^{-1}. HRMS: calcd. for $C_{22}H_{16}BrN_2O$ [M + H]$^+$ 403.0446; found 403.0438.

9-Chloro-12-phenyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3x): 88% yield; yellow solid; m.p. 197–198 °C; R_f = 0.29 (hexane/EtOAc, 90:10). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.16 (s, 1 H), 7.82 (d, J = 6.8 Hz, 2 H), 7.68 (d, J = 8.7 Hz, 1 H), 7.49–7.33 (m, 8 H), 6.78 (t, J = 6.8 Hz, 1 H), 6.05 (s, 1 H), 5.73 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 160.9, 145.0, 141.2, 137.6, 134.1, 131.8, 129.3, 129.2, 129.1, 128.3, 128.2, 125.8, 125.6, 123.3, 119.7, 117.3, 116.6, 115.8, 67.4 ppm. IR (KBr): $\tilde{\nu}$ = 3482, 3175, 3054, 2914, 1671, 1600, 1470, 1440, 1138, 755, 695 cm^{-1}. HRMS: calcd. for $C_{22}H_{16}ClN_2O$ [M + H]$^+$ 359.0951; found 359.0956.

7-Fluoro-12-hexyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3y): 65% yield; white solid; m.p. 180–181 °C; R_f = 0.27 (hexane/EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.34 (m, 1 H), 7.29–7.23 (m, 1 H), 7.11–7.10 (m, 2 H), 7.04–6.93 (m, 3 H), 5.97 (d, J = 2.8 Hz, 1 H), 5.89 (s, 1 H), 5.62 (s, 1 H), 2.18 (t, J = 6.9 Hz, 2 H), 1.21–1.10 (m, 8 H), 0.76 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 160.2, 159.6, 144.9, 141.6, 132.6, 132.4, 132.2, 129.3, 126.2, 125.9, 124.2, 120.0, 113.9, 113.6, 67.7, 32.4, 31.4, 28.8, 27.4, 22.4, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3480, 3195, 3079, 2923, 1671, 1605, 1465, 1369, 1177, 1118, 1052, 896, 816, 755, 614 cm^{-1}. HRMS: calcd. for $C_{22}H_{24}FN_2O$ [M + H]$^+$ 351.1873; found 351.1861.

8-Bromo-12-hexyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazolin-6-one (3z): 70% yield; white solid; m.p. 133–134 °C; R_f = 0.41 (hexane/EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 2.3 Hz, 1 H), 7.52 (dd, J = 8.5, 2.5 Hz, 1 H), 7.28–7.23 (m, 1 H), 7.10 (d, J = 4.2 Hz, 2 H), 7.01 (d, J = 7.4 Hz, 2 H), 5.99 (s, 2 H), 5.64 (s, 1 H), 2.19–2.09 (m, 2 H), 1.26–1.10 (m, 8 H), 0.77 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 147.5, 135.0, 134.1, 133.5, 132.2, 131.2, 130.6, 129.8, 128.8, 128.2, 127.9, 125.9, 124.2, 115.7, 67.9, 32.3, 31.4, 28.7, 27.4, 22.2, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3484, 3181, 3065, 2922, 2847, 1657, 1588, 1513, 1473, 1346, 1312, 1162, 892, 812, 760, 713, 628 cm^{-1}. HRMS: calcd. for $C_{22}H_{24}BrN_2O$ [M + H]$^+$ 411.0930; found 411.0947.

12-Phenyl-5,6-dihydro-4b*H*-6λ⁶-benzo[5,6][1,2,4]thiadiazino[3,4-*a*]-isoquinoline-6,6-dione (3aa): 75% yield; yellow solid; m.p. 109–110 °C; R_f = 0.72 (hexane/EtOAc, 90:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.3 Hz, 1 H), 7.36–7.21 (m, 9 H), 6.98 (t, J = 7.3 Hz, 1 H), 6.86 (t, J = 7.3 Hz, 1 H), 6.39 (s, 1 H), 6.29 (d, J = 8.3 Hz, 1 H), 6.25 (d, J = 11.5 Hz, 1 H), 5.27 (d, J = 11.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8, 139.1, 135.7, 132.4, 129.3, 128.7, 128.6, 128.2, 127.7, 127.6, 125.7, 125.3, 124.1, 123.6, 123.2, 120.9, 114.6, 112.8, 70.8 ppm. IR (KBr): $\tilde{\nu}$ = 3462, 3004, 2914, 2897, 1613, 1608, 1522, 1432, 1266, 1132, 1017, 849, 763, 697, 654 cm^{-1}. HRMS: calcd. for $C_{21}H_{17}N_2O_2S$ [M + H]$^+$ 361.1011; found 361.1007.

12-Phenyl-5,6-dihydro-4b*H*-isoquino[2,1-*a*]quinazoline (3ab): 95% yield; yellow solid; m.p. 173–174 °C; R_f = 0.24 (hexane/EtOAc, 90:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, J = 7.4 Hz, 1 H), 7.30–7.12 (m, 9 H), 7.01 (d, J = 7.4 Hz, 1 H), 6.86 (t, J = 7.4 Hz, 1 H), 6.75 (t, J = 7.4 Hz, 1 H), 6.17 (d, J = 8.1 Hz, 1 H), 6.05 (s, 1 H), 5.94 (s, 1 H), 5.13 (AB_q, J = 14.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 136.9, 133.3, 132.4, 130.4, 129.0, 128.9, 128.6, 128.0, 127.9, 126.9, 126.8, 126.1, 125.8, 124.8, 124.4, 123.8, 122.6, 105.7, 85.04, 68.1 ppm. IR (KBr): $\tilde{\nu}$ = 3398, 3055, 2915, 2848, 1638, 1602, 1522, 1449, 1266, 1144, 1003, 850, 752, 697 cm^{-1}. HRMS: calcd. for $C_{22}H_{17}N_2$ [M – H]$^+$ 309.1392; found 309.1396.

12-Phenyl-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoquinoline (3ac): 76% yield; yellow solid; m.p. 165–166 °C; R_f = 0.28 (hexane/EtOAc, 90:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, J = 7.3 Hz, 1 H), 7.26 (t, J = 7.3 Hz, 1 H), 7.21–7.17 (m, 6 H), 7.13 (d, J = 8.3 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.86 (t, J = 7.3 Hz, 1 H), 6.75 (t, J = 7.3 Hz, 1 H), 6.17 (d, J = 8.3 Hz, 1 H), 6.05 (s, 1 H), 5.94 (s, 1 H), 5.14 (AB_q, J = 14.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 136.9, 132.3, 129.5, 128.9, 128.6, 128.0, 127.9, 127.2, 126.8, 126.0, 125.8, 124.7, 124.3, 123.8, 105.7, 85.0, 68.0 ppm. IR (KBr): $\tilde{\nu}$ = 3098, 2923, 2853, 1714, 1657, 1599, 1484, 1382, 1278, 1129, 1093, 1024, 754, 695 cm^{-1}. HRMS: calcd. for $C_{22}H_{16}NO$ [M – H]$^+$ 310.1232; found 310.1227.

6-Phenyl-12,12a-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ad): 94% yield; yellow solid; m.p. 158–159 °C; R_f = 0.59 (hexane/EtOAc, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (d, J = 7.8 Hz, 1 H), 7.90 (d, J = 7.8 Hz, 1 H), 7.67–7.56 (m, 10 H), 7.34 (t, J = 7.8 Hz, 1 H), 6.95 (t, J = 7.3 Hz, 1 H), 6.84 (s, 1 H), 6.43 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 143.9, 134.6, 131.6, 130.6, 130.2, 129.9, 129.4, 129.0, 127.9, 126.7, 125.2, 124.3, 121.3, 119.6, 114.1, 112.7, 65.9 ppm. IR (KBr): $\tilde{\nu}$ = 3411, 3028, 2921, 2853, 1646, 1599, 1554, 1483, 1453, 1383, 1338, 1279, 1131, 1093, 811, 755, 694 cm^{-1}. HRMS: calcd. for $C_{21}H_{15}N_2$ [M – H]$^+$ 295.1235; found 295.1245.

8-Phenyl-5,6-dihydro-13b*H*-pyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoquinoline (3ae): 55% yield; yellow solid; m.p. 88–89 °C; R_f = 0.60 (hexane/EtOAc, 99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, J = 7.7, 2.0 Hz, 2 H), 7.36–7.29 (m, 3 H), 7.18–7.07 (m, 4 H), 6.61 (t, J = 2.0 Hz, 1 H), 6.37 (s, 1 H), 6.24 (t, J = 2.8 Hz, 1 H), 6.05 (s, 1 H), 5.41 (s, 1 H), 4.02 (ddd, J = 11.7, 9.6, 4.5 Hz, 1 H), 3.76 (dt, J = 11.7, 3.7 Hz, 1 H), 3.15 (ddd, J = 13.2, 9.6, 3.7 Hz, 1 H), 2.96 (dt, J = 13.2, 4.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 135.7, 131.0, 129.6, 128.8, 128.6, 127.6, 127.5, 126.8, 125.6, 123.9, 122.7, 120.7, 119.3, 113.6, 108.2, 106.7, 56.6, 45.2, 41.6 ppm. IR (KBr): $\tilde{\nu}$ = 3219, 3109, 2927, 2820, 1626, 1524, 1480, 1430, 1282, 1160, 1024, 916, 826, 752, 740, 685 cm^{-1}. HRMS: calcd. for $C_{21}H_{17}N_2$ [M – H]$^+$ 297.1391; found 297.1387.

10-Phenyl-15b*H*-[1,7]naphthyridino[7,8-*a*]pyrrolo[2,1-*c*]quinoxaline (3ah): 96% yield; yellow solid; m.p. 177–178 °C; R_f = 0.43 (hexane/EtOAc, 70:30). ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 8.39 (d, J = 2.9 Hz, 1 H), 7.84 (d, J = 6.8 Hz, 2 H), 7.60 (s, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.43–7.35 (m, 4 H), 7.16–7.13 (m, 2 H), 6.77 (t, J = 6.8 Hz, 1 H), 6.66 (t, J = 7.8 Hz, 1 H), 6.46 (s, 1 H), 6.36 (s, 1 H), 6.27 (d, J = 7.8 Hz, 1 H), 5.76 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 151.4, 148.4, 146.9, 134.6, 131.7, 131.4, 129.7, 129.2, 128.6, 126.2, 125.8, 124.3, 122.9, 121.6, 120.7, 118.2, 117.6, 115.8, 115.2, 110.6, 108.3, 55.5 ppm. IR (KBr): $\tilde{\nu}$ = 3111, 2927, 2850, 1716, 1606, 1583, 1514, 1430, 1343, 1291, 1156, 1053, 928, 852, 769, 741, 695 cm^{-1}. HRMS: calcd. for $C_{24}H_{16}N_3$ [M – H]$^+$ 346.1344; found 346.1333.

4-[2-(2-Phenyl-1-ethynyl)phenyl]-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (11): 99% yield; yellow liquid; R_f = 0.73 (hexane/EtOAc, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.54 (m, 1 H), 7.51–7.47 (m, 2 H), 7.34–7.31 (m, 4 H), 7.27–7.19 (m, 4 H), 6.90 (td, J = 7.6, 1.3 Hz, 1 H), 6.79 (td, J = 7.6, 1.3 Hz, 1 H) 6.66 (dd, J = 7.7, 1.3 Hz, 1 H) 6.28 (t, J = 3.4 Hz, 1 H) 6.23 (s, 1 H), 5.85 (d, J = 3.4 Hz, 1 H), 4.47 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 135.4, 132.4, 131.6, 128.9, 128.6, 128.5, 128.1, 127.7, 127.6, 125.3, 124.7, 122.8, 121.7, 119.2, 115.7, 115.5, 114.6, 114.2, 111.1, 110.4, 106.1, 94.3, 87.1, 53.1 ppm. IR (film): $\tilde{\nu}$ = 3365, 3060, 2961, 2925, 1717, 1604, 1514, 1490, 1338, 1287, 1261, 1091, 1025, 799, 755, 692 cm^{-1}. HRMS: calcd. for $C_{25}H_{17}N_2$ [M – H]$^+$ 345.1392; found 345.1388.

CCDC-766076 (for **3c**), -766077 (for **3q**), and -766078 (for **3w**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): All experimental procedures, analytical data, and copies of the ^{1}H and ^{13}C NMR spectra of all newly synthesized products; X-ray structural data of **3c**, **3q**, and **3w**.

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[20] For the X-ray crystal structure of **3q**, see the Supporting Information.
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[23] For the X-ray crystal structure of **3w**, see the Supporting Information.
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