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Tandem One-Pot Palladium-Catalyzed Coupling of Hydrazones, Haloindoles, and Amines: Synthesis of Amino-*N*-vinylindoles and Their Effect on Human Colon Carcinoma Cells

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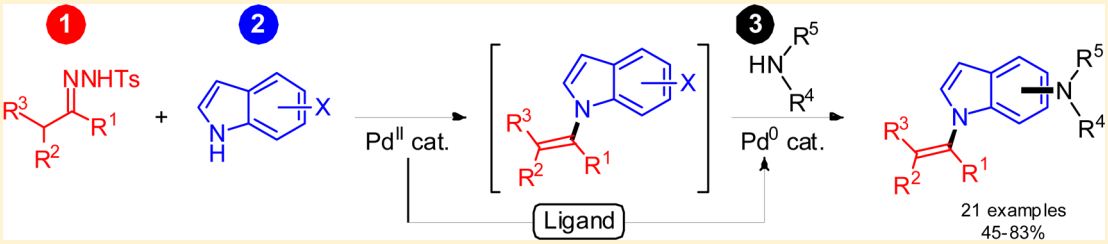
Supporting Information



ABSTRACT: The synthesis of amino-substituted *N*-vinylazoles was achieved by a new palladium-assisted tandem catalytic reaction involving *N*-tosylhydrazones, halo-substituted azoles, and amines. Accordingly, two Csp^2–N bonds were formed through two mechanistically distinct reactions using a single Pd^{II}/Pd^0 catalyst system in a one-pot fashion. This work paves the way for the design of biological relevant compounds in an amino-substituted *N*-vinylindole series. Among several polyoxygenated derivatives evaluated, compounds **5e** and **5u** were found to exhibit good antiproliferative activity.

INTRODUCTION

Palladium catalysts offer versatile methods for carbon–carbon and carbon–heteroatom bond formations. A fascinating myriad of transformations using palladium catalysts are found routinely to be a key step in target-oriented syntheses, affording complex natural products, pharmaceutical leads, and fluorescent compounds.[1] The involvement of Pd^{II}/Pd^0 complexes as intermediates in Pd-catalyzed cascade reactions has gained considerable interest over the years, due to the benefits over traditional stepwise methods, including rapid access of sophisticated products, reduction in cost, and multiple bond formations combined in one pot, thus reducing the amount of waste.[2]

On the other hand, metal carbenes are valuable intermediates in many catalytic transformations and represent an important domain in synthetic applications.[3] The most common precursors of metal carbenes are diazo compounds. This includes stable diazo compounds bearing an electron-withdrawing substituent on the diazo carbon or nonstabilized diazo compounds that can be generated in situ from *N*-tosylhydrazones through Bamford–Stevens reactions.[4] After the Barluenga and Valdes seminal report on palladium-catalyzed cross-coupling reactions with *N*-tosylhydrazones,[5] an array of Pd-catalyzed reactions was developed with these reagents, readily available from the corresponding ketones or aldehydes.[6]

We have recently reported a series of Pd-catalyzed cross-coupling reactions using *N*-tosylhydrazones as coupling partners.[7] As part of our ongoing drug discovery program to develop novel scaffolds, we reported the multicomponent reaction (MCR) of *N*-tosylhydrazones, dihaloarenes, and various amines,[8] producing nitrogen-containing 1,1′-diarylethylenes (Scheme 1) related to the potent antivascular isoamino-combretastatin A4 (*iso*NH_2CA-4).[9]

The two C–C and Csp^2–N bonds formed through this MCR have been catalyzed by a single Pd(0) catalyst in a one-pot manner (autotandem catalysis).[10] Very recently, we disclosed the palladium-catalyzed Csp^2–N bond formation through the oxidative coupling of N–H azoles with *N*-tosylhydrazones.[11] To be effective, this transformation does not require the addition of any external ligand but mechanistically requires the presence of an oxidant to form a Pd^{II} species from a Pd^0 catalyst.

As a continuation of our interest in sulfonylhydrazones as versatile coupling partners, we speculated that replacing the dihaloarene having two electrophilic centers (Scheme 1a) with a component having both an electrophilic and a nucleophilic center, such as halo-substituted azoles (Scheme 1b) would be a challenge. In this case, the reaction with *N*-tosylhydrazones and amines under Pd catalysis will allow the formation of two Csp^2–N bonds through two mechanistically distinct reactions. We thought that it might be possible to combine the *N*-vinylazole formation step and Buchwald–Hartwig amination into a sequential catalytic process with only one catalyst. Herein we report our study based on this idea, which would accelerate the synthesis of biologically active molecular scaffolds.

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Scheme 1. *N*-Tosylhydrazones in the Pd-Catalyzed Tandem Catalytic Process

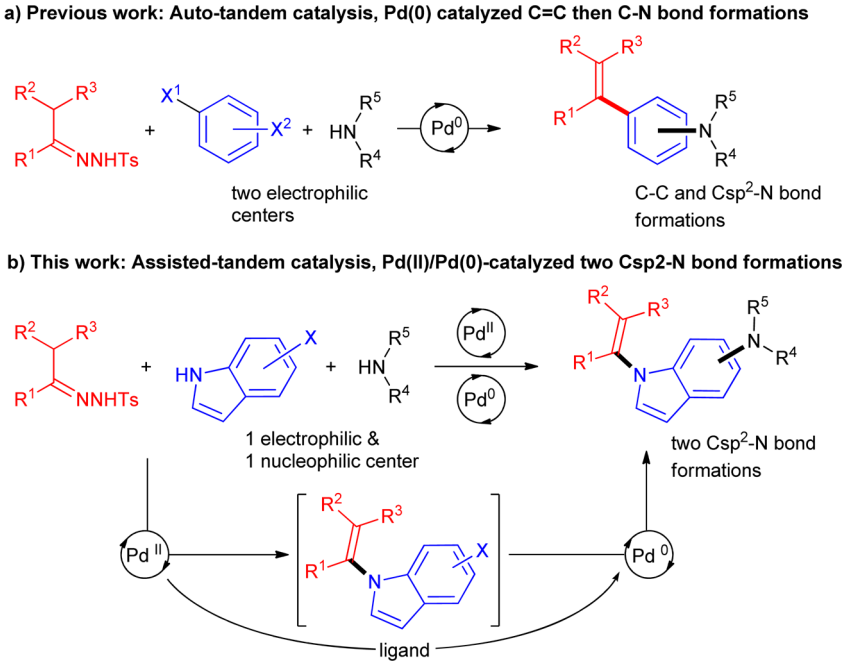
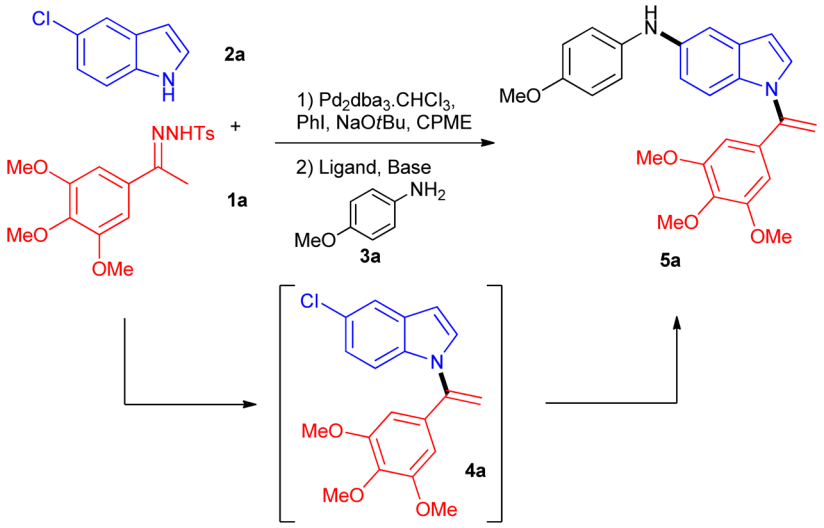


Table 1. Selected Optimization Experiments for the Pd^{II}/Pd^{0}-Catalyzed Reaction[a]



entry	ligand[b]	base[b]	**3a** (equiv)	**5a** yield (%)[c]
1	none	none	1.0	
2	none	NaO-*t*-Bu	1.0	
3	Binap	NaO-*t*-Bu	1.0	traces
4	dppp	NaO-*t*-Bu	1.0	traces
5	dppf	NaO-*t*-Bu	1.0	traces
6	PPh_3	NaO-*t*-Bu	1.0	traces
7	XPhos	NaO-*t*-Bu	1.0	67
8	XPhos	K_2CO_3	1.0	traces
9	XPhos	Cs_2CO_3	1.0	5
10	XPhos	K_3PO_4	1.0	traces
11	XPhos	NaO-*t*-Bu[d]	1.0	43
12	XPhos	NaO-*t*-Bu	1.2	76
13	XPhos	NaO-*t*-Bu	1.5	68

[a]First step: reactions were performed with hydrazone **1a** (1.2 equiv), indole **2a** (1 equiv), PhI (120 mol %), $Pd2(dba)_3{\cdot}CHCl_3$ (2 mol %), base (2.5 equiv), CPME (5 mL) at reflux for 1 h. [b]Second step: *p*-anisidine (see table), ligand (8 mol %), and base (1.2 equiv) were added after 1 h. [c]Yield of isolated product **5a**. [d]NaO-*t*-Bu (3.7 equiv) was added in one portion at the beginning of the reaction.

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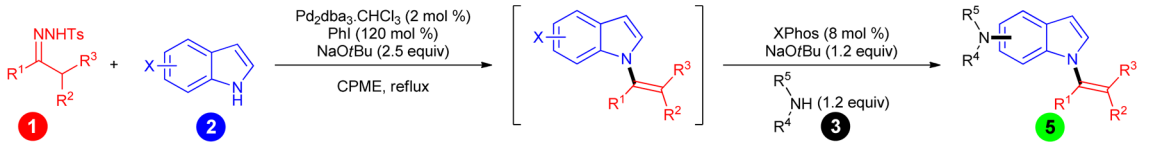
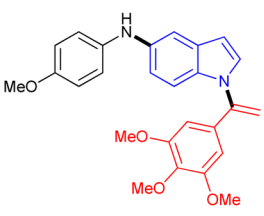
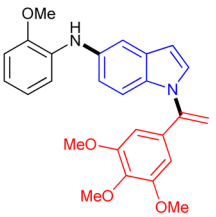
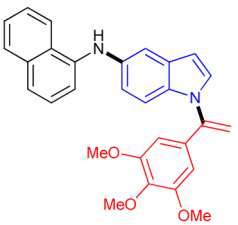
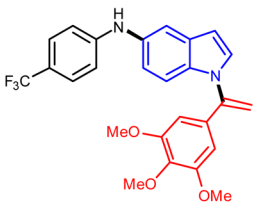
Table 2. Scope of Assisted Tandem Catalysis of *N*-Tosylhydrazones with Halo-Substituted Indoles and Amines[a,b]

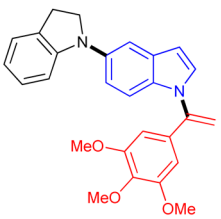


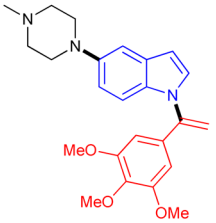

5a, X = Br, 81%[c]

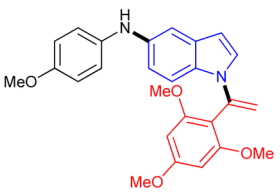

5b, X = Cl, 76%

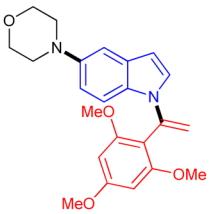

5c, X = Cl, 64%

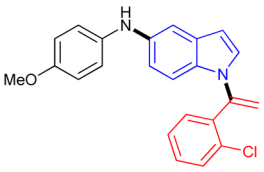

5d, X = Br, 66%

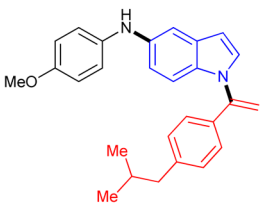

5e, X = Cl, 68%

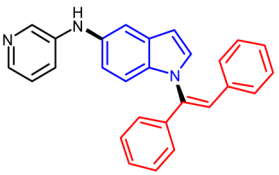

5f, X = Br, 80%

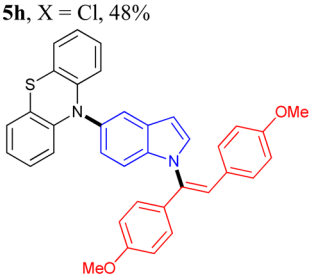

5g, X = Cl, 77%

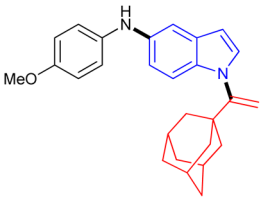

5h, X = Cl, 48%

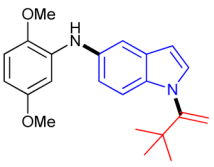

5i, X = Br, 53%

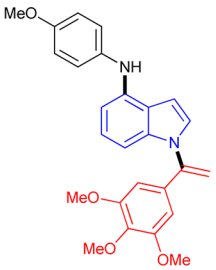

5j, X = Cl, 80%

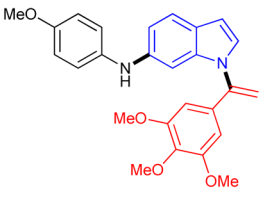

5k, X = Br, 85%

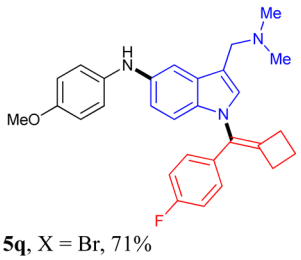

5l, X = Br, 76%

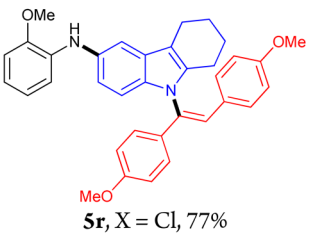

5m, X = Cl, 66%

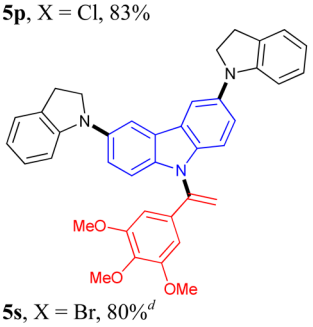

5n, X = Cl, 45%


5o, X = Br, 60%


5p, X = Cl, 83%


5q, X = Br, 71%


5r, X = Cl, 77%


5s, X = Br, 80%[d]

[a]First step: reactions were performed with *N*-tosylhydrazone **1** (1.2 equiv), indole **2** (1 equiv), PhI (120 mol %), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol %), NaO-*t*-Bu (2.5 equiv), CPME (5 mL) at reflux for 1 h. [b]Second step: XPhos (8 mol %), amine (1.2 equiv), and NaO-*t*-Bu (1.2 equiv) were added after 1 h. [c]Yield of isolated product **5**. [d]Amine (2.4 equiv) and NaO-*t*-Bu (2.4 equiv) were used.

RESULTS AND DISCUSSION

In the search for effective conditions, the coupling was studied with *N*-tosylhydrazone **1a**, 5-chloroindole **2a**, and *p*-anisidine **3a** under various ligands and bases to form amino-substituted vinylindole **5a** (Table 1). The reaction of **1a** and **2a** was carried out in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2 mol %), NaO-*t*-Bu (2.5 equiv), and iodobenzene (1.2 equiv) as the oxidant in refluxing cyclopentyl methyl ether (CPME). After 1 h, *p*-anisidine **3a** was

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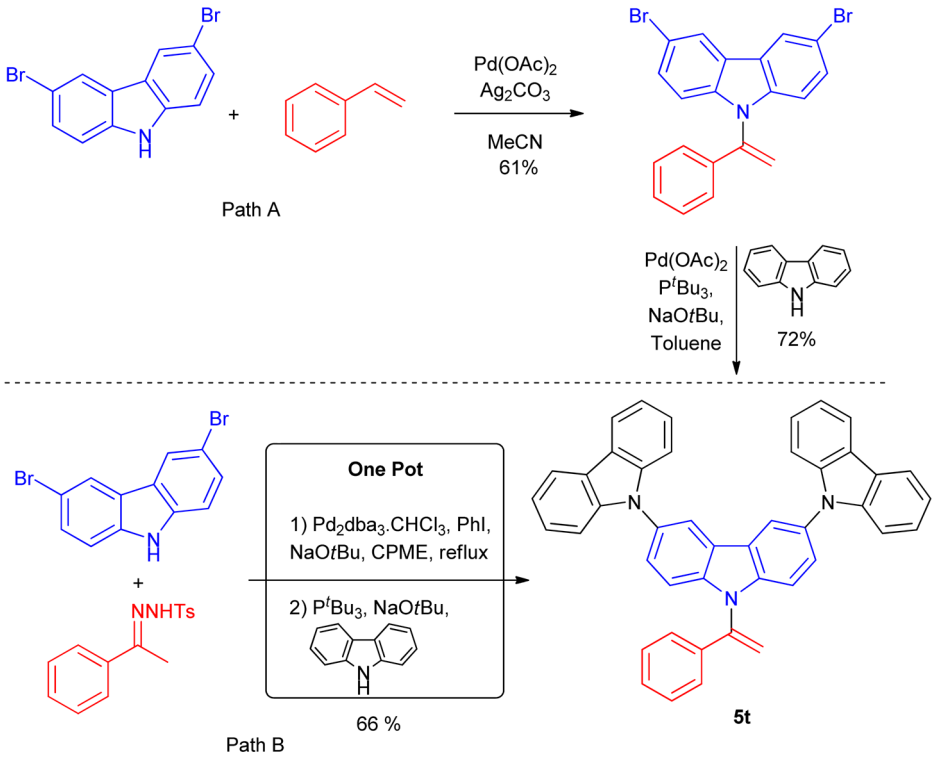
Scheme 2. Synthesis of Carbazole Trimer



added, and the reaction was heated at 105 °C for an additional 3 h. Under these conditions, the *N*-vinylindole **4a** was formed after 1 h but no trace of the desired product **5a** was detected in the crude NMR (Table 1, entry 1). Addition of a supplemental equivalent of NaO-*t*-Bu in the second step gave no improvement (entry 2). At this stage, we decided to add to the catalytic system, both NaO-*t*-Bu (1.2 equiv) and a phosphine ligand, which is well-known to be necessary for the Buchwald–Hartwig amination step.[12] Screening reactions with respect to the ligand revealed that the use of bulkier ligand XPhos is superior to all other choices, affording **5a** in a 67% isolated yield (entry 7). Other ligands were detrimental to the reaction (entries 3–6). It seems that the addition of the ligand XPhos triggers a change in palladium catalyst function, thus facilitating the second Csp^2–N cross-coupling. It should be noted that decreasing the amount of ligand (<8 mol %) resulted in significant decreases in the yield of **5a**. We further compared the base effect on the coupling. Among several bases tested (K_2CO_3, Cs_2CO_3, K_3PO_4), NaO-*t*-Bu furnished the best result. Since the same base was used for the two Csp^2–N bond formations, we tried to simplify the protocol by adding NaO-*t*-Bu in only one portion (3.7 equiv) at the beginning of the reaction. However, under these conditions, the yield of **5a** decreased (43%, entry 11) because *N*-tosylhydrazone **1a** reacted with excess NaO-*t*-Bu to give the corresponding etheral side product (entry 11).[13]

Eventually, we found that the yield of **5a** reached an optimal level of 76% when 1.2 equiv of *p*-anisidine **3a** was used (entry 12). It should be noted that lower yields were obtained with any reduction in the reaction temperature or the amount of catalyst. Thus, the conditions described in entry 12 were found to be optimal [1.2 equiv of hydrazone **1a**, 1 equiv of indole **2a**, $Pd_2dba_3{\cdot}CHCl_3$ (2 mol %), PhI (120 mol %), NaO-*t*-Bu (2.5 equiv), then aniline **3a** (1.2 equiv), XPhos (8 mol %), NaO-*t*-Bu (1.2 equiv)].

Having defined a highly effective protocol for the preparation of **5a**, a selection of other hydrazones, indoles, and amines was pursued to highlight the scope of this assisted tandem catalysis reaction (Table 2). As first observations, good to high yields of amino-substituted *N*-vinylindoles **5** were obtained with aniline substrates having electron-donating methoxy (**5a**, **5b**) or electron-withdrawing CF_3 (**5d**) groups. The use of 5-bromoindole instead of the chloro derivative led to a slight improvement in the yield of **5a** (81% vs 76%). In addition, the use of sterically hindered anilines with *ortho*-methoxy (**5b**) or *ortho*-phenyl (**5c**) groups was tolerated.

Gratifyingly, the new catalytic system appeared to be equally effective with other amines such as indoline (**5e**), *N*-methylpiperazine (**5f**), and morpholine (**5h**). It is remarkable that, under similar reaction conditions, this three-component coupling was also found to be efficient with heterocyclic amines, such as 3-aminopyridine and phenothiazine, providing **5k** and **5l** in very good yields.

To gauge the performance of this catalytic system, the substrate scope with respect to *N*-tosylhydrazone partners (compounds **5g–5n**) has been examined. As depicted in Table 2, the coupling was effective with *N*-tosylhydrazones derived from more challenging *ortho*/*ortho*′-substituted acetophenone (**5g**, **5h**), 1,2-diphenylethanone (**5k**, **5l**), or aliphatic ketones (**5m**, **5n**), furnishing the expected amino-substituted *N*-vinylindole products in excellent yields. Substrates containing a secondary carbon atom alpha to the hydrazone function were also successfully coupled to provide tetrasubstituted *N*-vinylindole **5q** in a 71% yield. Finally, we examined the coupling with respect to the azole partner. To our delight, satisfactory to good yields were obtained with 3-, 4-, or 6-substituted indoles (**5o–5q**).

In addition, it was found that the reaction is applicable to 1,2,3,4-tetrahydrocarbazole as well as carbazole, and compounds **5r**,**s** were obtained in good isolated yields. Finally, to highlight

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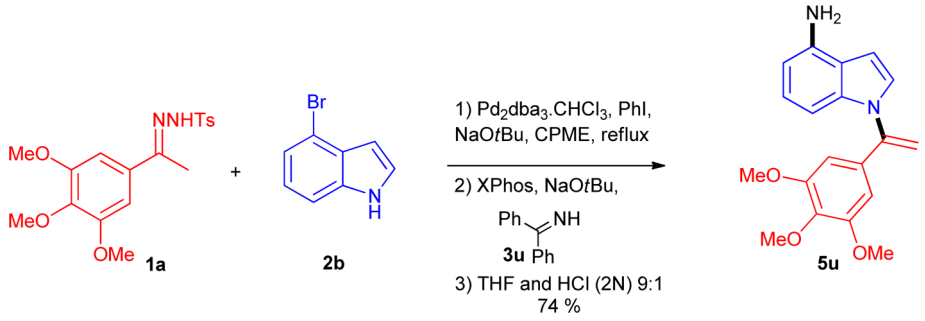
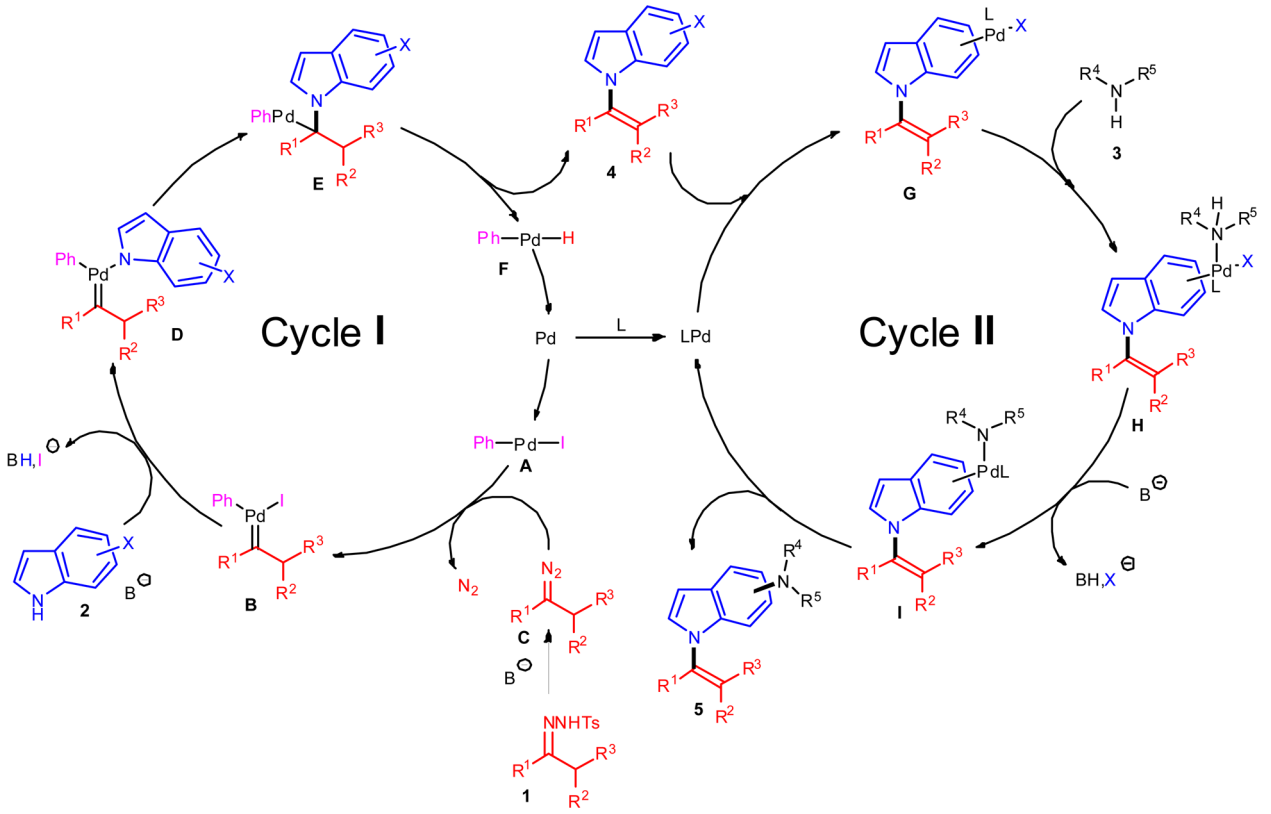
Scheme 3. Synthesis of Amino-Free Derivative



Scheme 4. Proposed Mechanism of the Tandem One-Pot Palladium-Catalyzed Coupling of Hydrazones, Haloindoles, and Amines



the power of this three-component reaction, and taking advantage of the chemoselectivity of this coupling toward the C−Br bond, we further extended our method for the construction of carbazole trimer **5t** (Scheme 2). The latter is known to be of high interest as a host material for phosphorescent devices.[14] In comparison with the palladium-catalyzed aza-Wacker reaction of N−H carbazoles with styrenes developed recently by Satoh and Miura,[15] our method offers the advantage of being realized in a one-pot fashion and with a better overall isolated yield (66% vs 44%, paths B vs A).[10]

Finally, to prepare a derivative with a free amino function **5u**, we used our standard conditions, and benzophenone imine served as ammonia equivalents (Scheme 3). At the end of the coupling, treatment with a mixture of THF and aqueous HCl (2 N) 9:1 led to the final product in a good isolated 74% yield.

A possible mechanism for the above-reported tandem reaction is depicted in Scheme 4. Overall, it involves two palladium species for the formation of the final product, a Pd^{II} complex for the first cycle (I) and Pd^0 for the second cycle (II). First, oxidative addition with iodobenzene forms a Pd^{II} intermediate **A**, which will be converted to palladium carbenoid **B** by reaction with the in situ generated diazo substrate (**C**). Subsequently, reaction with indole **2** under basic media leads to the species **D**, which undergoes a migratory insertion of the indole unit to furnish the alkyl palladium complex **E**. After β-hydride elimination, the cross-coupling products **4** and **F** were formed. Reductive elimination of **F** regenerates the Pd^0 catalyst to complete the second coupling. Next, the second cycle begins by oxidative addition of the indole halide **4** to the phosphane-liganded palladium and coordination of the amine leading to palladium species **H**. The latter evolves under basic media to produce complex **I**, which evolves by reductive elimination to produce the final amino-*N*-vinylindole product **5** and regenerates the catalyst.

Biological Results. To explore the chemical structure conferring cytotoxic activity to amino-*N*-vinylindole derivatives **5**, we selected and tested several analogues of this family of compounds (Table 3). In vitro cytotoxic assays were conducted on a human colon carcinoma (HCT116) cell line using

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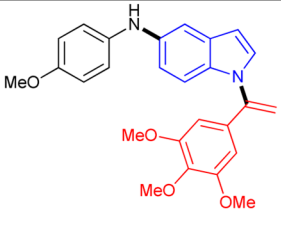
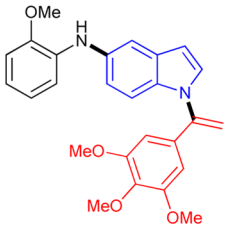
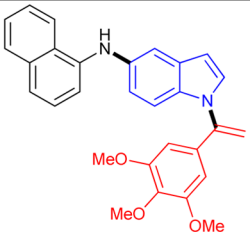
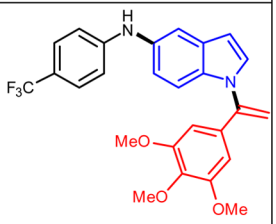
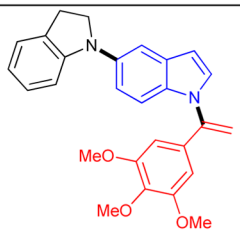
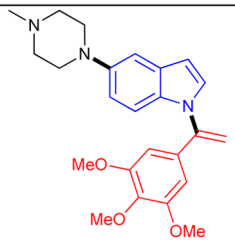
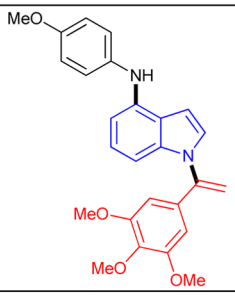
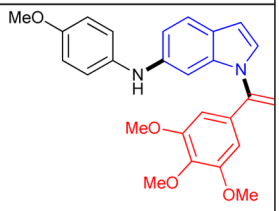
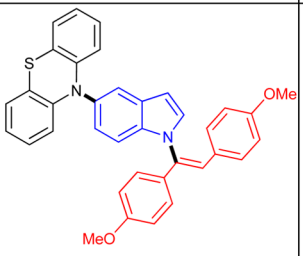
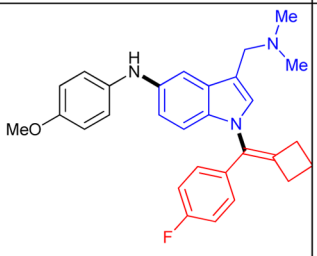
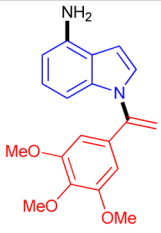
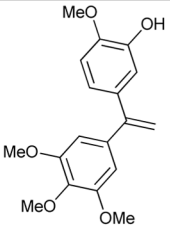
Table 3. Cytotoxic Activity of Selected Substituted Amino-*N*-vinylindoles 5 Against HCT-116 Cells[a]

Cytotoxicity against HCT116 cells.				
Cpnd				
GI_{50} (μM)[b]	**5a:** NA[c]	**5b:** 8 ± 1	**5c:** NA[c]	**5d:** NA[c]
Cpnd				
GI_{50} (μM)[b]	**5e:** 0.2 ± 0.1	**5f:** 6 ± 0.7	**5o:** 10 ± 1.2	**5p:** NA[c]
Cpnd				
GI_{50} (μM)[b]	**5l:** NA[c]	**5q:** 2 ± 0.1	**5u:** 0.4 ± 0.1	**isoCA-4:** 0.003

[a]HCT116 human colon carcinoma cells. [b]GI_{50}: compound concentration required to decrease cell growth by 50% following 72 h treatment with the tested drug; values represent the average ± SD of three experiments; [c]NA = not active.

isocombretastatin A-4 (*iso*CA-4) as a reference compound. We first investigated the presence of an aromatic group on position 5 of the indole ring. A low antiproliferative activity ($GI_{50} > 10\ \mu M$) was observed for *para*-substituted analogues (compounds **5a**, **5d**) or for naphthalene derivatives (**5c**). Switching the aromatic group from the 5 to 6 position on the indole moiety did not improve the activity (compound **5p**). However, moving the aromatic group on the 4 position gave a moderate activity of 10 μM (**5o**). Position 5 of the indole cannot be substituted by a large group (phenothiazine, **5l**); nevertheless, a smaller group like methylpiperazine is more tolerated (**5f**). Finally, the best antiproliferative activities, in sub-micromolar range, were obtained with compound **5e** having an indoline group on position 5 and with compound **5u** presenting a simple amino group on position 4 of the indole. Interestingly, compound **5q** presents an original template for further study because it is still active without the trimethoxyphenyl ring of our original lead, *iso*CA-4. These new compounds present an original template for further structure–activity relationship studies.

CONCLUSION

In summary, an assisted tandem catalytic reaction of *N*-tosylhydrazones, halo-substituted indoles, and amines into amino-substituted *N*-vinylindoles is described. This sequence, which requires only one precatalyst, relies on two Csp^2–N bond formations through two mechanistically distinct reactions. The Pd^{II}/Pd^0 catalyst system allows efficient sequential indole migratory insertion of a palladium carbene to construct the *N*-vinylazole bond followed by an intermolecular Buchwald–Hartwig amination. Good to excellent yields were obtained using a wide range of amine partners, including anilines, heterocyclic amines, as well as secondary aliphatic amines. The process is also very general with regard to other coupling partners. Among substituted amino-*N*-vinylindoles evaluated, compounds **5e** and **5u** described in the present study exert sub-micromolar cytostatic effects on human colon carcinoma cells.

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EXPERIMENTAL SECTION

General Methods. Solvent peaks were used as reference values, with $CDCl_3$ at 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR, with CD_3COCD_3 at 2.05 ppm for ^1H NMR and 29.84 ppm for ^{13}C NMR, and with DMSO-d_6 at 2.50 ppm for ^1H NMR and 39.5 ppm for ^{13}C NMR. Chemical shifts δ are given in parts per million, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m) and broad singlet (bs). Reaction courses and product mixtures were routinely monitored by TLC on silica gel, and compounds were visualized with phosphomolybdic acid/Δ, anisaldehyde/Δ, or vanillin/Δ. Flash chromatography was performed using silica gel 60 (40−63 mm, 230−400 mesh) at medium pressure (200 mbar). Fluorobenzene was used as received, and dioxane, dichloromethane, cyclohexane, and tetrahydrofuran were dried using the procedures described in D. Perrin Purification of Laboratory Chemicals.[16] Organic extracts were, in general, dried over $MgSO_4$ or Na_2SO_4. High-resolution mass spectra were recorded with the aid of a MicrOTOF-Q II. All products reported showed ^1H and ^{13}C NMR spectra in agreement with the assigned structures.

General Procedure for Preparation of Hydrazones.[17] To a rapidly stirred suspension of *p*-toluenesulfonohydrazide (5 mmol) in dry methanol (10 mL) at 60 °C was added dropwise the ketone (5 mmol). Within 5−60 min, the *N*-tosylhydrazone began to precipitate. The mixture was cooled to 0 °C, and the product was collected on a Büchner funnel, washed by petroleum ether, then was dried in vacuo to afford the pure product. The reaction provides the *N*-tosylhydrazone derivatives in about 88−99% yields.

Typical Pd-Catalyzed Tandem Catalysis of *N*-Tosylhydrazones with Halo-Substituted Indoles and Amines. A 10 mL round-bottom flask with condenser under argon atmosphere was charged with *N*-tosylhydrazone (1.2 equiv), iodobenzene (1.2 equiv), $Pd_2dba_3{\cdot}CHCl_3$ (2 mol %), NaO-*t*-Bu (2.5 equiv), and indole (1 equiv). Then 5 mL of CPME was added via syringe at room temperature. The flask was put into a preheated oil bath and stirred at reflux for 1 h. Then XPhos (8 mol %), amine (1.2 equiv), and NaO-*t*-Bu (1.2 equiv) were added, and reflux was continued for 4 h. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through Celite. The solvents were evaporated under reduced pressure, and the crude residue was purified by flash chromatography on silica gel.

*N-(4-Methoxyphenyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-5-amine (**5a**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 174 mg of **5a** (0.41 mmol, yield 81%): purple oil; TLC R_f = 0.25 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1581, 1508, 1462, 1413, 1375, 1233, 1127; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.26 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 3.3 Hz, 1H), 7.06−6.98 (m, 3H), 6.88−6.79 (m, 3H), 6.78 (bs, 1H), 6.65 (s, 2H), 6.48 (dd, J = 3.3, 0.7 Hz, 1H), 5.57 (s, 1H), 5.29 (s, 1H), 3.77 (s, 3H), 3.74 (s, 6H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.6 (C), 154.5 (2C), 146.0 (C), 140.4 (C), 139.9 (C), 139.5 (C), 133.6 (C), 132.9 (C), 131.3 (C), 129.9 (CH), 119.6 (2CH), 116.1 (CH), 115.4 (2CH), 113.2 (CH), 109.0 (CH), 106.9 (CH_2), 105.7 (2CH), 103.5 (CH), 60.7 (CH_3), 56.5 ($2CH_3$), 55.8 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1967.

*N-(2-Methoxyphenyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-5-amine (**5b**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 163 mg of **5b** (0.38 mmol, yield 76%); colorless oil; TLC R_f = 0.43 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1712, 1580, 1459, 1238, 1126; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.45 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.15−7.05 (m, 2H), 6.99 (dd, J = 8.8, 2.1 Hz, 1H), 6.92 (dd, J = 7.7, 1.7 Hz, 1H), 6.80−6.68 (m, 2H), 6.66 (s, 2H), 6.55 (dd, J = 3.3, 0.7 Hz, 1H), 6.52 (bs, 1H), 5.61 (s, 1H), 5.33 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.74 (s, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.5 (2C), 148.7 (C), 146.0 (C), 140.4 (C), 136.9 (C), 136.4 (C), 133.8 (C), 133.5 (C), 131.2 (C), 130.2 (CH), 121.6 (CH), 119.1 (CH), 118.4 (CH), 113.4 (CH), 113.2 (CH), 112.8 (CH), 111.4 (CH), 107.3 (CH_2), 105.7 (2CH), 103.7 (CH), 60.7 (CH_3), 56.5 ($2CH_3$), 56.0 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1973.

*N-(Naphthalen-1-yl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-5-amine (**5c**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 144 mg of **5c** (0.32 mmol, yield 64%): red solid, mp = 135−136 °C; TLC R_f = 0.34 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1711, 1580, 1413, 1288, 1126; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 8.34−8.21 (m, 1H), 7.86 (dd, J = 7.1, 2.3 Hz, 1H), 7.53−7.44 (m, 2H), 7.43−7.39 (m, 2H), 7.35−7.26 (m, 3H), 7.21−7.15 (m, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.05 (dd, J = 8.8, 2.0 Hz, 1H), 6.68 (s, 2H), 6.54 (dd, J = 3.3, 0.6 Hz, 1H), 5.63 (s, 1H), 5.35 (s, 1H), 3.79 (s, 3H), 3.76 (s, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.5 (2C), 146.0 (C), 143.1 (C), 140.4 (C), 138.3 (C), 135.8 (C), 133.7 (C), 133.5 (C), 131.3 (C), 130.1 (CH), 129.1 (CH), 127.1 (CH), 126.9 (C), 126.7 (CH), 125.6 (CH), 122.8 (CH), 120.5 (CH), 118.2 (CH), 113.3 (CH), 112.7 (CH), 111.4 (CH), 107.3 (CH_2), 105.7 (2CH), 103.6 (CH), 60.7(CH_3), 56.5 ($2CH_3$); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{29}H_{26}N_2O_3Na$ 473.1841, found 473.1849.

*N-(4-(Trifluoromethyl)phenyl)-1-(1-(3,4,5-trimethoxyphenyl)-vinyl)-1H-indol-5-amine (**5d**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 154 mg of **5d** (0.33 mmol, yield 66%): yellow oil; TLC R_f = 0.24 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1611, 1582, 1463, 1323, 1237, 1187; ^1H NMR (300 MHz, CD_3COCD_3) δ 7.68 (bs, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 3.3 Hz, 1H), 7.14−6.94 (m, 4H), 6.66 (s, 2H), 6.60 (dd, J = 3.3, 0.7 Hz, 1H), 5.66 (s, 1H), 5.35 (s, 1H), 3.77 (s, 3H), 3.75 (s, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm 153.6 (2C), 150.0 (C), 145.0 (C), 134.3 (C), 133.6 (C), 132.4 (C), 130.3 (C), 128.1 (q, J = 270 Hz, C), 126.4 (q, J = 4 Hz, C), 118.46 (q, J = 32 Hz, C), 118.2 (CH), 113.9 (CH), 113.4 (2CH), 112.5 (CH), 106.8 (CH_2), 104.8 (2CH), 102.9 (CH), 59.8 ($2CH_3$), 55.6 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{24}N_2O_3F_3$ 469.1739, found 469.1731.

*5-(Indolin-1-yl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indole (**5e**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 5/95) afforded 145 mg of **5e** (0.34 mmol, yield 68%): white solid, mp = 139−140 °C; TLC R_f = 0.53 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1580, 1411, 1287, 1235, 1121; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.49 (dd, J = 2.0, 0.7 Hz, 1H), 7.31 (d, J = 3.3 Hz, 1H), 7.22−7.08 (m, 3H), 6.99 (ddd, J = 8.0, 1.3, 0.6 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.68 (s, 2H), 6.67−6.62 (m, 1H), 6.60 (dd, J = 3.3, 0.6 Hz, 1H), 5.64 (s, 1H), 5.35 (s, 1H), 3.95 (t, J = 8.4 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 6H), 3.10 (t, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.5 (2C), 150.0 (C), 145.9 (C), 139.0 (C), 133.8 (C), 133.5 (C), 131.6 (C), 131.1 (C), 130.3 (C), 130.3 (CH), 127.8 (CH), 125.6 (CH), 118.8 (CH), 116.8 (CH), 113.2 (CH), 111.9 (CH), 108.0 (CH), 107.4 (CH_2), 105.7 (2CH), 103.8 (CH), 60.7 (CH_3), 56.6 ($2CH_3$), 54.2 (CH_2), 28.9 (CH_2); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{27}H_{27}N_2O_3$ 427.2022, found 427.2029.

*5-(4-Methylpiperazin-1-yl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indole (**5f**).* Flash chromatography on silica gel (MeOH/DCM, 5/95) afforded 164 mg of **5f** (0.40 mmol, yield 80%): white solid, mp = 126−127 °C; TLC R_f = 0.73 (MeOH/DCM, 10/90, SiO_2); ATR-FTIR (cm^{-1}) 1581, 1504, 1413, 1371, 1236, 1126; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.20 (d, J = 3.2 Hz, 1H), 7.11 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 6.87 (dd, J = 9.0, 2.3 Hz, 1H), 6.64 (s, 2H), 6.50 (dd, J = 3.3, 0.7 Hz, 1H), 5.55 (s, 1H), 5.27 (s, 1H), 3.77 (s, 3H), 3.74 (s, 6H), 3.19−3.03 (m, 4H), 2.57−2.43 (m, 4H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.5 (2C), 147.5 (C), 146.1 (C), 140.4 (C), 133.6 (C), 132.6 (C), 131.1 (C), 129.6 (CH), 115.8 (CH), 113.0 (CH), 108.0 (CH), 106.8 (CH_2), 105.8 (2CH), 103.8 (CH), 60.7 (CH_3), 56.5 ($2CH_3$), 56.3 ($2CH_2$), 51.8 ($2CH_2$), 46.4 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{24}H_{30}N_3O_3$ 408.2287, found 408.2287.

*N-(4-Methoxyphenyl)-1-(1-(2,4,6-trimethoxyphenyl)vinyl)-1H-indol-5-amine (**5g**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 166 mg of **5g** (0.39 mmol, yield 77%): off-white solid, mp = 128−129 °C; TLC R_f = 0.26 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1583, 1510, 1460, 1226, 1126; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.26 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.08 (d, J = 3.3 Hz, 1H), 7.03−6.95 (m, 2H), 6.87−6.76 (m, 3H), 6.69 (s, 1H), 6.36−6.25 (m, 3H), 5.52 (s, 1H), 4.98 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (75 MHz, acetone) δ (ppm) 163.0 (C), 160.4 (2C), 154.5 (C), 140.2 (C), 138.8

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(C), 138.3 (C), 132.3 (C), 131.5 (C), 128.8 (C), 119.3 (2CH), 116.0 (CH), 115.4 (2CH), 113.2 (CH), 109.7 (C), 109.3 (CH), 107.7 (CH_2), 102.5 (CH), 91.8 (2CH), 56.3 ($2CH_3$), 55.8 ($2CH_3$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1972.

*4-(1-(1-(2,4,6-Trimethoxyphenyl)vinyl)-1H-indol-5-yl)morpholine (**5h**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 20/80) afforded 95 mg of **5h** (0.24 mmol, yield 48%): off-white solid, mp = 127−130 °C; TLC R_f = 0.15 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1603, 1583, 1471, 1414, 1364, 1226, 1202, 1125; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.25 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 3.3 Hz, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.84 (dd, J = 9.0, 2.4 Hz, 1H), 6.34 (d, J = 3.3 Hz, 1H), 6.29 (s, 2H), 5.51 (s, 1H), 4.97 (s, 1H), 3.85 (s, 3H), 3.80−3.74 (m, 4H), 3.67 (s, 6H), 3.10−3.02 (m, 4H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 163.0 (C), 160.4 (2C), 146.9 (C), 138.3 (C), 132.0 (C), 131.3 (C), 128.7 (CH), 115.0 (CH), 113.0 (CH), 109.6 (C), 107.7 (CH), 107.6 (CH_2), 102.8 (CH), 91.8 (2CH), 67.7 ($2CH_2$), 56.3 ($2CH_3$), 55.7 (CH_3), 52.3 ($2CH_2$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{23}H_{27}N_2O_4$ 395.1971, found 395.1968.

*1-(1-(2-Chlorophenyl)vinyl)-N-(4-methoxyphenyl)-1H-indol-5-amine (**5i**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 2/98) afforded 99 mg of **5i** (0.26 mmol, yield 53%): white solid, mp = 106−108 °C; TLC R_f = 0.25 (EtOAc/cyclohexane, 5/95, SiO_2); ATR-FTIR (cm^{-1}) 1710, 1617, 1509, 1462, 1222; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.62−7.52 (m, 1H), 7.51−7.42 (m, 3H), 7.23 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 3.3 Hz, 1H), 7.05−6.98 (m, 3H), 6.85−6.80 (m, 3H), 6.77 (bs, 1H), 6.44 (dd, J = 3.3, 0.7 Hz, 1H), 5.58 (d, J = 0.6 Hz, 1H), 5.25 (d, J = 0.5 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.7 (C), 144.0 (C), 139.7 (C), 137.5 (C), 133.9 (C), 132.6 (CH), 132.1 (C), 131.7 (C), 131.5 (CH), 131.0 (CH), 128.8 (C), 128.8 (CH), 128.3 (CH), 119.8 (2CH), 116.0 (CH), 115.4 (2CH), 112.9 (CH), 108.9 (CH), 107.8 (CH_2), 104.2 (CH), 55.8 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{23}H_{20}ClN_2O$ 375.1264, found 375.1261.

*1-(1-(4-Isobutylphenyl)vinyl)-N-(4-methoxyphenyl)-1H-indol-5-amine (**5j**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 2/98) afforded 157 mg of **5j** (0.40 mmol, yield 80%): pink oil; TLC R_f = 0.23 (EtOAc/cyclohexane, 5/95, SiO_2); ATR-FTIR (cm^{-1}) 1711, 1507, 1461, 1242, 1194; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.31−7.16 (m, 6H), 7.08−6.98 (m, 2H), 6.92 (d, J = 8.8 Hz, 1H), 6.86−6.78 (m, 3H), 6.75 (bs, 1H), 6.48 (d, J = 3.2 Hz, 1H), 5.56 (s, 1H), 5.30 (s, 1H), 3.73 (s, 3H), 2.52 (d, J = 7.2 Hz, 2H), 1.89 (hept, J = 6.9 Hz, 1H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.6 (C), 146.1 (C), 143.8 (C), 139.9 (C), 139.4 (C), 135.6 (C), 132.9 (C), 131.2 (C), 130.2 (2CH), 129.9 (CH), 127.6 (2CH), 119.6 (2CH), 116.1 (CH), 115.4 (2CH), 113.1 (CH), 109.0 (CH), 107.1 (CH_2), 103.4 (CH), 55.8 (CH_3), 45.6 (CH_2), 30.9 (CH), 22.6 ($2CH_3$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{27}H_{29}N_2O$ 397.2280, found 397.2276.

*(Z)-1-(1,2-Diphenylvinyl)-N-(pyridin-3-yl)-1H-indol-5-amine (**5k**).* Flash chromatography on silica gel (EtOAc/DCM, 20/80) afforded 164 mg of **5k** (0.42 mmol, yield 85%): yellow solid, mp = 170−171 °C; TLC R_f = 0.41 (EtOAc/DCM, 50/50, SiO_2); ATR-FTIR (cm^{-1}) 1710, 1469, 1446, 1299, 1185; ^1H NMR (300 MHz, CD_3SOCD_3) δ (ppm) 8.28 (d, J = 2.4 Hz, 1H), 8.08 (bs, 1H), 7.96−7.87 (m, 1H), 7.43 (s, 1H), 7.40−7.28 (m, 5H), 7.27−7.22 (m, 2H), 7.20−7.10 (m, 5H), 6.89−6.79 (m, 4H), 6.65 (d, J = 3.1 Hz, 1H); ^{13}C NMR (75 MHz, CD_3SOCD_3) δ (ppm) 142.0 (C), 138.9 (CH), 137.9 (C), 137.7 (CH), 135.1 (C), 135.1 (C), 134.5 (C), 131.3 (C), 129.2 (CH), 129.0 (C), 128.7 (CH), 128.7 (2CH), 128.5 (2CH), 128.3 (2CH), 127.9 (CH), 125.6 (2CH), 125.3 (CH), 123.6 (CH), 120.0 (CH), 116.6 (CH), 111.6 (CH), 110.4 (CH), 103.4 (CH); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{27}H_{22}N_3$ 388.1814, found 388.1815.

*(Z)-10-(1-(1,2-Bis(4-methoxyphenyl)vinyl)-1H-indol-5-yl)-10H-phenothiazine (**5l**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 2/98) afforded 210 mg of **5l** (0.38 mmol, yield 76%): white solid, mp = 201−203 °C; TLC R_f = 0.62 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1606, 1512, 1461, 1303, 1250, 1177; ^1H NMR (300 MHz, CD_3SOCD_3) δ (ppm) 7.70 (d, J = 1.7 Hz, 1H), 7.40 (d, J = 3.2 Hz, 1H), 7.30−7.22 (m, 3H), 7.13 (d, J = 8.6 Hz, 1H), 7.04−6.94 (m, 5H), 6.89−6.78 (m, 5H), 6.71 (d, J = 9.1 Hz, 2H), 6.65 (d, J = 9.1 Hz, 2H), 6.06 (d, J = 1.5 Hz, 1H), 6.03 (d, J = 1.3 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, CD_3SOCD_3) δ (ppm) 160.1 (C), 159.2 (C), 144.8 (2C), 134.8 (C), 132.8 (C), 132.7 (C), 130.8 (C), 130.4 (C), 130.3 (CH), 130.3 (2CH), 127.5 (2CH), 127.5 (C), 127.2 (2CH), 126.8 (2CH), 124.7 (CH), 123.8 (CH), 123.0 (CH), 122.7 (2CH), 118.9 (2C), 116.1 (2CH), 114.8 (2CH), 114.2 (2CH), 113.7 (CH), 104.7 (CH), 55.7 (CH_3), 55.5 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{36}H_{28}N_2O_2S$ 553.1950, found 553.1948.

*1-(1-((1s,3s)-Adamantan-1-yl)vinyl)-N-(4-methoxyphenyl)-1H-indol-5-amine (**5m**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 2/98) afforded 132 mg of **5m** (0.33 mmol, yield 66%): colorless oil; TLC R_f = 0.26 (EtOAc/cyclohexane, 5/95, SiO_2); ATR-FTIR (cm^{-1}) 1711, 1507, 1280, 1178, 1130; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.23 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 3.1 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.91 (dd, J = 8.8, 2.1 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.69 (bs, 1H), 6.37 (dd, J = 3.1, 0.7 Hz, 1H), 5.48 (s, 1H), 5.08 (s, 1H), 3.73 (s, 3H), 1.99 (bs, 3H), 1.89−1.79 (m, 6H), 1.78−1.58 (m, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 155.9 (C), 154.4 (C), 140.5 (C), 138.4 (C), 135.2 (C), 130.4 (CH), 129.4 (C), 116.0 (2CH), 116.5 (CH), 115.4 (2CH), 113.8 (CH_2), 112.4 (CH), 109.3 (CH), 101.3 (CH), 55.8 (CH_3), 41.8 ($3CH_2$), 40.2 (C), 37.2 ($3CH_2$), 29.3 (3CH); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{27}H_{31}N_2O$ 399.2436, found 399.2436.

*N-(2,5-Dimethoxyphenyl)-1-(3,3-dimethylbut-1-en-2-yl)-1H-indol-5-amine (**5n**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 5/95) afforded 79 mg of **5n** (0.23 mmol, yield 45%): off-white solid, mp = 108−110 °C; TLC R_f = 0.32 (EtOAc/cyclohexane, 10/90, SiO_2); ATR-FTIR (cm^{-1}) 1600, 1520, 1461, 1287, 1211; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.43 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 3.2 Hz, 1H), 7.06 (dd, J = 8.7, 2.1 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.66 (d, J = 2.8 Hz, 1H), 6.51 (bs, 1H), 6.48 (dd, J = 3.2, 0.8 Hz, 1H), 6.23 (dd, J = 8.7, 2.9 Hz, 1H), 5.60 (s, 1H), 5.12 (s, 1H), 3.83 (s, 3H), 3.64 (s, 3H), 1.19 (s, 9H).^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 155.5 (C), 155.3 (C), 143.0 (C), 138.1 (C), 135.9 (C), 135.5 (C), 130.4 (CH), 129.4 (C), 119.0 (CH), 113.9 (CH_2), 113.6 (CH), 112.3 (CH), 112.0 (CH), 101.9 (CH), 101.5 (CH), 100.5 (CH), 56.6 (CH_3), 55.5 (CH_3), 38.5 (C), 29.6 ($3CH_3$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2073.

*N-(4-Methoxyphenyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-4-amine (**5o**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 130 mg of **5o** (0.30 mmol, yield 60%): yellow solid, mp = 155−157 °C; TLC R_f = 0.26 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1581, 1509, 1362, 1236, 1121; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.22−7.14 (m, 3H), 7.12 (bs, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.92−6.87 (m, 2H), 6.76 (dd, J = 3.4, 0.7 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 6.67−6.58 (m, 3H), 5.67 (s, 1H), 5.33 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.74 (s, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 155.7 (C), 154.5 (2C), 153.7 (C), 146.1 (C), 139.4 (C), 138.7 (C), 137.7 (C), 133.6 (C), 127.6 (CH), 123.7 (CH), 122.4 (2CH), 120.8 (C), 115.2 (2CH), 108.1 (CH_2), 105.6 (2CH), 104.8 (CH), 104.4 (CH), 101.4 (CH), 60.7 (CH_3), 56.6 ($2CH_3$), 55.7 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1964.

*N-(4-Methoxyphenyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-6-amine (**5p**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 10/90) afforded 130 mg of **5p** (0.30 mmol, yield 83%); purple oil; TLC R_f = 0.26 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1581, 1508, 1413, 1349, 1233, 1126; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.41 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 3.3 Hz, 1H), 6.91 (bs, 1H), 6.88−6.81 (m, 2H), 6.80−6.69 (m, 4H), 6.61 (s, 2H), 6.50 (d, J = 3.3 Hz, 1H), 5.48 (s, 1H), 5.24 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.72 (s, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.9 (C), 154.5 (2C), 146.4 (C), 141.5 (C), 140.3 (C), 138.2 (C), 138.2 (C), 133.5 (C), 127.9 (CH), 124.0 (C), 122.1 (CH), 120.2 (2CH), 115.2 (2CH), 113.4 (CH), 107.0 (CH_2), 105.7 (2CH), 104.0 (CH), 99.2 (CH), 60.7 (CH_3), 56.5 ($2CH_3$), 55.7 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1974.

*1-(Cyclobutylidene(4-fluorophenyl)methyl)-3-((dimethylamino)-methyl)-N-(4-methoxyphenyl)-1H-indol-5-amine (**5q**).* Flash chromatography on silica gel (MeOH/DCM, 5/95) afforded 162 mg of **5q**

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(0.36 mmol, yield 71%): gray solid, mp = 210−212 °C; TLC R_f = 0.36 (MeOH/DCM, 5/95, SiO_2); ATR-FTIR (cm^{-1}) 1710, 1506, 1467, 1224, 1159; ^1H NMR (300 MHz, CD_3SOCD_3) δ (ppm) 9.63 (bs, 1H), 7.58 (d, J = 27.3 Hz, 2H), 7.43 (s, 1H), 7.25−7.11 (m, 2H), 7.10−6.96 (m, 3H), 6.94−6.75 (m, 4H), 4.40 (s, 2H), 3.69 (s, 3H), 3.21 (t, J = 6.4 Hz, 2H), 2.75 (s, 6H), 2.65 (t, J = 7.6 Hz, 2H), 2.10 (dt, J = 14.8, 7.5 Hz, 2H); ^{13}C NMR (75 MHz, CD_3SOCD_3) δ (ppm) 161.2 (d, J = 244 Hz, C), 152.6 (C), 142.1 (C), 138.4 (2C), 132.5 (d, J = 2 Hz, C), 132.1 (CH), 130.9 (C), 128.1 (C), 127.8 (d, J = 8 Hz, 2CH), 126.4 (C), 117.7 (2CH), 115.9 (CH), 115.5 (d, J = 21 Hz, 2CH), 114.5 (2CH), 111.6 (CH), 105.4 (CH), 103.5 (C), 55.3 (CH_3), 51.0 (CH_2), 41.3 ($2CH_3$), 30.9 (CH_2), 29.7 (CH_2), 16.7 (CH_2); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{29}H_{31}FN_3O$ 456.2451, found 456.2449.

*(Z)-9-(1,2-Bis(4-methoxyphenyl)vinyl)-N-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-6-amine (**5r**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 2/98) afforded 205 mg of **5r** (0.39 mmol, yield 77%): white solid, mp = 149−151 °C; TLC R_f = 0.56 (EtOAc/cyclohexane, 20/80, SiO_2); ATR-FTIR (cm^{-1}) 1712, 1604, 1511, 1460, 1245, 1175; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.35 (s, 1H), 7.24 (s, 1H), 7.20−7.11 (m, 2H), 7.08 (dd, J = 7.7, 1.7 Hz, 1H), 6.94−6.82 (m, 5H), 6.82−6.62 (m, 6H), 6.45 (bs, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 2.84−2.63 (m, 2H), 2.43−2.18 (m, 2H), 1.94−1.64 (m, 4H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 160.9 (C), 160.2 (C), 148.4 (C), 137.0 (C), 136.7 (C), 136.1 (C), 133.0 (C), 132.6 (C), 132.3 (C), 130.8 (2CH), 129.7 (C), 129.0 (C), 127.5 (2CH), 125.3 (CH), 121.6 (CH), 118.7 (CH), 117.8 (CH), 114.9 (2CH), 114.7 (2CH), 113.0 (CH), 111.9 (C), 111.8 (CH), 111.3 (CH), 110.9 (CH), 56.0 (CH_3), 55.6 (CH_3), 55.5 (CH_3), 24.1 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 21.9 (CH_2); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{35}H_{35}N_2O_3$ 531.2648, found 531.2642.

*3,6-Di(indolin-1-yl)-9-(1-(3,4,5-trimethoxyphenyl)vinyl)-9H-carbazole (**5s**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 2/98) afforded 237 mg of **5s** (0.40 mmol, yield 80%): colorless oil; TLC R_f = 0.17 (EtOAc/cyclohexane, 10/90, SiO_2); ATR-FTIR (cm^{-1}) 1711, 1580, 1485, 1363, 1126; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 8.06 (d, J = 1.9 Hz, 2H), 7.34 (dd, J = 8.8, 2.2 Hz, 2H), 7.27−7.22 (m, 2H), 7.12 (d, J = 7.1 Hz, 2H), 7.02−6.93 (m, 4H), 6.70−6.61 (m, 4H), 6.09 (s, 1H), 5.53 (s, 1H), 3.97 (t, J = 8.4 Hz, 4H), 3.75 (s, 3H), 3.66 (s, 6H), 3.09 (t, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.6 (2C), 149.9 (2C), 143.8 (C), 140.5 (C), 138.7 (2C), 138.3 (2C), 133.1 (C), 131.6 (2C), 127.8 (2CH), 125.6 (2CH), 124.9 (2C), 120.3 (2CH), 118.9 (2CH), 112.5 (2CH), 111.9 (CH_2), 111.8 (2CH), 108.0 (2CH), 105.2 (2CH), 60.7 (CH_3), 56.6 ($2CH_3$), 54.2 ($2CH_2$), 28.9 ($2CH_2$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{39}H_{36}N_3O_3$ 594.2757, found 594.2755.

*9′-(1-Phenylvinyl)-9′H-9,3′:6′,9″-tercarbazole (**5t**).* Flash chromatography on silica gel (EtOAc/cyclohexane, 1/99) afforded 197 mg of **5t** (0.33 mmol, yield 66%): white solid, mp = 254−255 °C; TLC R_f = 0.13 (cyclohexane, SiO_2); ATR-FTIR (cm^{-1}) 1495, 1468, 1450, 1314, 1230; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 1.5 Hz, 2H), 8.16 (d, J = 7.7 Hz, 4H), 7.71−7.34 (m, 15H), 7.35−7.00 (m, 6H), 6.24 (s, 1H), 5.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.8 (C), 141.9 (4C), 140.7 (2C), 136.1 (C), 130.5 (2C), 129.7 (CH), 129.2 (2CH), 126.4 (2CH), 126.3 (2CH), 126.0 (4CH), 124.2 (2CH), 123.3 (4C), 120.4 (4CH), 119.8 (4CH), 119.7 (2CH), 113.8 (CH_2), 112.4 (2CH), 109.9 (4CH); HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{44}H_{30}N_3$ 600.2440, found 600.2438.

*1-(1-(3,4,5-Trimethoxyphenyl)vinyl)-1H-indol-4-amine (**5u**).* Compound **5u** was synthesized according the general procedure using benzophenone imine as nucleophile. Deprotection is realized on the crude mixture, and after filtration on Celite and evaporation, a mixture of THF and HCl (2 N) 9:1 10 mL is added. The mixture is stirred at room temperature for 30 min, then quenched with $NaHCO_3$ and extracted with DCM. Flash chromatography on silica gel (EtOAc/cyclohexane, 20/80) afforded 120 mg of **5u** (0.37 mmol, yield 74%): yellow solid, mp = 151−153 °C; TLC R_f = 0.32 (EtOAc/cyclohexane, 30/70, SiO_2); IR (neat) 1515, 1475, 1365, 1331; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.09 (d, J = 3.4 Hz, 1H), 6.86−6.77 (m, 1H), 6.71 (dd, J = 3.4, 0.7 Hz, 1H), 6.62 (s, 2H), 6.45 (d, J = 8.3 Hz, 1H), 6.33 (dd, J = 7.5, 0.6 Hz, 1H), 5.62 (s, 1H), 5.29 (s, 1H), 4.85 (bs, 2H), 3.76 (s, 3H), 3.73 (s, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 154.4 (3C), 146.2 (C), 142.3 (C), 138.6 (C), 133.7 (C), 127.0 (CH), 124.1 (CH), 119.0 (C), 107.7 (CH2), 105.5 (2CH), 104.6 (CH), 102.1 (CH), 101.1 (CH), 60.6 (CH3), 56.5 (2CH3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{19}H_{21}N_2O_3$ 325.1552, found 325.1559.

Biology. Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD) and were cultured according to the supplier's instructions. HCT116 colorectal carcinoma cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. Cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using Promega CellTiter-Blue TM reagent according to the manufacturer's instructions. Cells were seeded in 96-well plates (5 × 103 cells/well) containing 50 μL of growth medium. After 24 h of culture, the cells were supplemented with 50 μL of the tested compound dissolved in DMSO (less than 0.1% in each preparation). After 72 h of incubation, 20 μL of resazurin was added for 2 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (PerkinElmer,USA). The GI_{50} corresponds to the concentration of the tested compound that caused a decrease of 50% in fluorescence of drug-treated cells compared with untreated cells. Experiments were performed in triplicate. The GI_{50} values for all compounds were compared to the GI_{50} of *iso*CA-4 and measured the same day under the same conditions.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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