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Preparation of 2-arylindole-4-carboxylic amide derivatives

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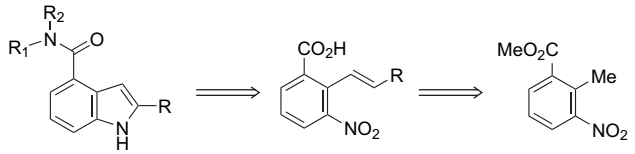
Abstract—A practical, highly efficient protocol has been developed for the synthesis of functionalized 2-arylindole-4-carboxylic amide derivatives. Commercially available methyl 2-methyl-3-nitrobenzoate gave substituted nitrostyrene benzoic acids by reaction with aromatic aldehydes in the presence of DBU in DMSO. Conversion of these products to the desired amides was followed by Pd-catalyzed reductive cyclization employing carbon monoxide as the terminal reductant to provide the 2-arylindole-4-carboxylic amide derivatives in excellent overall yield for the simple three-step sequence.

1. Introduction

The synthesis and functionalization of indoles continues to be a major area of focus for both academic and industrial researchers.[1,2] The prevalence of this important heterocycle as the central pharmacophore in a wide range of medicinal agents is a testament to the powerful biological activity that this key subunit provides as it is recognized as one of the most important 'privileged structures'.[3] Recently, we have outlined highly efficient methodologies for the synthesis of variously functionalized indoles[4] and tetrahydrobenzofurans[5] by taking advantage of the underlying versatility of nitrobenzenes. In a continuing program to exploit these methodologies which rapidly enhance molecular complexity with excellent atom economy and synthetic practicality, we have identified that commercially available methyl 2-methyl-3-nitrobenzoate **3** is an extremely attractive raw material for the preparation of indoles of type **1**.

Indoles of general type **1** have been shown to possess a wide range of biological activity including CC chemokine receptor 5 (CCR5) antagonists,[6] serotonin (5-HT) subtype 2A receptor antagonist,[7] muscarinic M_2 receptor antagonists,[8] bradycardic agents,[9] histone deacetylase inhibitors,[10] p38α mitogen activated protein kinases (MAPK) inhibitors,[11] matrix metalloproteinases (MMPs) inhibitors,[12] and poly(ADP-ribose) polymerase-1-inhibitors.[13] Typically indoles of this subclass have been prepared from commercially available indole 4-carboxylic acid or 4-bromoindole,[14] both of which are expensive reagents and require extensive manipulation if a more substituted pharmacophore is needed. A concise route to indoles **1** from **3** would feature reaction with a substituted aldehyde followed by reductive cyclization (Scheme 1). In this paper, we document the implementation of this strategy.



1 2 3

Scheme 1.

2. Results and discussion

The widespread use of *ortho*-nitrostyrenes as synthetically useful intermediates has been limited by available methods for their preparation. Traditional approaches have relied on Wittig reactions of either 2-nitrobenzaldehydes or 2-nitrophosphonium and phosphonate salts.[15] Alternatively, cross-coupling approaches involving 2-halonitrobenzenes or 2-nitrophenylstannanes have received considerable attention as an attractive method for the preparation of a range of *ortho*-nitrostyrenes.[16] While each of these approaches offers certain advantages, they often require multiple steps for the construction of the appropriate starting materials and generally require purification by chromatography. In addition, these strategies have a high environmental burden since they suffer from poor atom economy and generate a significant amount of phosphorous or tin by-products. We have recently demonstrated that reactions of 2-nitrotoluenes or 2-trimethylsilylmethylnitrobenzenes with aromatic aldehydes via an addition/elimination protocol is an effective, high yielding method for the construction of *ortho*-nitrostyrenes.[4] In order to access indoles of class **1**, an efficient synthesis of nitrostyrenes of type **2** was imperative and we

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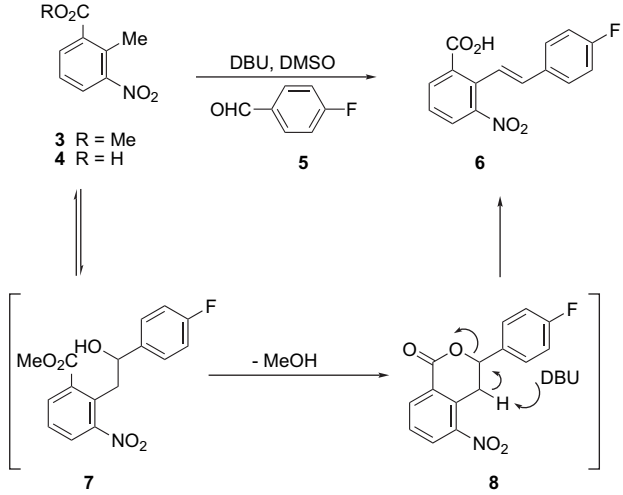
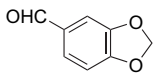
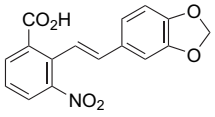
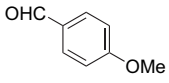
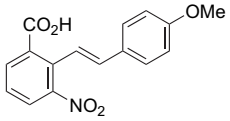
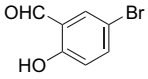
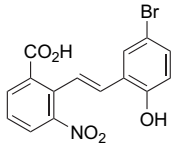
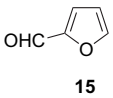
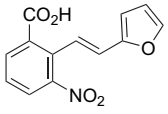
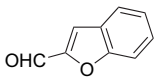
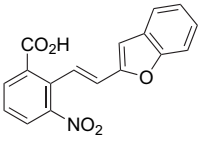
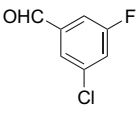
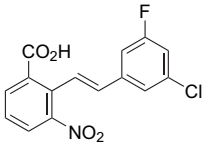
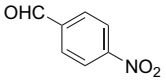
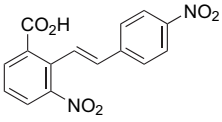
envisioned that reaction of commercially available nitrotoluene **3** with simple aldehydes would allow for a remarkably straightforward synthesis of these high value targets.

Our investigations began with the reaction of methyl 2-methyl-3-nitrobenzoate **3** with 4-fluorobenzaldehyde (Scheme 2). It has previously been demonstrated that the reaction of *ortho*-nitrotoluenes with aromatic aldehydes in the presence of DBU in DMSO is a reversible process[5] and only modest to good yields of the corresponding nitro alcohols are obtained.[17] Based on the juxtaposition of the methyl ester with the reacting center and its capacity to serve as an intramolecular electrophilic trap of the intermediate nitro alcohol, reaction of **3** with aldehydes was anticipated to lead to formation of a lactone intermediate. Treatment of **3** with 1.0 equiv of 4-fluorobenzaldehyde **5** with 1.0 equiv of DBU in DMSO for 6 h at rt gave nitrostyrene benzoic acid **6** in 57% yield. Analysis of the crude reaction mixture by HPLC and NMR revealed the presence of unreacted starting material **3** (36%), 4-fluorobenzaldehyde **5**, and carboxylic acid **4** (7%). The presence of acid **4** suggested that competitive hydrolysis of the starting material was occurring under the reaction conditions. The overall sequence involved deprotonation of the nitrotoluene **3** by DBU followed by the addition to **5** to give nitro alcohol intermediate **7**, which undergoes intramolecular cyclization to lactone **8**. Deprotonation of **8** by DBU was followed by elimination of the carboxylate anion to furnish the observed nitrostyrene benzoic acid product **6** upon workup. Optimization of the reaction parameters revealed that upon treatment of **3** with 1.5 equiv of **5** with 2.0 equiv of DBU in dry DMSO for 12 h followed by heating to 50 °C for 30 min afforded **6** in 90% HPLC assay yield.[18] Under these conditions, <5% of the corresponding hydrolyzed starting material **4** was observed. Furthermore, none of the intermediate lactone **8** was observed in the crude reaction mixture. After an extractive workup to remove excess **5**, the product **6** was obtained in 84% isolated yield by crystallization from MeOH/water. The reaction sequence was general and allowed for the preparation of an array of structurally diverse nitrostyrene benzoic acids in good to excellent yield (Table 1). Substrates containing electron donating (entries 1–5) or electron withdrawing groups (entries 6 and 7) participated equally as well. In all cases, the *trans*-nitrostyrene benzoic acids were the exclusive products.



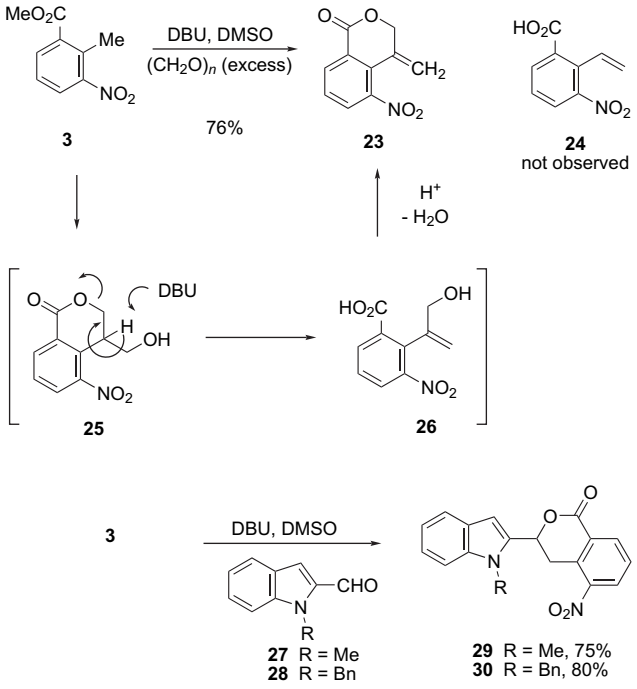
Scheme 2.

Table 1

Entry	Aldehyde	Nitrostyrene
1	 **9**	 **10** 68%
2	 **11**	 **12** 61%
3	 **13**	 **14** 79%
4	 **15**	 **16** 90%
5	 **17**	 **18** 82%
6	 **19**	 **20** 88%
7	 **21**	 **22** 82%

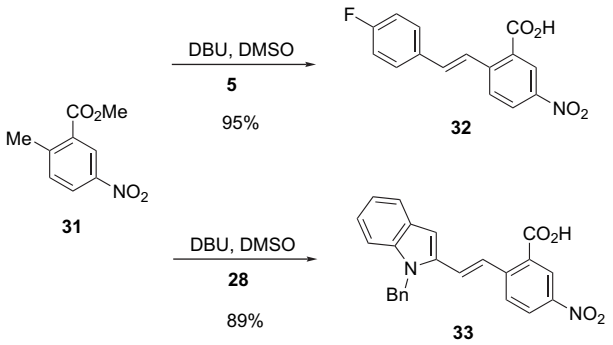
Interesting reactivity was noted when nitrobenzoate **3** was allowed to react with excess paraformaldehyde and indole-2-carboxaldehydes **27** and **28** (Scheme 3). For example, treatment of **3** with an excess of paraformaldehyde in the presence of 2 equiv of DBU in DMSO at 50 °C for 12 h followed by an extractive workup and acidification with aqueous HCl did not give the expected vinyl nitrobenzoic acid **24**. Isochromanone **23** was isolated as the sole product in 76% yield.[19] Presumably, reaction of **3** with paraformaldehyde was followed by deprotonation and reaction with a second equivalent of paraformaldehyde leading to intermediate

25. Although the exact order of transformations leading to **25** was not explicitly clear, elimination of the carboxylate anion affords intermediate **26**, which upon acidification and intramolecular cyclization gave **23**. Reaction of **3** with **27** or **28** only led to trace amounts of the corresponding nitrostyrene benzoic acids (<8%), and isochromanones **29** and **30** were isolated in 75% and 80% yields, respectively. A satisfactory rationale to account for the interruption of the pathway leading to the expected nitrostyrene carboxylic acid products in the presence of *N*-methyl- or *N*-benzyl substituents is currently unavailable. However, we speculate that steric influences of the indole substituents and the close proximity of the nitro group prevent the approach of the base and elimination of the carboxylate anion.



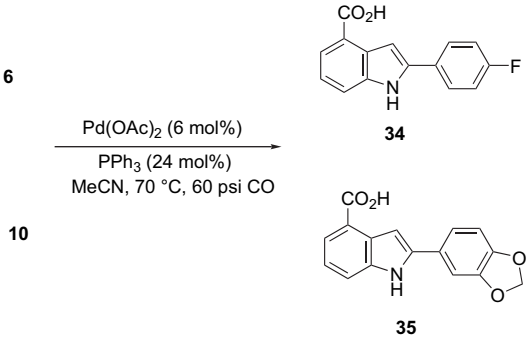
Scheme 3.

We have also examined the reaction of the regio-isomeric methyl 2-methyl-5-nitrobenzoate **31** with aldehydes **5** and **28** (Scheme 4).[20] Reaction of **31** with **5** under the optimized reaction conditions described above led to the formation of nitrostyrene benzoic acid **32** in 95% isolated yield. In this case, the product could be obtained by direct crystallization from the crude reaction mixture. In similar fashion, nitrostyrene benzoic acid **33** was obtained in 89% yield when reacted with aldehyde **28**.



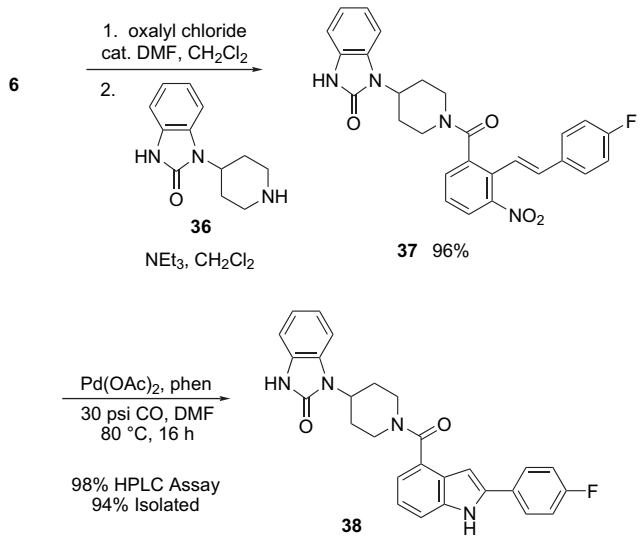
Scheme 4.

Reductive cyclization of aromatic nitrocompounds is an extremely powerful method for the preparation of the indole nucleus.[21] Transition metal catalyzed reductive cyclizations employing carbon monoxide as the stoichiometric reductant has recently emerged as a highly versatile method for the construction of indoles due to superior yields, diminished amounts of reaction by-products, and favorable environmental impact.[16,17,21] For the preparation of indoles of subclass **1** bearing an amido-substituent in the four position of the indole ring, a two-step sequence involving either reductive cyclization of the *ortho*-nitrostyrenes followed by amide formation or amide formation followed by reductive cyclization was required. With nitrostyrene benzoic acids in hand, initial efforts were focused on reductive cyclization of these substrates (Scheme 5). For example, reductive cyclization of nitrostyrenes **6** and **10** was accomplished under the conditions discovered by Söderberg.[16] Reaction of **6** and **10** with 6 mol % $Pd(OAc)_2$, 24 mol % PPh_3 in acetonitrile at 70 °C under an atmosphere of 60 psi CO for 16 h afforded indole carboxylic acids **34** and **35** in 89% and 92% HPLC assay yields,[18] respectively. The isolation of **34** and **35** in pure form was plagued by both solubility issues of the corresponding products and the difficulty in removing the excess triphenylphosphine and triphenylphosphine oxide. Consequently, the isolated yields of **34** and **35** were <50% after crystallization. Due to this difficulty, our attention turned to conversion of the benzoic acid moiety to the required amide functionality prior to reductive cyclization.



Scheme 5.

Treatment of nitrostyrene benzoic acid **6** with oxalyl chloride in the presence of a catalytic amount of DMF in CH_2Cl_2 afforded the intermediate acid chloride, which was not isolated (Scheme 6). Reaction with 4-(2-keto-1-benzimidazolinyl)piperadine **36** in the presence of NEt_3 gave, after workup, amido nitrostyrene **37**, which was isolated as a highly crystalline solid in 96% yield. The reductive cyclization of **37** was conducted under the optimized reaction conditions previously disclosed from these laboratories.[17,22] Thus, reaction of **37** with 1 mol % $Pd(OAc)_2$, 7 mol % 1,10-phenanthroline (phen), in DMF at 80 °C under an atmosphere of 30 psi CO for 16 h afforded indole **38** in 98% HPLC assay yield.[18] In this case, isolation of **38** was simply a matter of filtering the reaction mixture through Celite, followed by the addition of 1 M H_3PO_4, which precipitated the



Scheme 6.

product in analytically pure form and in 94% isolated yield. The sequence whereby the appropriately substituted nitrostyrene carboxylic acid was converted to the required amide followed by reductive cyclization provided an excellent, high yielding means of preparing the highly functionalized derivatives shown in Table 2. The use of 1 M H_3PO_4 for the isolation of the product aided in the removal of trace amounts of 1,10-phenanthroline from the product and was mild enough that sensitive functionalities such as a Boc-protecting group were preserved (see Table 2, entry 3).

In conclusion, a concise three-step method for the preparation of many highly functionalized 'drug-like' 2-aryl-indole-4-carboxylic amide derivatives has been developed. This efficient protocol involved reaction of nitrotoluene **3** with substituted aldehydes in the presence of DBU in DMSO to provide the nitrostyrene benzoic acids, which were subsequently converted to their amide derivatives. Catalytic reductive cyclization provided the desired 2-aryl-indole-4-carboxylic amide derivatives in excellent overall

Table 2

Entry, acid	Amine	Amide	Indole[a]
1, **16**	$NHMe_2$	**39** 99%	**40** 98%, (91%)
2, **6**	**41**	**42** 99%	**43** 97% (93%)
3, **10**	**44**	**45** 98%	**46** 99% (95%)
4, **20**	**47**[23]	**48** 98%	**49** 98% (94%)
5, **10**	**50**	**51** 97%	**52** 98% (92%)

[a] Yield in parenthesis reflects isolated yield after crystallization from the crude reaction mixture.

yield. The overall sequence does not require the use of chromatography and offers an extremely attractive strategy for direct entry into this uniquely substituted pharmacophore. The biological activity of these substrates is currently under active investigation and will be reported in due course.

3. Experimental

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate/hexanes mixture as the eluent unless specified otherwise.

3.1. General procedure for the preparation of 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzoic acid (2)

To a stirred containing 1.50 g (7.69 mmol) of methyl 2-methyl-3-nitrobenzoate **3** and 11.5 mmol of the appropriately substituted aldehyde in 10 mL of dry DMSO was added 2.34 g (15.38 mmol) of DBU. The resulting mixture was stirred at rt for 12 h, heated to 50 °C for 30 min, and then cooled to rt. To the crude reaction mixture was added 20 mL of 1 N NaOH solution and the mixture was washed with EtOAc (2×25 mL) to remove the excess aldehyde. The aqueous layer was then made acidic with concd HCl, extracted with EtOAc, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue recrystallized from MeOH/water to give the 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzoic acid (**2**) in analytically pure form.

3.1.1. Preparation of 2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrobenzoic acid (6). According to the general procedure, treatment of a mixture of 2.32 g (11.90 mmol) of **3** and 2.21 g (17.83 mmol) of 4-fluorobenzaldehyde **5** with 3.61 g (23.77 mmol) of DBU afforded 2.87 g (84%) of **6** as a bright yellow solid: mp 156–157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.50 (d, 1H, J=16.5 Hz), 7.03 (m, 2H), 7.46 (m, 4H), 7.95 (dd, 1H, J=8.0 and 1.0 Hz), 8.17 (dd, 1H, J=8.0 and 1.0 Hz), 12.71 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 115.7 (d, J=22 Hz), 122.4, 127.7, 128.0, 128.6 (d, J=8 Hz), 131.3, 132.6, 133.2, 134.2, 134.4, 151.0, 162.3 (d, J=247 Hz), 171.4; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{15}H_{10}FNO_4$: C, 62.72; H, 3.51; N, 4.88. Found: C, 62.43; H, 3.22; N, 4.79.

3.1.2. Preparation of 2-(*trans*-2-benzo[1,3]dioxol-5-yl-vinyl)-3-nitrobenzoic acid (10). According to the general procedure, treatment of a mixture of 1.50 g (7.69 mmol) of **3** and 1.73 g (11.50 mmol) of piperonal **9** with 2.34 g (15.38 mmol) of DBU afforded 1.64 g (68%) of **10** as a bright yellow solid: mp 134–135 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.01 (s, 2H), 6.43 (d, 1H, J=16.5 Hz), 6.88 (m, 2H), 7.16 (s, 1H), 7.32 (d, 1H, J=16.5 Hz), 7.57 (t, 1H, J=7.9 Hz), 8.01 (d, 1H, J=7.9 Hz), 8.02 (d, 1H, J=7.9 Hz), 12.0 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 101.7, 106.2, 108.9, 121.6, 122.5, 126.6, 128.8, 131.3, 132.0, 133.4, 133.5, 134.7, 148.0, 148.4, 150.5, 168.2. Anal. Calcd for $C_{16}H_{11}NO_4$: C, 61.35; H, 3.54; N, 4.47. Found: C, 60.99; H, 3.49; N, 4.43.

3.1.3. Preparation of 2-[*trans*-2-(4-methoxyphenyl)-vinyl]-3-nitrobenzoic acid (12). According to the general procedure, treatment of a mixture of 1.50 g (7.69 mmol) of **3** and 1.57 g (11.50 mmol) of 4-methoxybenzaldehyde **11** with 2.34 g (15.38 mmol) of DBU afforded 1.40 g (61%) of **12** as a yellow solid: mp 158–159 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.74 (s, 3H), 6.47 (d, 1H, J=16.6 Hz), 6.91 (d, 2H, J=8.7 Hz), 7.32 (d, 1H, J=16.6 Hz), 7.41 (d, 2H, J=8.7 Hz), 7.57 (t, 1H, J=8.1 Hz), 8.01 (d, 1H, J=8.1 Hz), 8.02 (d, 1H, J=8.1 Hz), 12.10 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.7, 114.7, 120.9, 126.6, 128.6, 128.7, 129.4, 132.1, 133.3, 133.6, 134.7, 150.5, 160.1, 168.2. Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 63.92; H, 4.22; N, 4.21.

3.1.4. Preparation of 2-[*trans*-2-(5-bromo-2-hydroxy-phenyl)-vinyl]-3-nitrobenzoic acid (14). According to the general procedure, treatment of a mixture of 1.20 g (6.15 mmol) of **3** and 1.85 g (9.22 mmol) of 5-bromosalicylaldehyde **13** with 1.87 g (12.30 mmol) of DBU afforded 1.77 g (79%) of **14** as a tan solid: mp 154 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.70 (d, 1H, J=16.7 Hz), 6.82 (d, 1H, J=8.5 Hz), 7.28 (d, 1H, J=8.5 Hz), 7.65 (m, 3H), 8.05 (m, 2H), 10.15 (br s, 1H), 12.10 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.1, 118.4, 124.2, 125.9, 126.5, 127.6, 128.9, 129.4, 131.9, 132.1, 133.3, 134.7, 150.4, 154.8, 168.1. Anal. Calcd for $C_{15}H_{10}BrNO_5$: C, 49.47; H, 2.77; N, 3.85. Found: C, 49.11; H, 2.76; N, 3.89.

3.1.5. Preparation of 2-(*trans*-2-furan-2-yl-vinyl)-3-nitrobenzoic acid (16). According to the general procedure, treatment of a mixture of 2.50 g (12.81 mmol) of **3** and 1.85 g (19.21 mmol) of 2-furaldehyde **15** with 3.90 g (25.62 mmol) of DBU afforded 2.99 g (90%) of **16** as a yellow solid: mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (m, 3H), 7.47 (m, 3H), 7.90 (dd, 1H, J=7.9 and 1.2 Hz), 8.15 (dd, 1H, J=7.9 and 1.2 Hz), 12.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.5, 111.6, 120.1, 122.7, 127.5, 127.7, 131.2, 133.6, 134.0, 143.1, 150.8, 151.9, 171.4. Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 59.99; H, 3.51; N, 5.43.

3.1.6. Preparation of 2-(*trans*-2-benzofuran-2-yl-vinyl)-3-nitrobenzoic acid (18). According to the general procedure, treatment of a mixture of 630 mg (3.23 mmol) of **3** and 708 mg (4.85 mmol) of 2-benzofurancarboxaldehyde **17** with 983 mg (6.46 mmol) of DBU afforded 820 mg (82%) of **18** as a yellow solid: mp 154–155 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.63 (m, 1H), 7.01 (s, 1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.65 (m, 4H), 8.12 (m, 2H), 12.03 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 107.5, 111.5, 121.9, 122.0, 123.8, 124.6, 125.9, 126.9, 128.8, 129.4, 131.0, 133.6, 134.5, 150.3, 153.9, 154.7, 167.9. Anal. Calcd for $C_{17}H_{11}NO_5$: C, 66.02; H, 3.58; N, 4.53. Found: C, 66.10; H, 3.66; N, 4.54.

3.1.7. Preparation of 2-[*trans*-2-(3-chloro-5-fluoro-phenyl)-vinyl]-3-nitrobenzoic acid (20). According to the general procedure, treatment of a mixture of 1.58 g (8.10 mmol) of **3** and 1.92 g (12.14 mmol) of 3-chloro-5-fluorobenzaldehyde **19** with 2.47 g (15.38 mmol) of DBU afforded 2.29 (88%) of **20** as a yellow solid: mp

142–143 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.41 (d, 1H, J=16.4 Hz), 7.05 (m, 2H), 7.21 (s, 1H), 7.55 (m, 2H), 7.99 (d, 1H, J=7.4 Hz), 8.23 (d, 1H, J=7.4 Hz), 11.49 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.9 (d, J=20 Hz), 115.9 (d, J=20 Hz), 123.0, 125.8, 126.6, 127.8, 128.4, 131.2, 131.3, 133.7, 134.3, 135.4 (d, J=10 Hz), 139.5 (d, J=10 Hz), 150.8, 162.4 (d, J=250 Hz), 170.9; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −111.2. Anal. Calcd for $C_{15}H_9ClFNO_4$: C, 56.00; H, 2.82; N, 4.35. Found: C, 55.83; H, 2.73; N, 4.33.

3.1.8. Preparation of 3-nitro-2-[*trans*-(4-nitrophenyl)-vinyl]-benzoic acid (22). According to the general procedure, treatment of a mixture of 1.50 g (7.69 mmol) of **3** and 1.74 g (11.50 mmol) of 4-nitrobenzaldehyde **21** with 2.34 g (15.38 mmol) of DBU afforded 1.98 (82%) of **22** as a yellow solid: mp 172–173 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.64 (d, 1H, J=16.6 Hz), 7.65 (t, 1H, J=8.0 Hz), 7.77 (m, 3H), 8.10 (m, 2H), 8.20 (d, 2H, J=8.8 Hz), 12.12 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 124.6, 127.1, 128.1, 129.0, 129.7, 130.9, 131.9, 133.9, 134.5, 143.3, 147.3, 150.3, 167.8. Anal. Calcd for $C_{15}H_{10}N_2O_6$: C, 57.33; H, 3.21; N, 8.91. Found: C, 57.32; H, 3.19; N, 8.88.

3.1.9. Preparation of 4-methylene-5-nitro-isochroman-1-one (23). According to the general procedure, treatment of a mixture of 1.00 g (5.12 mmol) of **3** and 2.00 g of solid paraformaldehyde with 1.56 g (10.25 mmol) of DBU afforded 799 mg (76%) of **23** as a white solid: mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.00 (s, 2H), 5.55 (s, 1H), 5.72 (s, 1H), 7.61 (t, 1H, J=8.0 Hz), 7.86 (d, 1H, J=8.0 Hz), 8.33 (d, 1H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.2, 121.8, 126.7, 128.5, 129.6, 129.8, 130.1, 134.0, 147.3, 162.3. Anal. Calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.79; H, 3.78; N, 6.69.

3.1.10. Preparation of 3-(1-methyl-1*H*-indol-2-yl)-5-nitro-isochroman-1-one (29). According to the general procedure, treatment of a mixture of 2.00 g (10.25 mmol) of **3** and 2.45 g (15.4 mmol) of 1-methylindole-2-carboxaldehyde **27** with 3.12 g (20.50 mmol) of DBU afforded 2.48 g (75%) of **29** as a yellow solid: mp 166–167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.47 (dd, 1H, J=15.7 and 5.7 Hz), 3.73 (s, 3H), 3.78 (dd, 1H, J=15.7 and 3.3 Hz), 6.05 (s, 1H), 6.36 (m, 1H), 7.03 (dt, 1H, J=7.9 and 0.8 Hz), 7.15 (dt, 1H, J=7.9 and 0.8 Hz), 7.23 (d, 1H, J=8.3 Hz), 7.41 (d, 1H, J=7.9 Hz), 7.70 (t, 1H, J=7.9 Hz), 8.06 (d, 1H, J=7.9 Hz), 8.50 (d, 1H, J=7.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.8, 81.5, 102.4, 109.4, 119.6, 120.2, 121.5, 127.4, 129.3, 130.0, 131.2, 132.0, 133.2, 137.6, 143.2, 167.1. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.89; H, 4.22; N, 8.66.

3.1.11. Preparation of 3-(1-benzyl-1*H*-indol-2-yl)-5-nitro-isochroman-1-one (30). According to the general procedure, treatment of a mixture of 1.56 g (7.99 mmol) of **3** and 2.82 g (12.00 mmol) of 1-benzylindole-2-carboxaldehyde **28** with 2.43 g (15.99 mmol) of DBU afforded 2.55 g (80%) of **30** as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29 (dd, 1H, J=15.8 and 6.6 Hz), 3.71 (dd, 1H, J=15.8 and 3.1 Hz), 5.45 (d, 1H, J=17.5 Hz), 5.54 (d, 1H, J=17.5 Hz), 6.26 (m, 1H), 6.28 (s, 1H), 6.90 (m, 2H), 7.09 (m, 2H), 7.22 (m, 4H), 7.51 (d, 1H, J=7.8 Hz), 7.67 (t, 1H, J=7.8 Hz), 8.09 (d, 1H, J=7.8 Hz), 8.45 (dd, 1H, J=8.0 and 0.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.4, 46.5, 81.3, 103.4, 109.9, 119.9, 120.4, 121.8, 125.8, 127.4, 127.8, 128.9, 129.5, 129.9, 131.3, 132.0, 133.6, 137.4, 137.7, 143.3, 143.5, 167.3. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.43; H, 4.66; N, 7.00.

3.1.12. Preparation of 2-[*trans*-2-(4-fluorophenyl)-vinyl]-5-nitrobenzoic acid (32). According to the general procedure, treatment of a mixture of 2.00 g (10.25 mmol) of **31** and 1.91 g (15.37 mmol) of 4-fluorobenzaldehyde **5** with 3.12 g (20.50 mmol) of DBU afforded 2.80 g (95%) of **32** as a bright yellow solid: mp 216–217 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.21 (m, 2H), 7.37 (d, 1H, J=16.4 Hz), 7.61 (m, 2H), 7.89 (d, 1H, J=16.4 Hz), 8.03 (d, 1H, J=8.8 Hz), 8.29 (m, 1H), 8.53 (s, 1H), 12.61 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 116.3 (d, J=20.0 Hz), 125.6, 126.0, 126.6, 128.5, 129.6 (d, J=8.0 Hz), 130.7, 133.5, 134.1, 144.7, 146.2, 163.1 (d, J=245.0 Hz), 167.3. Anal. Calcd for $C_{15}H_{10}FNO_4$: C, 62.72; H, 3.51; N, 4.88. Found: C, 62.77; H, 3.55; N, 4.93.

3.1.13. Preparation of 2-[*trans*-2-(1-benzyl-1*H*-indol-2-yl)-vinyl]-5-nitrobenzoic acid (33). According to the general procedure, treatment of a mixture of 2.30 g (11.78 mmol) of **31** and 4.16 g (17.68 mmol) of 1-benzylindole-2-carboxaldehyde **28** with 3.59 g (23.57 mmol) of DBU afforded 4.18 g (89%) of **33** as a red solid: mp 168–169 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.67 (s, 2H), 6.97 (s, 1H), 7.14 (m, 7H), 7.43 (d, 1H, J=8.3 Hz), 7.56 (d, 1H, J=7.8 Hz), 7.64 (d, 1H, J=16.1 Hz), 8.13 (m, 2H), 8.26 (dd, 1H, J=8.8 and 2.3 Hz), 8.54 (s, 1H), 13.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 46.2, 110.9, 120.7, 121.1, 123.1, 124.0, 126.0, 126.4, 126.8, 126.9, 127.7, 128.1, 128.2, 129.1, 130.9, 137.9, 138.4, 139.0, 144.2, 146.0, 167.5. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.36; H, 4.66; N, 7.05.

3.1.14. Preparation of 2-(4-fluorophenyl)-1*H*-indole-4-carboxylic acid (34). In a 10 mL pressure tube was added sequentially 115 mg (0.400 mmol) of **6**, 5.4 mg (0.024 mmol) of $Pd(OAc)_2$, 25.2 mg of PPh_3 (0.096 mmol), and 3 mL of MeCN. The resulting mixture was heated at 70 °C under an atmosphere of 60 psi CO for 16 h and then cooled to rt. HPLC assay of the crude reaction mixture revealed 91 mg (89%) of **34**. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was recrystallized (2×) from an EtOAc/hexane mixture followed by recrystallization from MeOH/water to afford 50 mg (49%) of **34** as a light tan solid: mp 170 °C (decomp.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (m, 2H), 7.27 (m, 1H), 7.53 (s, 1H), 7.64 (d, 1H, J=8.0 Hz), 7.29 (m, 2H), 8.04 (d, 1H, J=7.5 Hz), 8.58 (br s, 1H), 12.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.5, 116.2 (d, J=20 Hz), 116.5, 120.4, 121.5, 124.8, 127.3, 128.1, 129.4, 137.7, 139.4, 163.2 (d, J=250.0 Hz), 173.0; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95; N, 5.49. Found: C, 70.66; H, 3.98; N, 5.53.

3.1.15. Preparation of 2-benzo[1,3]dioxol-5-yl-1*H*-indole-4-carboxylic acid (35). In a 10 mL pressure tube

was added sequentially 198 mg (0.632 mmol) of **10**, 8.51 mg (0.038 mmol) of $Pd(OAc)_2$, 39.8 mg (0.152 mmol) of PPh_3, and 4 mL of MeCN. The resulting mixture was heated at 70 °C under an atmosphere of 60 psi CO for 16 h and then cooled to rt. HPLC assay of the crude reaction mixture revealed 163 mg (92%) of **35**. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was recrystallized (2×) from an EtOAc/hexane mixture followed by recrystallization from MeOH/water to afford 76 mg (43%) of **35** as a tan solid: mp 275–276 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.05 (s, 2H), 6.99 (d, 1H, J=8.0 Hz), 7.13 (t, 1H, J=7.8 Hz), 7.25 (s, 1H), 7.38 (d, 1H, J=8.0 Hz), 7.44 (s, 1H), 7.58 (d, 1H, J=8.0 Hz), 7.67 (d, 1H, J=7.8 Hz), 11.69 (br s, 1H), 12.61 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 99.7, 101.8, 106.3, 109.3, 116.2, 119.9, 120.9, 121.5, 123.2, 126.5, 128.9, 138.3, 140.2, 147.7, 148.5, 169.0. Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.49; H, 4.01; N, 4.99.

3.2. General procedure for the preparation of 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzamides

To a stirred solution of 10 mmol of the appropriate nitrostyrene benzoic acid in 30 mL of CH_2Cl_2 was added 1.65 g (13.00 mmol) of oxalyl chloride followed by one drop of DMF. The resulting mixture was stirred for 1.5 h at rt and concentrated under reduced pressure and then re-dissolved in 15 mL of CH_2Cl_2. The resulting solution of the acid chloride was then added dropwise to a mixture of 13.0 mmol of the appropriately substituted amine and 1.52 g (15.00 mmol) of NEt_3. The mixture was stirred at rt for 30 min, diluted with 15 mL of 1 N HCl, and the layers separated. The organic layer was washed with 15 mL of 2 N NaOH, washed with 15 mL of brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude amide, which was recrystallized from MeOH/water.

3.3. General procedure for the preparation of 2-aryl-indole-4-carboxylic amides

In a 20 mL pressure tube was sequentially added 1.0 mmol of the appropriately substituted 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzamide, 0.01 mmol of $Pd(OA)_2$, 0.07 mmol of 1,10-phenanthroline, and 4 mL of DMF. The resulting mixture was then heated at 80 °C under an atmosphere of 30 psi CO for 16 h, and cooled to rt, and was filtered through a pad of Celite eluting with 2 mL of DMF. Quantitative HPLC analysis of the crude reaction mixture was conducted at this point. The solution was then added dropwise to a solution of 10 mL of 1 M H_3PO_4. The resulting slurry of the product was stirred at rt for 30 min and filtered. The solid was dried under vacuum/N_2 sweep for 6–12 h to give the desired indole.

3.3.1. Preparation of 1-(1-{2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrobenzoyl}-piperidin-4-yl)-1,3-dihydro-benzimidazol-2-one (37). According to the general procedure, treatment of a mixture of 600 mg (2.09 mmol) of **6** with 345 mg (2.72 mmol) of oxalyl chloride followed by reaction with 590 mg (2.72 mmol) of **36** in the presence of 317 mg (3.13 mmol) of NEt_3 afforded 980 mg (96%) of **37** as a yellow solid: mp 242–243 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76 (m, 1H), 1.92 (m, 1H), 2.07 (m, 1H), 2.25 (m, 1H), 2.47 and 2.48 (m, due to rotamers, 1H), 2.92 and 3.12 (m, due to rotamers, 1H), 3.52 (m, 1H), 4.41 and 4.52 (m, due to rotamers, 1H), 5.01 (m, 1H), 6.15 and 6.55 (m, due to rotamers, 1H), 6.86–7.70 (m, 11H), 7.95 (m, 1H), 10.30 and 10.41 (m, due to rotamers, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7 and 29.2 (due to rotamers), 29.3 and 30.1 (due to rotamers), 41.5, 46.1, and 46.9 (due to rotamers), 50.6 and 50.7 (due to rotamers), 108.8, 109.9, and 110.1 (due to rotamers), 116.1 and 116.3 (d, due to rotamers J=22 Hz), 120.4 and 120.5 (due to rotamers), 121.1 and 121.2 (due to rotamers), 121.5 and 121.6 (due to rotamers), 125.1 and 125.2 (due to rotamers), 128.0 and 128.2 (due to rotamers), 128.5 and 128.6 (due to rotamers), 128.7 (d, J=10 Hz), 128.9 and 129.0 (due to rotamers), 129.5 and 129.9 (due to rotamers), 131.6 and 131.7 (due to rotamers), 132.5 and 132.6 (due to rotamers), 135.5 and 135.8 (due to rotamers), 137.8, 148.8, and 148.9 (due to rotamers), 155.0 and 155.1 (due to rotamers), 163.1 (d, J=250 Hz), 167.9 and 168.1 (due to rotamers); ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{27}H_{23}FN_4O_4$: C, 66.66; H, 4.77; N, 11.52. Found: C, 66.43; H, 4.63; N, 11.51.

3.3.2. Preparation of 1-{1-[2-(4-fluorophenyl)-1*H*-indole-4-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one (38). According to the general procedure, reductive cyclization of 98 mg (0.201 mmol) of **37** in the presence of 0.500 mg (2.02 μmol) of $Pd(OAc)_2$ and 2.54 mg (0.014 mmol) of 1,10-phenanthroline afforded 90 mg (98%) of **38** by HPLC assay of the crude reaction mixture. Workup afforded 86 mg (94%) of **38** as a colorless solid: mp 215–216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.90 (br m, 2H), 2.54 (br m, 2H), 3.24 (br m, 2H), 3.80 (br m, 1H), 4.56 (m, 1H), 4.96 (br m, 1H), 6.96 (m, 4H), 7.11 (m, 4H), 7.29 (m, 1H), 7.41 (m, 1H), 7.91 (m, 2H), 10.10 (s, 1H), 11.05 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 29.1, 30.2, 41.5, 46.5, 50.7, 98.3, 108.6, 109.0, 112.2, 115.7 (d, J=10 Hz), 118.2, 120.7, 121.6, 125.8, 126.6, 127.2, 127.4, 128.7, 129.1, 137.6, 138.2, 155.5, 163.3 (d, J=250 Hz), 168.0; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −113.3. Anal. Calcd for $C_{27}H_{23}FN_4O_2$: C, 71.35; H, 5.10; N, 12.33. Found: C, 70.99; H, 5.05; N, 12.29.

3.3.3. Preparation of 2-(*trans*-2-furan-2-yl-vinyl)-*N*,*N*-dimethyl-3-nitrobenzamide (39). According to the general procedure, treatment of a mixture of 650 mg (2.51 mmol) of **16** with 414 mg (3.26 mmol) of oxalyl chloride followed by reaction with 170 mg (3.13 mL of a 2 M solution in THF, 3.77 mmol) of *N*,*N*-dimethylamine afforded 710 mg (99%) of **39** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.74 (s, 3H), 3.03 (s, 3H), 6.40 (m, 2H), 6.71 (d, 1H, J=16.4 Hz), 7.19 (d, 1H, J=16.4 Hz), 7.44 (m, 2H), 7.53 (d, 1H, J=7.6 Hz), 7.88 (dd, 1H, J=8.1 and 1.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.0, 38.1, 111.2, 111.9, 118.2, 124.0, 124.8, 128.2, 129.1, 131.5, 137.9, 143.3, 148.9, 152.0, 169.4. Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.01; H, 4.95; N, 9.80.

3.3.4. Preparation of 2-furan-2-yl-1*H*-indol-4-carboxylic acid kemethylamide (40). According to the general procedure, reductive cyclization of 150 mg (0.524 mmol) of **39** in the presence of 1.18 mg (5.24 μmol) of $Pd(OAc)_2$ and

6.61 mg (0.037 mmol) of 1,10-phenanthroline afforded 131 mg (98%) of **40** by HPLC assay of the crude reaction mixture. Workup afforded 121 mg (91%) of **40** as a white solid: mp 233 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.84 (br s, 3H), 3.02 (br s, 3H), 6.59 (m, 2H), 6.90 (d, 1H, J=3.2 Hz), 6.96 (d, 1H, J=7.5 Hz), 7.11 (t, 1H, J=7.5 Hz), 7.40 (d, 1H, J=7.5 Hz), 7.74 (s, 1H), 11.73 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 35.0, 38.9, 97.3, 107.0, 112.5, 112.7, 118.7, 121.9, 126.0, 128.7, 130.8, 137.1, 143.4, 147.8, 170.5. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.55; H, 5.32; N, 10.89.

3.3.5. Preparation of {2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrophenyl}-pyrrolidin-1-yl-methanone (42). According to the general procedure, treatment of a mixture of 300 mg (1.04 mmol) of **6** with 172 mg (1.36 mmol) of oxalyl chloride followed by reaction with 111 mg (1.36 mmol) of pyrrolidine **41** in the presence of 158 mg (1.57 mmol) of NEt_3 afforded 352 mg (99%) of **42** as a yellow solid: mp 94–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 4H), 3.05 (t, 2H, J=6.2 Hz), 3.52 (t, 2H, J=6.2 Hz), 6.90 (d, 1H, J=16.4 Hz), 7.02 (m, 2H), 7.23 (d, 1H, J=16.4 Hz), 7.42 (m, 3H), 7.58 (d, 1H, J=8.0 Hz), 7.92 (dd, 1H, J=8.0 and 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 25.8, 45.9, 47.8, 115.8 (d, J=20.0 Hz), 120.2, 124.9, 128.4 (d, J=10.0 Hz), 128.6, 129.2, 131.5, 132.6, 135.3, 139.2, 148.7, 163.0 (d, J=250.0 Hz), 167.5; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C, 67.05; H, 5.03; N, 8.23. Found: C, 66.82; H, 4.99; N, 8.15.

3.3.6. Preparation of [2-(4-fluorophenyl)-1*H*-indol-4-yl]-pyrrolidin-1-yl-methanone (43). According to the general procedure, reductive cyclization of 140 mg (0.411 mmol) of **42** in the presence of 0.923 mg (4.11 μmol) of $Pd(OAc)_2$ and 5.19 mg (0.029 mmol) of 1,10-phenanthroline afforded 123 mg (97%) of **43** by HPLC assay of the crude reaction mixture. Workup afforded 118 mg (93%) of **43** as a white solid: mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (m, 2H), 1.95 (m, 2H), 3.37 (t, 2H, J=6.7 Hz), 3.75 (t, 2H, J=6.7 Hz), 6.71 (s, 1H), 6.94 (m, 2H), 7.05 (t, 1H, J=7.5 Hz), 7.12 (d, 1H, J=7.5 Hz), 7.35 (d, 1H, J=7.5 Hz), 7.60 (m, 2H), 10.4 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.2, 45.9, 49.0, 98.3, 112.8, 115.5 (d, J=30.0 Hz), 118.3, 121.1, 126.2, 127.2, 128.5 (d, J=10.0 Hz), 128.6, 137.6, 138.5, 162.3 (d, J=250.0 Hz), 170.3; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −111.1. Anal. Calcd for $C_{19}H_{17}FN_2O$: C, 74.01; H, 5.56; N, 9.08. Found: C, 74.36; H, 5.73; N, 8.89.

3.3.7. Preparation of 4-[2-*trans*-(2-benzo[1,3]-dioxol-5-yl-vinyl)-3-nitrobenzoyl]-piperazine-1-carboxylic acid *tert*-butyl ester (45). According to the general procedure, treatment of a mixture of 2.00 g (6.38 mmol) of **10** with 1.05 g (8.30 mmol) of oxalyl chloride followed by reaction with 1.55 g (8.30 mmol) of **44** in the presence of 1.00 g (9.60 mmol) of NEt_3 afforded 3.00 mg (98%) of **45** as a yellow solid: mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.08 (m, 2H), 3.29 (m, 3H), 3.41 (m, 1H), 3.61 (m, 1H), 3.70 (m, 1H), 5.98 (s, 2H), 6.88 (m, 3H), 6.99 (s, 1H), 7.10 (d, 1H, J=16.4 Hz), 7.46 (t, 1H, J=7.8 Hz), 7.55 (dd, 1H, J=7.8 and 1.2 Hz), 7.94 (dd, 1H, J=8.1 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 41.6, 43.4, 45.9, 46.4, 80.5, 101.5, 105.7, 108.6, 118.4, 122.5, 125.1, 128.2, 130.0, 130.5, 131.7, 136.8, 137.5, 148.5, 148.6, 148.8, 154.3, 168.1. Anal. Calcd for $C_{25}H_{27}N_3O_7$: C, 62.36; H, 5.65; N, 8.73. Found: C, 62.33; H, 5.66; N, 8.71.

3.3.8. Preparation of (2-benzo[1,3]dioxol-5-yl-1*H*-indol-4-yl)-piperazin-1-yl methanone hydrochloride (46). According to the general procedure, reductive cyclization of 160 mg (0.332 mmol) of **45** in the presence of 0.75 mg (3.32 μmol) of $Pd(OAc)_2$ and 4.19 mg (0.023 mmol) of 1,10-phenanthroline afforded 147 mg (99%) of **46** by HPLC assay of the crude reaction mixture. Workup afforded 142 mg (95%) of **46** as a colorless solid: mp 157–158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 3.30–4.10 (br m, 8H), 6.01 (s, 2H), 6.64 (s, 1H), 6.83 (d, 1H), 7.11 (m, 4H), 7.35 (m, 1H), 9.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 25.9, 27.3, 43.1, 62.6, 80.3, 97.7, 101.3, 106.2, 108.8, 112.5, 118.9, 119.2, 121.5, 126.3, 126.6, 126.7, 137.0, 139.4, 147.6, 148.3, 154.6, 170.6. Anal. Calcd for $C_{25}H_{27}ClN_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.79; H, 6.01; N, 9.32.

3.3.9. Preparation of {2-[*trans*-2-(3-chloro-5-fluorophenyl)-vinyl]-3-nitrophenyl}-(4-methanesulfonyl-piperazin-1-yl)-methanone (48). According to the general procedure, treatment of a mixture of 890 mg (2.77 mmol) of **20** with 457 mg (3.60 mmol) of oxalyl chloride followed by reaction with 591 mg (3.60 mmol) of **47**[23] in the presence of 420 mg (4.15 mmol) of NEt_3 afforded 1.27 g (98%) of **48** as a yellow solid: mp 179–180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 2.79 (m, 2H), 3.24 (m, 4H), 3.69 (m, 1H), 3.95 (m, 1H), 6.78 (d, 1H, J=16.4 Hz), 7.07 (m, 2H), 7.25 (m, 1H), 7.33 (d, 1H, J=16.4 Hz), 7.59 (m, 2H), 8.06 (dd, 1H, J=7.6 and 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.3, 41.3, 45.5, 45.6, 46.3, 1120 (d, J=22 Hz), 116.6 (d, J=25 Hz), 122.8, 123.9, 125.6, 129.0, 129.3, 131.9, 134.1, 136.0 (d, J=11 Hz), 137.4, 139.2 (d, J=8.0 Hz), 148.5, 163.4 (d, J=250 Hz), 167.5; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −111.1. Anal. Calcd for $C_{20}H_{19}ClFN_3O_5S$: C, 51.34; H, 4.09; N, 8.98. Found: C, 51.22; H, 4.02; N, 8.96.

3.3.10. Preparation of [2-(3-chloro-5-fluorophenyl)-1*H*-indol-4-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (49). According to the general procedure, reductive cyclization of 145 mg (0.310 mmol) of **48** in the presence of 0.70 mg (3.10 μmol) of $Pd(OAc)_2$ and 3.91 mg (0.022 mmol) of 1,10-phenanthroline afforded 132 mg (98%) of **49** by HPLC assay of the crude reaction mixture. Workup afforded 127 mg (94%) of **49** as a colorless solid: mp 143–144 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz) δ 2.77 (s, 3H), 3.17 (br m, 4H), 3.70 (br m, 4H), 6.78 (s, 1H), 6.95 (d, 1H, J=8.0 Hz), 7.00 (d, 1H, J=7.9 Hz), 7.11 (t, 1H, J=7.9 Hz), 7.41 (d, 1H, J=7.9 Hz), 7.45 (d, 1H, J=7.9 Hz), 7.61 (d, 1H, J=7.9 Hz), 11.5 (br s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 100 MHz) δ 27.0, 34.9, 46.0, 99.3, 110.8 (d, J=30.0 Hz), 113.4, 114.8 (d, J=20.0 Hz), 118.8, 121.4, 122.1, 126.0, 126.8, 135.2 (d, J=10.0 Hz), 135.6 (d, J=10.0 Hz), 136.9, 137.8, 162.3 (d, J=250.0 Hz), 170.0; ^{19}F NMR ($CDCl_3$/DMSO-d_6, 75 MHz) δ −110.9. Anal. Calcd for $C_{20}H_{19}ClFN_3O_3S$: C, 55.11; H, 4.39; N, 9.64. Found: C, 55.23; H, 4.38; N, 9.66.

3.3.11. Preparation of [2-*trans*-2-benzo[1,3]dioxol-5-yl-vinyl]-morpholin-4-yl methanone (51). According to the general procedure, treatment of a mixture of 2.50 g (7.98 mmol) of **10** with 1.32 g (10.4 mmol) of oxalyl chloride followed by reaction with 900 mg (10.4 mmol) of morpholine **50** in the presence of 1.21 g (12.0 mmol) of NEt_3 afforded 2.96 g (97%) of **51** as a yellow solid: mp 134–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (m, 2H), 3.50 (m, 3H), 3.67 (m, 3H), 5.99 (s, 2H), 6.77–6.91 (m, 3H), 7.01 (s, 1H), 7.10 (d, 1H, J=16.4 Hz), 7.45 (t, 1H, J=7.9 Hz), 7.55 (dd, 1H, J=7.6 and 1.3 Hz), 7.93 (dd, 1H, J=7.9 and 1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.8, 46.7, 66.2, 66.4, 101.3, 105.5, 108.4, 118.2, 122.4, 124.9, 128.0, 129.8, 129.9, 130.3, 131.7, 136.6, 137.2, 148.3, 148.5, 167.8. Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.49; H, 4.55; N, 7.29.

3.3.12. Preparation of (2-benzo[1,3]dioxol-5-yl-1*H*-indol-4-yl)-morphorlin-4-yl methanone (52). According to the general procedure, reductive cyclization of 180 mg (0.471 mmol) of **51** in the presence of 1.06 mg (4.71 μmol) of $Pd(OAc)_2$ and 5.94 mg (0.033 mmol) of 1,10-phenanthroline afforded 162 mg (98%) of **52** by HPLC assay of the crude reaction mixture. Workup afforded 152 mg (92%) of **52** as a colorless solid: mp 181–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (br m, 8H), 5.90 (s, 2H), 6.61 (s, 1H), 6.73 (d, 1H, J=8.0 Hz), 7.03 (m, 2H), 7.14 (dd, 1H, J=8.0 and 1.1 Hz), 7.18 (s, 1H), 7.29 (dd, 1H, J=7.3 and 1.1 Hz), 10.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.6, 46.0, 63.8, 67.2, 97.2, 101.2, 106.2, 108.6, 112.8, 118.7, 119.4, 121.1, 126.2, 126.5, 126.6, 137.3, 139.7, 147.4, 148.2, 170.8. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.66; H, 5.20; N, 7.99.

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