JOC The Journal of Organic Chemistry

Article

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Chemoselective Synthesis of Polycyclic Spiroindolines and Polysubstituted Pyrroles via the Domino Reaction of 2-Isocyanoethylindoles

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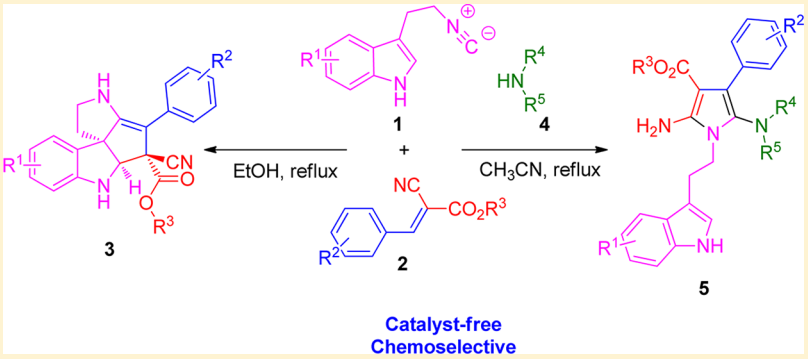
Supporting Information



ABSTRACT: Chemoselective 2-isocyanoethylindole-based domino reactions for the construction of polycyclic spiroindoline derivatives and polysubstituted pyrroles have been developed. The reaction of 2-isocyanoethylindoles and *gem*-diactivated olefins lead to the polycyclic spiroindoline derivatives (up to 92% yields) in EtOH under reflux conditions. Furthermore, the three-component reaction of 2-isocyanoethylindoles with *gem*-diactivated olefins and secondary amines afford polysubstituted pyrroles (in moderate yields) in CH_3CN under reflux conditions.

INTRODUCTION

The development of green and sustainable methods for the highly efficient synthesis of complex molecules with important biological activities has become a topic of interest in modern organic chemistry.[1] In this regard, domino reactions are highly step-economic reactions that can maximize the buildup of structural complexity in a single operation, providing a very attractive strategy for the design and synthesis of polycylic alkaloids and synthetic intermediates.[2,3] In the past several decades, great efforts have been devoted to the assembly of fused-polycyclic molecular skeletons with indole units due to their extensive utility as therapeutic agents.[4] For example, yuehchukene[5] and fischer indoles[6] are characteristic members of biologically active natural products (Figure 1). Isocyanide is an extraordinarily useful reactant for the development of novel domino reactions. An increasing number of isocyanide-based domino reactions have been reported.[7] Nevertheless, the scaffolds that are obtained by these processes are still limited. To enlarge the structural diversity accessible by these domino reactions, a number of functionalized isocyanides[8−13] have been developed for the synthesis of novel heterocyclic compounds.

For example, α-isocyano acetate[9] (I) and toluenesulfonylmethyl isocyanide[10](II, TosMIC) have found wide application in the synthesis of a diverse class of useful molecules. Recently,

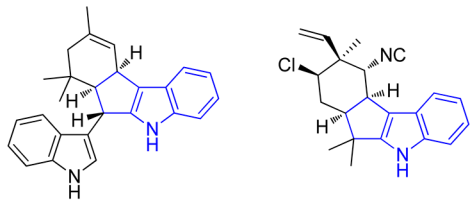


Figure 1. Biologically active compounds containing the cyclopenta[*b*]-indole unit.

Zhu et al. reported the chemistry of α-isocyanoacetic acid[11] (III) and α-isocyano acetamide[12] (IV). In all of the transformations, the reaction sequence based on I and II is triggered by the nucleophilic addition of the α-carbanion; however, the reaction of III and IV is initiated by the nucleophilicity of the isonitrile carbon. Dömling et al. reported[13] an efficient two-step procedure to give complex polycyclic indole alkaloids involving a domino Ugi and Pictet−Spengler reaction, in which 2-isocyanoethylindole (V) was employed as the key component of the reaction (Figure 2).

Received: May 23, 2014
Published: August 22, 2014

   dx.doi.org/10.1021/jo501143m | *J. Org. Chem.* 2014, 79, 8577−8583

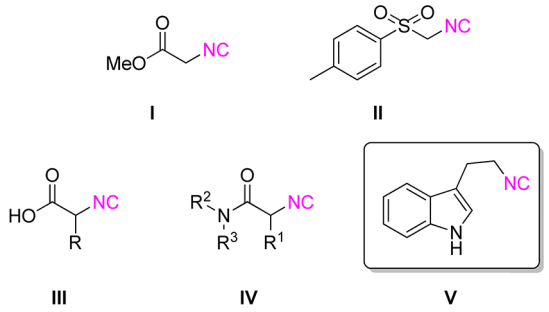
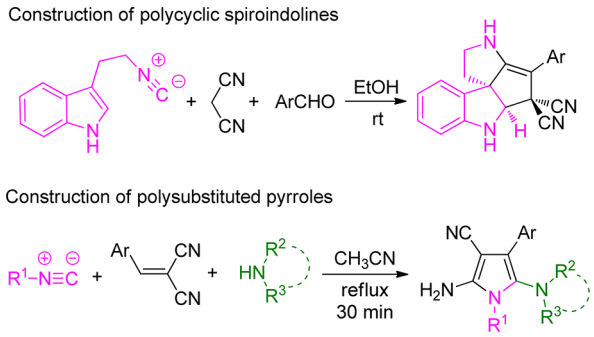


Figure 2. Functionalized isocyanides.

We have recently described[14] an efficient MCR (multicomponent reaction) between 2-isocyanoethylindole (V), malononitrile, and aromatic aldehydes, which affords excellent yields of polycyclic spiroindolines under catalyst-free conditions. Subsequently, we developed a highly efficient strategy for the synthesis of polysubstituted pyrrole derivatives,[15] in which amines were employed as nucleophiles in the reaction (Scheme 1).

Scheme 1. Novel Isocyanide-Based MCRs for the Synthesis of Heterocycles



MCRs involving an aldehyde, an active methylene group compound, and an isocyanate have become an important research area in modern organic chemistry.[16] The most commonly used active methylene compounds are 1,3-dicarbonyl and α-cyano derivatives. Surprisingly, the use of methyl cyanoacetate in these reactions is rare. As a continuation of our research program, we report herein two efficient domino reactions for the chemoselective synthesis of polycyclic spiroindolines and polysubstituted pyrroles from 2-isocyanoethylindole and *gem*-diactivated olefins under catalyst-free conditions.

RESULTS AND DISCUSSION

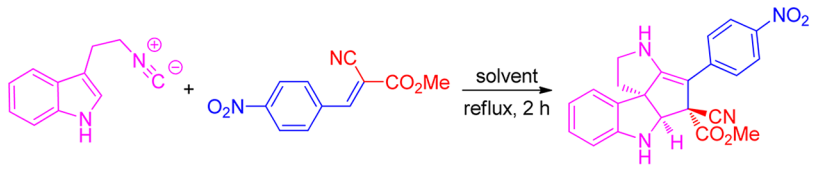
The synthesis of the pyrrolo[3′,2′:2,3]cyclopenta[1,2-*b*]indole derivatives **3** was attempted by a one-pot reaction of 2-isocyanoethylindole **1a** (1 mmol), methyl 2-cyanoacetate (1 mmol), and 4-nitrobenzaldehyde (1 mmol) in EtOH under reflux conditions. Unfortunately, this reaction did not work because 2-cyano-3-(4-nitrophenyl)acrylate **2d** could not be easily formed in situ under the above conditions. We further explored the reaction of **1a** with **2d** in EtOH under reflux conditions, and to our delight, the pyrrolo[3′,2′:2,3]cyclopenta-[1,2-*b*]indole derivative **3d** was obtained. With a view to identifying an ideal solvent for this transformation, various solvents were investigated, and the results are summarized in Table 1. Investigational results indicated that EtOH was the best reaction madium, and the reaction was found to yield 88% of the desired product **3d** (Table 1, entry 5).

Under the above modified conditions, the scope of 2-isocyanoethylindoles and *gem*-diactivated olefins was evaluated (Table 2). The reaction of 2-isocyanoethylindole **1a** with various substituted 2-cyano-3-phenyl acrylates **2** afforded the desired pyrrolo[3′,2′:2,3]cyclopenta[1,2-*b*]indole derivatives **3** in moderate to good yields, in most cases.

Notably, 2-cyano-3-phenyl acrylate substrates with a strongly electron-withdrawing substituent (−NO_2 or −SO_2Me, **2c** or **2g**) afforded the desired products **3c** or **3g** in 92% and 80% yields, respectively. When 2-cyano-3-phenyl acrylate substrates bearing −Cl and −Br groups were used, the reactions afforded the desired products (**3e** and **3f**) in moderate yields. While 2-isocyanoethylindole **1a** was replaced by 3-(2-isocyanoethyl)-5-methyl-1*H*-indole **1b** and was used to react with methyl 2-cyano-3-(4-cyanophenyl)acrylate, the desired product **3k** was obtained in 66% yield. Subsequently, 5-chloro-3-(2-isocyanoethyl)-1*H*-indole **1c** was used to react with methyl 2-cyano-3-(4-cyanophenyl)acrylate, and the reaction afforded the desired product **3l** in 85% yield (Scheme 2). However, when the 2-cyano-3-phenyl acrylate substrate with an electron-donating substituent was employed in this reaction, no desired product was obtained. The structure of product **3d** was further confirmed by X-ray analysis.

During our investigation, the chemoselectivity of this reaction was evaluated by using an equivalent amount of secondary amine as nucleophile.[15] For this aim, we have examined the reaction of

Table 1. Optimization of the Reaction Conditions



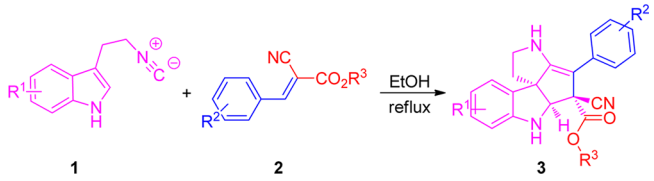
1a **2d** **3d**

entry	solvent	yield (%)[a]
1	MeOH	26
2	$CHCl_3$	36
3	MeCN	71
4	THF	28
5	EtOH	92 (88[b])

[a]Reaction conditions: **1a** (1 mmol), **2d** (1 mmol), solvent (2 mL). The yields were determined by LC analysis using biphenyl as the internal standard. [b]Isolated yield.

dx.doi.org/10.1021/jo501143m | J. Org. Chem. 2014, 79, 8577−8583

Table 2. Construction of Pyrrolo[3′,2′:2,3]cyclopenta[1,2-*b*]indoles 3[a]



1 2 3

entry	R^1	R^2	R^3	product	time (h)	*dr*	yield (%)
1	H	H	Me	**3a**	5	>20:1	35
2	H	2-NO_2	Et	**3b**	3	>20:1	77
3	H	3-NO_2	Et	**3c**	2	>20:1	92
4	H	4-NO_2	Me	**3d**	2	>20:1	88
5	H	4-Cl	Me	**3e**	5	>20:1	42
6	H	4-Br	Me	**3f**	5	>20:1	53
7	H	4-SO_2Me	Me	**3g**	2	>20:1	80
8	H	4-SO_2Me	Et	**3h**	3	>20:1	75
9	H	4-CN	Et	**3i**	2	>20:1	66
10	H	4-CN	Me	**3j**	2	>20:1	82
11	5-Me	4-CN	Me	**3k**	2	>20:1	66
12	5-Cl	4-CN	Me	**3l**	2	>20:1	85

[a]Isolated yield.

Scheme 2. Proposed Mechanism

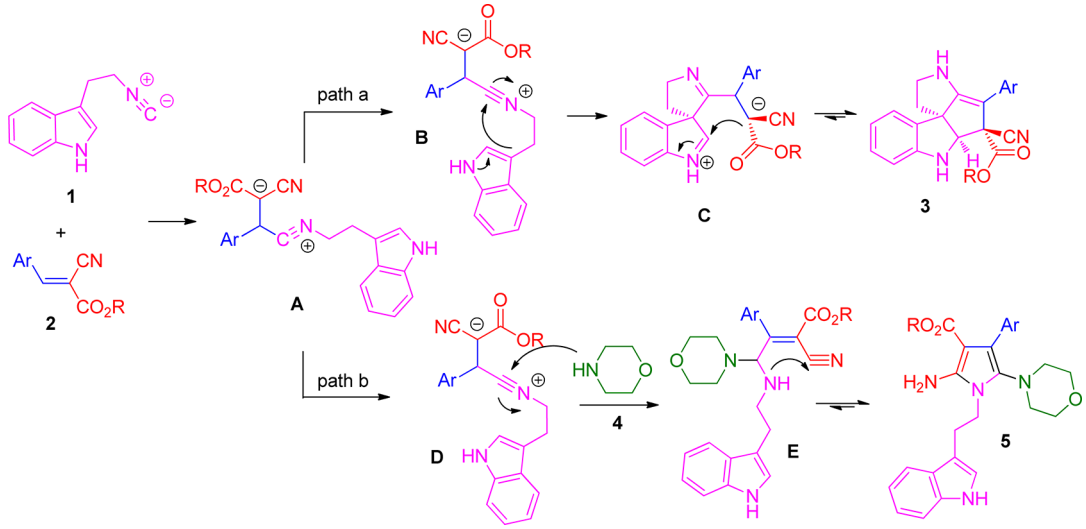
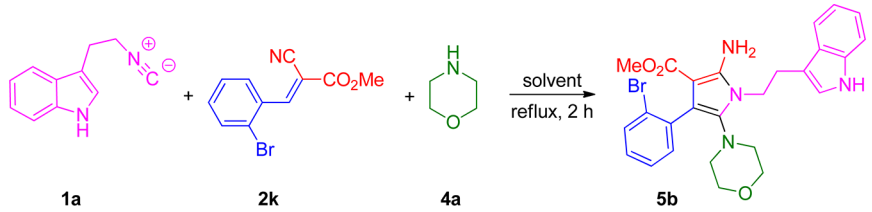


Table 3. Optimization of the Reaction Conditions[a]



1a 2k 4a 5b

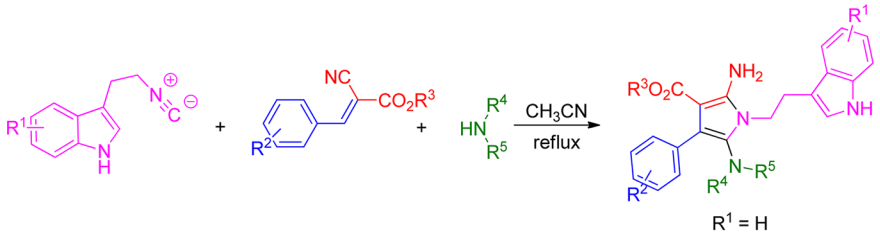
entry	solvent	yield (%)[b]
1	MeOH	25
2	toluene	33
3	CH_3CN	59
4	THF	33
5	EtOH	40

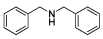
[a]Reaction conditions: **1a** (1 mmol), **2k** (1 mmol), **4a** (1 mmol), solvent (2 mL). [b]Isolated yield.

methyl 3-(2-bromophenyl)-2-cyanoacrylate with 2-isocyanoethylindole and morpholine in EtOH under reflux conditions, and the expected product polycyclic spiroindoline **3** was not obtained. With the isolation and characterization of the main

dx.doi.org/10.1021/jo501143m | *J. Org. Chem.* 2014, 79, 8577−8583

Table 4. Scope of the Construction of Polysubstituted Pyrroles 5[a]



1		2	4			5
Entry	R^2	R^3	R_3NHR_4	Product	Time (h)	Yield (%)
1	H	Me		**5a**	4	38
2	2-Br	Me		**5b**	2	59
3	3-OMe	Me		**5c**	3	44
4	4-Cl	Me		**5d**	2	24
5	2-Cl	Me		**5e**	3	58
6	2-Cl	Et		**5f**	3	50
7	2-Cl	Me		**5g**	2	57
8	2-Cl	Et		**5h**	2	55
9	4-Me	Me		**5i**	2	44
10	4-Me	Me		**5j**	4	34
11	4-Me	Me		**5k**	4	46
12	4-Me	Me		**5l**	4	22

[a]Isolated yield.

product, the reaction afforded polysubstituted pyrrole **5** under this condition. Then, we investigated the model reaction in various other solvents (Table 3). The desired product **5b** was obtained in all the tested solvents, but MeCN gave the best isolated yield (59%) (Table 3, entry 3).

The substrate scope of the reaction was evaluated by using readily available starting materials under the optimized solvent conditions (Table 4). All reactions of **1a** with various *gem*-diactivated olefins **2** and secondary amines **4** led to the corresponding polysubstituted pyrroles **5a**–**l**. When the *gem*-diactivated olefin **2** with a strongly electron-donating substituent (−OCH_3) on the aromatic ring was utilized, the reactions afforded the desired product **5c** in 44% yield. When *gem*-diactivated olefins **2** bearing −Br and −Cl groups were used, the corresponding polysubstituted pyrroles **5b** and **5e** could be obtained in 59% and 58% yields, respectively. Then, reactions of a variety of substituted secondary amines **4** with 2-isocyanoethylindole **1a** and methyl 2-cyano-3-*p*-tolyl)acrylate **2o** were also surveyed. When cyclic secondary amines such as morpholine, piperidine, and 1,2,3,4-tetrahydroisoquinoline were used in the reaction, the desired products (**4i**, **4j**, and **4k**, respectively) were obtained in moderate yields (34%–46%). The use of dibenzyl amine afforded the desired product **5l** in 22% yield.

On the basis of the above outcomes, a possible reaction mechanism was proposed in Scheme 2. First, the *gem*-diactivated olefin **2** undergoes nucleophilic addition by isocyanide **1** to provide intermediate **A**, followed by two intramolecular nucleophilic additions to afford desired products **3**. When a secondary amine was employed in this reaction system, intermediate **A** can undergo nucleophilic attack by the amine to afford intermediate **E**. Subsequent nucleophilic attack by the nitrogen atom on the nitrile of intermediate E afforded polysubstituted pyrroles **5**.

CONCLUSION

In conclusion, two highly efficient isocyanide-based domino reactions for the chemoselective synthesis of novel polycyclic spiroindolines and polysubstituted pyrroles from 2-isocyanoethylindoles with *gem*-diactivated olefins and secondary amines have been developed. These reactions proceeded smoothly and afforded the desired products in moderate to good yields under catalyst-free conditions.

EXPERIMENTAL SECTION

General Experimental Information. All the solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using silica gel (300–400 mesh) with the indicated solvents. Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and number of protons. High-resolution mass spectra were obtained using a high-resolution ESI-TOF mass spectrometer.

General Procedure for the Synthesis of Polycyclic Spiroindolines 3 and Polysubstituted Pyrroles 5. (**3a**–**3l**): Typically, in a 25 mL round-bottom flask, substituted 2-cyano-3-phenyl acrylate (1.0 mmol) with 3-(2-isocyanoethyl)-1*H*-indole (1.0 mmol) was carried out in EtOH (2.0 mL) under reflux conditions. Upon completion, monitored by TLC, the residue was directly purified by

dx.doi.org/10.1021/jo501143m | J. Org. Chem. 2014, 79, 8577–8583

flash column chromatography by using ethyl acetate and petroleum ether as eluents to afford the pure product.

(**5a**−**5h**) Typically, in a 25 mL round-bottom flask, substituted 2-cyano-3-phenyl acrylate (1.0 mmol) was dissolved in CH_3CN (2.0 mL), and then amine (1.0 mmol) with 3-(2-isocyanoethyl)-1*H*-indole (1.0 mmol) was added to the reaction system under reflux conditions. Upon completion, monitored by TLC, the residue was directly purified by flash column chromatography by using ethyl acetate and petroleum ether as eluents to afford the pure product.

*Methyl 5-Cyano-4-phenyl-1,2,3,5,5a,6-hexahydropyrrolo-[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3a**).* (0.125g, 35%), White solid; m.p.: 186−187 °C; IR (KBr, ν, cm^{-1}): 3369, 3347, 2233, 1733, 1648, 1469, 1421; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.26−7.24 (m, 2H), 7.11−7.00 (m, 6H), 6.92 (s, 1H), 6.68−6.63 (m, 2H), 4.36 (s, 1H), 4.04−4.00 (m, 1H), 3.88−3.86 (m, 1H), 3.73(s, 3H), 2.17−2.14 (m, 1H), 1.80−1.78 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) (δ, ppm): 171.3, 158.1, 149.3, 135.3, 131.8, 129.1, 128.9, 123.9, 123.8, 122.7, 118.4, 117.8, 109.8, 107.9, 93.7, 72.4, 68.8, 67.9, 53.9, 51.2, 36.6; HRMS (ESI-TOF) *m*/*z*: [M] Calcd for $C_{22}H_{19}N_3O_2$ 357.1477; Found 357.1466.

*Ethyl 5-Cyano-4-(2-nitrophenyl)-1,2,3,5,5a,6-hexahydropyrrolo-[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3b**).* (0.320g, 77%), Yellow solid; m.p.: 198−199 °C; IR (KBr, ν, cm^{-1}): 3412, 2225, 1746, 1687, 1601, 1525, 1471, 1350, 1228, 1068; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.94 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.77 (s, 1H), 6.67 (t, *J* = 8.4 Hz, 2H), 6.35 (s, 1H), 4.54 (s, 1H), 4.09−3.97 (m, 2H), 3.86−3.84 (m, 1H), 3.71−3.68 (m, 1H), 3.16−3.14 (m, 1H), 1.83−1.79 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 168.01, 160.3, 149.8, 149.2, 132.6, 131.8, 130.7, 128.9, 128.6, 128.0, 124.6, 122.4, 118.1, 117.5, 109.3, 86.6, 71.8, 69.6, 65.5, 62.1, 49.6, 37.0, 13.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{23}H_{20}N_4NaO_4$ 439.1382; Found 439.1385.

*Ethyl 5-Cyano-4-(3-nitrophenyl)-1,2,3,5,5a,6-hexahydropyrrolo-[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3c**).* (0.383g, 92%), Yellow solid; m.p.: 216−217 °C; IR (KBr, ν, cm^{-1}): 3417, 2235, 1742, 1646, 1528, 1470, 1349, 1238, 1076, 1029; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.82 (d, *J* = 6.8 Hz, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.58−7.53 (m, 2H), 7.15 (d, *J* = 6.8 Hz, 1H), 7.07 (t, *J* = 6.8 Hz, 1H), 7.02 (s, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 4.40 (s, 1H), 4.24−4.22(m, 2H), 4.09−4.07 (m, 1H), 3.93−3.91 (m, 1H), 2.23−2.16 (m, 1H), 1.83−1.81 (m, 1H), 1.17 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 169.8, 160.4, 148.8, 148.1, 136.7, 130.9, 129.9, 129.8, 128.9, 122.3, 118.1, 117.6, 117.0, 116.9, 109.4, 91.4, 71.9, 68.1, 67.8, 62.6, 51.1, 36.1, 13.7; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{23}H_{21}N_4O_4$ 417.1563; Found 417.1562.

*Methyl 5-Cyano-4-(4-nitrophenyl)-1,2,3,5,5a,6-hexahydro-pyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3d**).* (0.354g, 88%), Yellow solid; m.p.: 192−193 °C; IR (KBr, ν, cm^{-1}): 3381, 2238, 1739, 1639, 1582, 1505, 1342, 1251, 1108, 1074; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 8.12 (s, 2H), 8.10 (s, 1H),7.20 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.09−7.07 (m, 1H), 7.06 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 4.43 (s, 1H), 4.16−4.13 (m, 1H), 3.98−3.94 (m, 1H), 3.77 (s, 3H), 2.24−2.22 (m, 1H), 1.86−1.81 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 170.3, 162.8, 148.7, 142.1, 141.7, 130.6, 129.0, 124.1, 122.9, 122.3, 118.2, 116.9, 109.6, 92.4, 71.7, 68.3, 67.8, 53.8, 51.6, 35.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{22}H_{18}N_4NaO_4$ 425.1226; Found 425.1226.

*Methyl 4-(4-Chlorophenyl)-5-cyano-1,2,3,5,5a,6-hexahydro-pyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3e**).* (0.164g, 42%), White solid; m.p.: 147−148 °C; IR (KBr, ν, cm^{-1}): 3370, 3347, 2227, 1732, 1649, 1607, 1496, 1469, 1434; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.32−7.30 (m, 3H), 7.11−7.06 (m, 4H), 6.94 (s, 1H), 6.69−6.64 (m, 2H), 4.37 (s, 1H), 4.03−4.00 (m, 1H), 3.88−3.86 (m, 1H), 3.73 (s, 3H), 2.17−2.15 (m, 1H), 1.80−1.79 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) (δ, ppm): 171.0, 158.9, 149.3, 134.3, 131.6, 129.2, 128.8, 127.8, 125.4, 122.7, 118.5, 117.7, 109.8, 92.5, 72.3, 68.7, 68.0, 54.0, 51.3, 36.6; HRMS (ESI-TOF) *m*/*z*: [M] Calcd for $C_{22}H_{18}ClN_3O_2$ 391.1088; Found 391.1078.

*Methyl 4-(4-Bromophenyl)-5-cyano-1,2,3,5,5a,6-hexahydro-pyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3f**).* (0.231g, 53%), White solid; m.p.: 140−141 °C; IR (KBr, ν, cm^{-1}): 3370, 3347, 2236, 1733, 1648, 1605, 1492, 1468, 1435; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.44−7.40 (m, 2H), 7.28 (s, 1H), 7.11−7.02 (m, 4H), 6.93 (s, 1H), 6.65−6.63 (m, 2H), 4.35 (s, 1H), 4.02−4.00 (m, 1H), 3.88−3.86 (m, 1H), 3.73 (s, 3H), 2.17−2.15 (m, 1H), 1.79−1.77 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) (δ, ppm): 171.0, 159.0, 149.2, 134.6, 131.7, 131.5, 129.2, 125.8, 122.7, 118.5, 117.7, 116.0, 109.8, 92.5, 72.3, 68.6, 68.0, 54.0, 51.4, 36.5; HRMS (ESI-TOF) *m*/*z*: [M] Calcd for $C_{22}H_{18}BrN_3O_2$ 435.0582; Found 435.0582.

*Methyl 5-Cyano-4-(4-(methylsulfonyl)phenyl)-1,2,3,5,5a,6-hexahydropyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3g**).* (0.348g, 80%), White solid; m.p.: 171−172 °C; IR (KBr, ν, cm^{-1}): 3389, 2235, 1734, 1639, 1583, 1468, 1302, 1247; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.79 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 6.69−6.62 (m, 2H), 4.40 (s, 1H), 4.12−4.11 (m, 1H), 3.92−3.90 (m, 1H), 3.77 (s, 3H), 3.15 (s, 3H), 2.22−2.19 (m, 1H), 1.84−1.81 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) (δ, ppm): 170.9, 161.7, 149.2, 140.5, 134.5, 131.3, 129.4, 127.8, 123.5, 122.7, 118.6, 117.5, 109.9, 92.5, 72.2, 68.5, 68.3, 54.2, 51.8, 44.2, 36.3; HRMS (ESI-TOF) *m*/*z*: [M] Calcd for $C_{23}H_{21}N_3O_4S$ 435.1253; Found 435.1243.

*Ethyl 5-Cyano-4-(4-(methylsulfonyl)phenyl)-1,2,3,5,5a,6-hexa-hydropyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3h**).* (0.337g, 75%), White solid; m.p.: 138−139 °C; IR (KBr, ν, cm^{-1}): 3391, 2234, 1732, 1644, 1584, 1472, 1306, 1245, 1146, 1095, 1073; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.77 (s, 2H), 7.75 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.09−7.05(m, 1H) 7.03 (s, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.64 (t, *J* = 7.2 Hz, 1H), 4.37 (s, 1H), 4.25−4.22 (m, 2H), 4.11−4.09 (m, 1H), 3.96−3.94 (m, 1H), 3.14 (s, 3H), 2.22−2.19 (m, 1H), 1.84−1.81 (m, 1H), 1.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) (δ, ppm): 169.8, 161.2, 148.8, 140.1, 134.1, 130.9, 128.9, 127.2, 123.2, 122.2, 118.1, 117.1, 109.5, 92.2, 71.8, 68.0, 67.9, 62.6, 51.2, 43.8, 35.9, 13.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{24}H_{23}N_3NaO_4S$ 472.1307; Found 472.1306.

*Ethyl 5-Cyano-4-(4-cyanophenyl)-1,2,3,5,5a,6-hexahydropyrrolo-[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3i**).* (0.261g, 66%), White solid; m.p.: 162−163 °C; IR (KBr, ν, cm^{-1}): 3409, 2222, 1737, 1643, 1594, 1514, 1471, 1401, 1249, 1075; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.81 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 4.35 (s, 1H), 4.23−4.20 (m, 2H), 4.10−4.08 (m, 1H), 3.95−3.90 (m, 1H), 2.21−2.18(m, 1H), 1.82−1.78 (m, 1H), 1.59 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 169.8, 161.3, 148.8, 139.7, 132.2, 130.8, 128.9, 123.4, 122.3, 119.4, 118.1, 117.1, 109.5, 104.1, 92.2, 71.7, 68.1, 67.9, 62.5, 51.3, 36.0, 13.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{24}H_{20}N_4NaNO_2$ 419.1484; Found 419.1492.

*Methyl 5-Cyano-4-(4-cyanophenyl)-1,2,3,5,5a,6-hexahydro-pyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3j**).* (0.313g, 82%), White solid; m.p.: 225−226 °C; IR (KBr, ν, cm^{-1}): 3409, 2217, 1740, 1643, 1592, 1512, 1301, 1249, 1029; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.82(s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.17−7.12(m, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.01(s, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.64 (t, *J* = 7.2 Hz, 1H), 4.39 (s, 1H), 4.18−4.08 (m, 1H), 3.94−3.92 (m, 1H), 3.73 (s, 3H), 2.23−2.16 (m, 1H), 1.83−1.79 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 170.4, 161.4, 148.7, 139.7, 132.3, 130.8, 128.9, 123.3, 122.3, 119.4, 118.1, 117.0, 109.5, 104.2, 92.2, 71.7, 68.1, 67.8, 53.7, 51.4, 35. 9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{23}H_{18}N_4NaNO_2$ 405.1327; Found 405.1333.

*Methyl 5-Cyano-4-(4-cyanophenyl)-9-methyl-1,2,3,5,5a,6-hexahydropyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3k**).* (0.261g, 66%), White solid; m.p.: 246−247 °C; IR (KBr, ν, cm^{-1}): 3424, 3395, 2228, 1750, 1649, 1601, 1492, 1432, 1247; ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.81 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 4.37 (s, 1H), 4.12−4.09 (m, 1H), 3.95−3.93 (m, 1H), 3.75 (s, 3H), 2.20 (s, 3H), 2.19−2.16(m, 1H), 1.84−1.73 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 170.9, 162.0, 147.0, 140.2, 132.8, 131.5, 129.9, 127.3, 123.8, 123.2, 119.9, 117.5, 110.1,

dx.doi.org/10.1021/jo501143m | J. Org. Chem. 2014, 79, 8577−8583

104.6, 92.6, 72.6, 68.6, 68.3, 54.1, 51.9, 36.3, 21.0; HRMS (ESI-TOF) m/z: [M] Calcd for $C_{24}H_{20}N_4O_2$ 396.1586; Found 396.1587.

*Methyl 9-Chloro-5-cyano-4-(4-cyanophenyl)-1,2,3,5,5a,6-hexahydropyrrolo[3′,2′:2,3]cyclopenta[1,2-b]indole-5-carboxylate (**3l**).* (0.354g, 85%), White solid; m.p.: 262−263 °C; IR (KBr, ν, cm^{-1}): 3429, 3398, 2228, 1750, 1648, 1600, 1472, 1430, 1245; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.84 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.22 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.12−7.10 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 4.46 (s, 1H), 4.10−4.09 (m, 1H), 3.92−3.91 (m, 1H), 3.76 (s, 3H), 2.25−2.17(m, 1H), 1.88−1.84 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 170.6, 161.0, 148.3, 139.9, 133.1, 132.8, 129.2, 123.9, 122.6, 121.7, 119.0, 117.5, 111.1, 105.0, 92.9, 72.4, 68.5, 68.2, 54.2, 51.8, 36.0; HRMS (ESI-TOF) m/z: [M] Calcd for $C_{23}H_{17}ClN_4O_2$ 416.1040; Found 416.1033.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-5-morpholino-4-phenyl-1H-pyrrole-3-carboxylate (**5a**).* (0.169g, 38%), White solid; m.p: 215−216 °C; IR (KBr, ν, cm^{-1}): 3419, 3338, 3301, 1670, 1608, 1503, 1440, 1428, 1369, 1110; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.84 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.30−7.20 (m, 3H), 7.17−6.98 (m, 5H), 6.11 (s, 2H), 4.03−3.99 (m, 2H), 3.36−3.35 (m, 5H), 3.05−3.01 (m, 4H), 2.50−2.30 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.3, 144.2, 136.7, 136.6, 131.8, 131.3, 127.7, 127.3, 126.4, 123.5, 121.4, 118.8, 118.7, 114.3, 111.8, 111.8, 90.1, 67.1, 52.9, 49.9, 41.6, 24.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{29}N_4O_3$ 445.2240; Found 445.2239.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(2-bromophenyl)-5-morpholino-1H-pyrrole-3-carboxylate (**5b**).* (0.308g, 59%), White solid; m.p: 136−138 °C; IR (KBr, ν, cm^{-1}): 3443, 3335, 1638, 1613, 1517, 1443, 1373, 1291, 1264, 1212, 1186; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 8.12 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.25−7.15 (m, 5H), 6.82 (d, J = 2.0 Hz, 1H), 4.64 (s, 2H), 4.10−3.96 (m, 2H), 3.46 (s, 3H), 3.36−1.70 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 166.7, 142.4, 137.4, 136.2, 132.6, 131.9, 131.6, 128.3, 127.0, 126.6, 126.4, 122.8, 122.3, 119.8, 118.3, 114.2, 112.0, 111.4, 92.3, 67.4, 50.1, 41.4, 25.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}BrN_4O_3$ 523.1345; Found 523.1321.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(3-methoxyphenyl)-5-morpholino-1H-pyrrole-3-carboxylate (**5c**).* (0.209g, 44%), White solid; m.p: 208−209 °C; IR (KBr, ν, cm^{-1}): 3329, 3282, 1664, 1605, 1524, 1502, 1492, 1461, 1449, 1282; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.83 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.19−6.97 (m, 4H), 6.81−6.70 (m, 3H), 6.11 (s, 2H), 4.01−3.98 (m, 2H), 3.73 (s, 3H), 3.38−3.34 (m, 5H), 3.04−3.00 (m, 4H), 2.49−2.28 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.3, 158.4, 144.2, 138.0, 136.6, 131.7, 128.2, 127.7, 123.9, 123.5, 121.4, 118.8, 118.7, 117.1, 114.1, 111.8, 111.8, 90.0, 67.1, 60.2, 55.3, 52.8, 49.9, 41.6, 24.8, 21.2, 14.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{31}N_4O_4$ 475.2345; Found 475.2338.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(4-chlorophenyl)-5-morpholino-1H-pyrrole-3-carboxylate (**5d**).* (0.115g, 24%), White solid; m.p: 235−236 °C; IR (KBr, ν, cm^{-1}): 3463, 3336, 1671, 1618, 1503, 1488, 1425, 1363, 1137, 1105; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.83 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.33−7.31 (m, 3H), 7.17−6.99 (m, 5H), 6.13 (s, 2H), 4.02−3.98 (m, 2H), 3.39−3.34 (m, 5H), 3.04−3.00 (m, 4H), 2.49−2.28 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.1, 144.3, 136.6, 135.7, 133.0, 132.0, 131.1, 127.7, 127.3, 123.5, 121.4, 118.8, 118.7, 112.9, 111.8, 89.8, 67.1, 52.9, 50.0, 41.7, 24.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}ClN_4O_3$ 479.1850; Found 479.1845.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(2-chlorophenyl)-5-morpholino-1H-pyrrole-3-carboxylate (**5e**).* (0.277g, 58%), White solid; m.p: 125−126 °C; IR (KBr, ν, cm^{-1}): 3459, 3364, 3257, 1637, 1599, 1511, 1452, 1378, 1285; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.81 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.39−7.00 (m, 8H), 6.05 (s, 2H), 4.04−4.01 (m, 2H), 3.34−3.02 (m, 9H), 2.49−2.19 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.0, 143.9, 136.6, 136.0, 135.4, 133.4, 131.6, 128.8, 128.7, 127.7, 126.3, 123.6, 121.4, 118.8, 118.7, 111.8, 111.6, 111.1, 90.3, 67.0, 50.0, 41.5, 24.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}ClN_4O_3$ 479.1850; Found 479.1845.

*Ethyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(2-chlorophenyl)-5-morpholino-1H-pyrrole-3-carboxylate (**5f**).* (0.246g, 50%), White solid; m.p: 190−191 °C; IR (KBr, ν, cm^{-1}): 3420, 3249, 1660, 1604, 1511, 1439, 1285, 1261, 1207, 1159; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.82 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.41−7.22 (m, 5H), 7.07−7.00 (m, 3H), 6.04 (s, 2H), 4.04−3.68 (m, 4H), 3.33−3.03 (m, 6H), 2.49−2.22 (m, 4H), 0.76 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 165.8, 144.0, 136.6, 136.3, 135.5, 133.4, 131.4, 128.7, 128.6, 127.7, 126.2, 123.6, 121.4, 118.8, 118.7, 111.8, 111.6, 111.1, 90.6, 67.0, 57.8, 41.4, 24.8, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{30}ClN_4O_3$ 493.2006; Found 493.2011.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(2-chlorophenyl)-5-(3,4-dihydroisoquinolin-2(1H)-yl)-1H-pyrrole-3-carboxylate (**5g**).* (0.299g, 57%), White solid; m.p: 209−211 °C; IR (KBr, ν, cm^{-1}): 3426, 3322, 1640, 1613, 1519, 1442, 1375, 1291, 1265, 1243, 1211; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.83 (s, 1H), 7.44−6.85 (m, 12H), 6.60 (s, 1H), 6.13 (s, 2H), 4.00−3.66 (m, 4H), 3.38 (s, 3H), 3.08−2.49 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.1, 144.1, 136.5, 134.2, 129.2, 128.9, 128.7, 127.6, 126.4, 126.3, 125.9, 123.6, 121.3, 118.8, 118.5, 111.7, 90.5, 50.0, 41.7, 25.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{30}ClN_4O_2$ 525.2057; Found 525.2047.

*Ethyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-4-(2-chlorophenyl)-5-(3,4-dihydroisoquinolin-2(1H)-yl)-1H-pyrrole-3-carboxylate (**5h**).* (0.296g, 55%), White solid; m.p: 175−176 °C; IR (KBr, ν, cm^{-1}): 3459, 3363, 3263, 1632, 1599, 1512, 1452, 1378, 1284, 1208; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.80 (s, 1H), 7.42−7.40 (m, 6H), 7.27−6.95 (m, 6H), 6.56 (s, 1H), 6.09 (s, 2H), 3.96−3.71 (m, 6H), 3.04−2.49 (m, 6H), 0.77 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 165.8, 144.1, 136.5, 134.2, 129.2, 128.8, 128.6, 127.5, 126.4, 126.2, 125.9, 123.6, 121.3, 118.8, 118.5, 111.7, 90.7, 57.9, 41.7, 25.3, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{32}ClN_4O_2$ 539.2214; Found 539.2200.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-5-morpholino-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**5i**).* (0.202g, 44%), White solid; m.p: 225−226 °C; IR (KBr, ν, cm^{-1}): 3465, 1667, 1617, 1512, 1502, 1427, 1363, 1136; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.84 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.12−6.98 (m, 7H), 6.10 (s, 2H), 4.00−3.98 (m, 2H), 3.37−3.35 (m, 5H), 3.05−3.00 (m, 4H), 2.49−2.32 (m, 7H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.4, 144.1, 136.6, 135.1, 133.6, 131.8, 131.2, 128.0, 127.7, 123.5, 121.4, 118.8, 118.7, 114.2, 111.8, 111.8, 90.1, 67.1, 52.9, 49.9, 41.6, 24.9, 21.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{31}N_4O_3$ 459.2396; Found 459.2407.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-5-(piperidin-1-yl)-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**5j**).* (0.155g, 34%), White solid; m.p: 101−102 °C; IR (KBr, ν, cm^{-1}): 3414, 3331, 1647, 1604, 1511, 1453, 1341, 1244, 1107; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.86 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.09−7.05 (m, 5H), 6.99 (t, J = 7.6 Hz, 1H), 6.04 (s, 2H), 3.98−3.94 (m, 2H), 3.37 (s, 3H), 3.02−2.98 (m, 2H), 2.63−2.61 (m, 2H), 2.35−2.31 (m, 5H), 1.50−1.32 (m, 5H), 0.89−0.87 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.4, 144.2, 136.6, 134.9, 133.8, 133.1, 131.2, 127.8, 127.7, 123.4, 121.4, 118.8, 118.7, 113.6, 111.8, 111.8, 90.0, 60.2, 54.1, 49.8, 41.6, 26.8, 25.1, 24.1, 21.3, 14.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{33}N_4O_2$ 457.2604; Found 457.2613.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-5-(3,4-dihydroisoquinolin-2(1H)-yl)-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**5k**).* (0.232g, 46%), White solid; m.p: 198−199 °C; IR (KBr, ν, cm^{-1}): 3434, 3347, 3258, 1656, 1611, 1501, 1439, 1365, 1341, 1189; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.79 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.13−6.89 (m, 11H), 6.57 (d, J = 7.2 Hz, 1H), 6.13 (s, 2H), 3.95−3.83 (m, 4H), 3.40 (s, 3H), 3.02−2.49 (m, 6H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.4, 144.3, 136.5, 135.4, 135.2, 134.3, 133.6, 131.8, 131.1, 129.2, 128.0, 127.5, 126.5, 126.3, 125.9, 123.5, 121.3, 118.8, 118.5, 114.8, 111.7, 111.5, 90.1, 54.8, 51.3, 49.9, 41.7, 30.3, 25.3, 21.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{33}N_4O_2$ 505.2604; Found 505.2600.

*Methyl 1-(2-(1H-Indol-3-yl)ethyl)-2-amino-5-(dibenzylamino)-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**5l**).* (0.125g, 22%), Colorless oil; IR (KBr, ν, cm^{-1}): 3406, 3325, 1638, 1609, 1512, 1439, 1371, 1292, 1245, 1112; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 10.88 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.37−7.31 (m, 4H), 7.24−7.19 (m, 8H),

dx.doi.org/10.1021/jo501143m | J. Org. Chem. 2014, 79, 8577−8583

7.14−7.12 (m, 3H), 7.07−7.05 (m, 2H), 6.99−6.95 (m, 1H), 5.94 (s, 2H), 3.87−3.68 (m, 6H), 3.39 (s, 3H), 2.74−2.70 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 166.4, 144.2, 141.2, 139.3, 136.5, 135.4, 133.8, 131.4, 130.0, 129.0, 128.6, 128.4, 128.2, 127.5, 127.0, 123.2, 121.5, 119.1, 118.7, 116.1, 111.8, 111.6, 90.5, 59.0, 52.6, 49.9, 41.3, 24.3, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{37}N_4O_2$ 569.2917; Found 569.2902.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all pure products, density functional theory calculation results, and X-ray structure of compound **3d**. 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Natural Science Foundation of China (Nos. 21172162, 21372174), the Ph.D. Programs Foundation of Ministry of Education of China (20132011300004), the Young National Natural Science Foundation of China (No. 21202111), the Young Natural Science Foundation of Jiangsu Province (BK2012174), Key Laboratory of Organic Synthesis of Jiangsu Province (KJS1211), PAPD, and Soochow University for financial support.

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