JOC The Journal of Organic Chemistry

Article

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Allylic Amination and *N*-Arylation-Based Domino Reactions Providing Rapid Three-Component Strategies to Fused Pyrroles with Different Substituted Patterns

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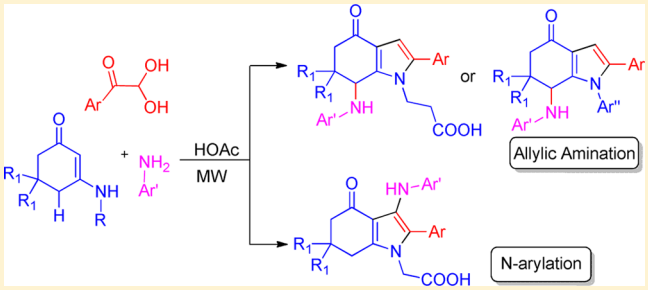
Supporting Information

ABSTRACT: New three-component domino reaction providing divergent approaches to multifunctionalized fused pyrroles with different substituted patterns have been established (40 examples). The direct C(sp^3)−N bond formation was achieved through intermolecular allylic amination in a one-pot operation, and *N*-arylation of amines was realized by varying *N*-amino acid enaminones. The reaction is easy to perform simply by mixing three common reactants in acetic acid under microwave heating. The reaction proceeds at fast rates and can be finished within 30 min, which makes workup convenient to give good chemical yields.



INTRODUCTION

Fused pyrroles are among the most ubiquitous heterocycles in nature. They are common structural motifs in many biologically active molecules and pharmaceutical substances.[1] These compounds are also widely employed as versatile building blocks in synthetic organic chemistry. In the past several decades, many methodologies for the synthesis of fused pyrroles have been developed, which involved rearrangement−cyclization of alkynol,[2a] alkynyl ketones,[2b] cycloketone annulations,[3] metal-catalyzed cascade cyclization of alkynes,[4] and 1,3-dipolar cycloadditions of müchnone derivatives.[5] The development of new alternate and more efficient strategies to this family of heterocyclic compounds, minimizing the formation of waste and byproduct, continues to be of great interest and challenging. To the best of our knowledge, a one-pot multicomponent synthesis of fused pyrroles via metal-free domino reaction involving intermolecular allylic amination has not been well documented yet.

In the meanwhile, allylic sp^3 C−H amination processes that allow the direct conversion of C−H bonds to C−N bonds are of utmost importance regarding their potential in organic chemistry for the synthesis of biologically active nitrogen-containing compounds.[6−9] Many efforts have been devoted to this methodology to improve its efficiency and selectivity, which made it more powerful and applicable.[10] Among them, the metal-catalyzed amination reactions have taken a dominant position, and a variety of transition metal species have been utilized in *N*-functionalization of saturated hydrocarbons, such as Rh,[11] Ru,[12] Mn,[13a] Ag,[13b] Cu,[14] Pd,[15a] Co,[15b,c] and Fe.[15d] The prevalence of amines in natural products along with their unique industrial and pharmaceutical applications via intermolecular amination remains to be a challenge. On the other hand, there has been urgent demand in the design of green and sustainable transformations since the transition metals involved in these procedures are generally thought not to be environmentally friendly. Therefore, the development of an efficient and broadly applicable intermolecular allylic amination without the use of metal catalysts is more desirable.

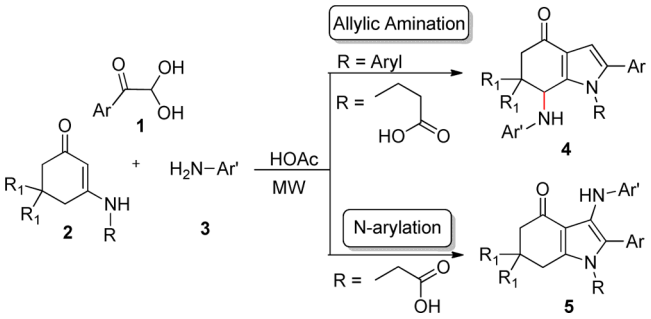
In the past several years, we and others have developed a series of domino reactions that provided easy access to multiple functionalized ring structures of chemical and pharmaceutical interest.[16−19] We also established new allylic functionalization to highly substituted indole derivatives.[17f] During the continuation of this project, we reasoned that whether the reaction can be directed toward allylic amination to form fused pyrrole derivatives when aliphatic carboxylic acids with soft nucleophilicity were replaced by aromatic amines with stronger nucleophilicity. With this notion in mind, the one-pot reaction of arylglyoxal monohydrate, *N*-aryl enaminones, and aromatic amines was performed to realize this type of intermolecular allylic amination. Interestingly, during the study on scope of enaminones, *N*-carboxyethyl enaminones were formed and led to the desired allylic ammoniated products **4**, whereas *N*-carboxymethyl counterparts occurred along another direction to form fused pyrroles **5** with different substituted patterns.

Received: June 25, 2012
Published: August 1, 2012

 © 2012 American Chemical Society dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

Herein, we would like to disclose these novel domino reactions for the synthesis of polyfunctionalized fused pyrroles with arylamino groups residing in different positions by varying *N*-substituted enaminones (Scheme 1). The attractive aspect of the present domino reaction is shown by the fact that the construction of pyrrole skeleton and the direct C(sp^3)−N bond formation were readily achieved via metal-free allylic amination in an intermolecular manner and in a one-pot operation. The metal-free *N*-arylation of amines was easily realized in domino fashion for the second reaction. During these domino processes, *N*-amino acid enaminones play a key role in the control of reaction pathways.

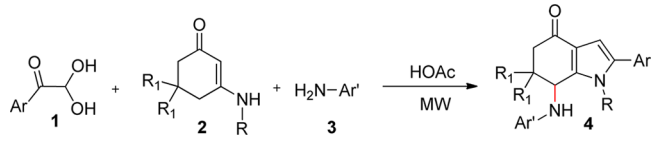
Scheme 1. Three-Component Domino Synthesis of Fused Pyrroles 4 and 5



RESULTS AND DISCUSSION

β-Enaminones, as important 1,3-bidonors, had been extensively applied to the construction of nitrogen-containing heterocycles.[20] Arylglyoxal monohydrate, as readily available 1,2-biacceptors,[21] can provide two active sites (C−O and C═O bonds), which can be attacked by the electron-rich *β*-C atom and NH group in *β*-enaminones for C−C and C−N bond formation via [3 + 2] cyclization mechanism. We devoted our efforts on this study by using the reaction of 4-tolylglyoxal monohydrate **1a**, a preformed 5,5-dimethyl-3-(4-bromophenylamino)cyclohex-2-enone **2a** and 4-chlorobenzenamine **3a** as the model reaction. Experiments were carried out in various solvents, such as DMF, tetrahydrofuran (THF), and acetic acid (HOAc), at 80 °C to search for suitable conditions under microwave (MW) irradiation. Only a trace amount of product was observed when DMF or THF was used as the solvent without the use of Brønsted acid catalyst. The incomplete reaction was observed in HCOOH and TFA. When HOAc was used as the solvent, the reaction proceeded smoothly to give product **4a** in 85% yield. Since metal triflates were known to show effective Lewis acidity even in the presence of water,[22] two of these Lewis acids, Sc(OTf)$_3$ and Cu(OTf)$_2$, were then employed attempting to enhance yields, but complex mixtures were formed, which made purification difficult. It is anticipated that acetic acid serves as Brønsted acid catalyst and reaction media for the allylic amination simultaneously.

Table 1. Domino Synthesis of Fused Pyrroles 4 under MW[a]



entry	4	Ar	R	R_1	Ar′	time[b]	yield[d]/%
1	**4a**	4-Tolyl (**1a**)	4-Bromophenyl (**2a**)	Me	4-Chlorophenyl (**3a**)	16/60[c]	85/80[c]
2	**4b**	4-Tolyl (**1a**)	4-Chlorophenyl (**2b**)	Me	4-Bromophenyl (**3b**)	20	84
3	**4c**	4-Tolyl (**1a**)	4-Chlorophenyl (**2b**)	Me	4-Nitrophenyl (**3c**)	24	83
4	**4d**	4-Tolyl (**1a**)	Phenyl (**2c**)	Me	Phenyl (**3d**)	18	75
5	**4e**	4-Tolyl (**1a**)	Phenyl (**2c**)	Me	4-Bromophenyl (**3b**)	25	81
6	**4f**	4-Fluorophenyl (**1b**)	4-Chlorophenyl (**2b**)	Me	4-Bromophenyl (**3b**)	18	84
7	**4g**	4-Chlorophenyl (**1c**)	4-Tolyl (**2d**)	Me	4-Bromophenyl (**3b**)	20	80
8	**4h**	4-Bromophenyl (**1d**)	4-Bromophenyl (**2a**)	Me	4-Chlorophenyl (**3a**)	15	87
9	**4i**	Phenyl (**1e**)	4-Bromophenyl (**2a**)	Me	4-Chlorophenyl (**3a**)	24	82
10	**4j**	Phenyl (**1e**)	4-Chlorophenyl (**2b**)	Me	4-Nitrophenyl (**3c**)	18	86
11	**4k**	4-Methoxyphenyl (**1f**)	4-Chlorophenyl (**2b**)	Me	4-Bromophenyl (**3b**)	15	80
12	**4l**	4-Methoxyphenyl (**1f**)	4-Chlorophenyl (**2b**)	Me	4-Tolyl (**3e**)	20	78
13	**4m**	4-Methoxyphenyl (**1f**)	Phenyl (**2c**)	Me	4-Chlorophenyl (**3a**)	25	83
14	**4n**	4-Methoxyphenyl (**1f**)	3,4-Dichlorophenyl (**2e**)	Me	4-Chlorophenyl (**3a**)	22	85
15	**4o**	4-Chlorophenyl (**1c**)	4-Bromophenyl (**2f**)	H	4-Nitrophenyl (**3c**)	28	82
16	**4p**	4-Bromophenyl (**1d**)	4-Chlorophenyl (**2g**)	H	3-Chlorophenyl (**3f**)	20	84
17	**4q**	Phenyl (**1e**)	4-Bromophenyl (**2f**)	H	4-Nitrophenyl (**3c**)	30	79
18	**4r**	Phenyl (**1e**)	4-Chlorophenyl (**2g**)	H	4-Tolyl (**3e**)	18	85
19	**4s**	Phenyl (**1e**)	4-Chlorophenyl (**2g**)	H	4-Nitrophenyl (**3c**)	30	81
20	**4t**	4-Tolyl (**1a**)	Carboxyethyl (**2h**)	Me	4-Bromophenyl (**3b**)	26	76
21	**4u**	4-Chlorophenyl (**1c**)	Carboxyethyl (**2h**)	Me	4-Fluorophenyl (**3g**)	28	85
22	**4v**	4-Bromophenyl (**1d**)	Carboxyethyl (**2h**)	Me	4-Chlorophenyl (**3a**)	20	67
23	**4w**	4-Methoxyphenyl (**1f**)	Carboxyethyl (**2h**)	Me	4-Chlorophenyl (**3a**)	20	86
24	**4x**	4-Methoxyphenyl (**1f**)	Carboxyethyl (**2h**)	Me	4-Tolyl (**3e**)	25	65
25	**4y**	4-Methoxyphenyl (**1f**)	Carboxyethyl (**2h**)	Me	4-Bromophenyl (**3b**)	30	83

[a]Reagents and conditions: 80 °C, HOAc (1.5 mL) microwave heating. [b]Time (min). [c]Conventional heating (80 °C, HOAc, sealed). [d]Isolated yield.

dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

Table 2. Domino Synthesis of Fused Pyrroles 5 under MW[a]

entry	5	Ar	R	R_1	Ar′	time/min	yield[b]/%
1	**5a**	4-Tolyl (**1a**)	Carboxymethyl (**2i**)	Me	4-Chlorophenyl (**3a**)	26	88
2	**5b**	4-Tolyl (**1a**)	Carboxymethyl (**2i**)	Me	4-Bromophenyl (**3b**)	22	82
3	**5c**	4-Tolyl (**1a**)	Carboxymethyl (**2i**)	Me	4-Fluorophenyl (**3g**)	20	75
4	**5d**	4-Chlorophenyl (**1c**)	Carboxymethyl (**2i**)	Me	4-Bromophenyl (**3b**)	28	67
5	**5e**	4-Bromophenyl (**1d**)	Carboxymethyl (**2i**)	Me	4-Chlorophenyl (**3a**)	28	62
6	**5f**	4-Bromophenyl (**1d**)	Carboxymethyl (**2i**)	Me	4-Bromophenyl (**3b**)	25	79
7	**5g**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2i**)	Me	4-Chlorophenyl (**3a**)	20	65
8	**5h**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2i**)	Me	4-Bromophenyl (**3b**)	26	63
9	**5i**	4-Tolyl (**1a**)	Carboxymethyl (**2j**)	H	4-Chlorophenyl (**3a**)	25	71
10	**5j**	4-Tolyl (**1a**)	Carboxymethyl (**2j**)	H	4-Fluorophenyl (**3g**)	32	66
11	**5k**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2j**)	H	4-Chlorophenyl (**3a**)	30	89
12	**5l**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2j**)	H	4-Bromophenyl (**3b**)	32	87
13	**5m**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2j**)	H	4-Tolyl (**3e**)	26	74
14	**5n**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2j**)	H	4-Fluorophenyl (**3g**)	28	74
15	**5o**	4-Methoxyphenyl (**1f**)	Carboxymethyl (**2j**)	H	3-Bromophenyl (**3h**)	30	85

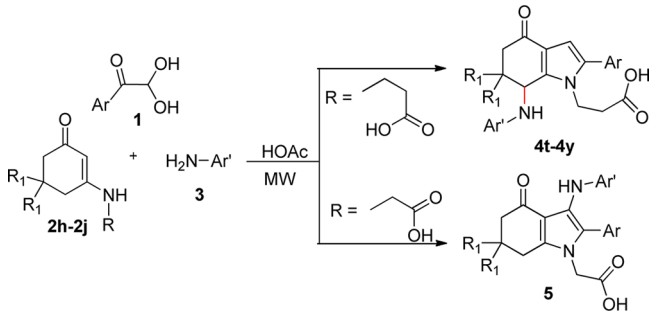
[a]Reagents and conditions: 80 °C, HOAc (1.5 mL) microwave heating. [b]Isolated yield.

With these optimized conditions in hand, we examined the scope of this intermolecular C−H amination process by using various easily available starting materials. As revealed in Table 1, the reaction resulted in corresponding target products in good to excellent yields. The intermolecular C−H amination is easy to perform simply by subjecting a mixture of arylglyoxal monohydrate, various enaminones **2**, and aromatic amines **3** in acetic acid to microwave heating. Subsequently, the enaminones scope of this transformation was investigated (Table 1). The intermolecular C−H amination showed tolerance of some functional groups in the substrates including ether and C−Cl (or Br) bonds. The 5,5-unsubstituted enaminones **2f** and **2g** were subjected to this reaction providing corresponding amination products **4o**−**4s** in 79−85% yields. Next, we began to examine the generality of this system. Various amine substrates **3** were used to give the corresponding arylamino substituted fused pyrroles through metal-free intermolecular allylic amination. 4-Nitrophenylamine **3c** was also suitable for this domino reaction. Furthermore, functional groups like bromide and chloride were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions.[24,25]

In view of these results, we turned our attention to investigate several differently substituted enamines. The reactions of arylglyoxal monohydrate **1**, *N*-amino acid enaminones **2** with aromatic amines **3** in acetic acid were performed under the conditions described above for a short period (20−32 min). Interestingly, *N*-carboxyethyl substituents afforded the allylic aminates **4t**−**4y**, whereas the reaction underwent another direction of *N*-arylation to form multifunctionalized fused pyrroles **5** with different substituted patterns when the *N*-carboxymethyl counterparts were employed in these reactions (Table 2 and Scheme 2). The resulting functionalities of these fused pyrroles offer a great flexibility for further structural modifications. These special *N*-protected α-amino acids may be directly useful for drug design, discovery and development and for peptide/protein mimetic research. Indeed, the protocol provides a straightforward pathway to *N*-arylation of amines, which are generally prepared via metal-catalyzed coupling reactions.[23,24]

In all cases, the functional complexity of resulting products from this new reaction illustrates the remarkable chemo- and regioselectivity of the sequence starting from very common and easily accessible inexpensive starting materials. The structural elucidation and the attribution of regioselectivity were unequivocally determined by NMR spectroscopic analysis. In order to further ascertain structures of the newly synthesized fused pyrrole derivatives, single crystals of **4f** and **5a** were successfully obtained with their structures unambiguously confirmed by X-ray diffraction analysis (see the Supporting Information). Furthermore, the reaction occurred at a very fast speed with all cases finished within 15−32 min. Water is nearly a sole byproduct, which makes the workup convenient. In most cases, the products can precipitate out after cold water was poured into the reaction mixture.

Scheme 2. Selective Synthesis of Fused Pyrroles 4t−4y and 5

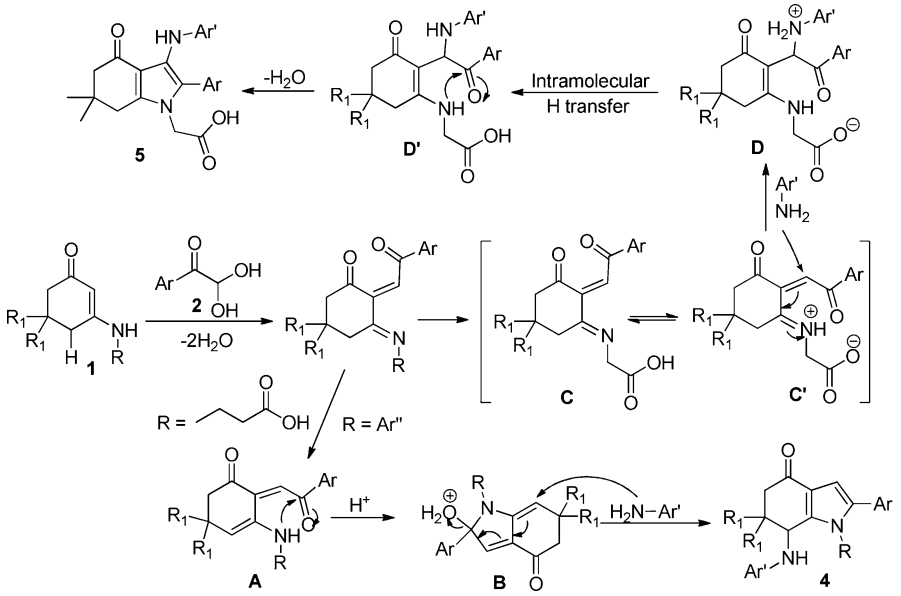


During these domino processes, the formation of pyrrole skeleton and its amination were readily achieved via regioselective three-component domino reaction in a one-pot operation. *Up to three sigma-bonds including a C(sp^3)−N bond were formed accompanied by the cleavage of C═O and C−O bonds of the aryl glyoxal via intermolecular allylic amination* (Scheme 3).

On the basis of all the above results, reasonable mechanisms have been proposed for the divergent formations of multifunctionalized fused pyrroles **4** and **5** as shown in Scheme 3. The former involves the ring closure cascade reactions that consist of initial condensation, isomerization, intramolecular cyclization (**A** to **B**), and double bonds nucleophilic substitution (**B** to **4**). The latter underwent protonation of imines (**C** to **C**′), intermolecular nucleophilic addition (**C**′ to **D**), intramolecular proton transfer (**D** to **D**′), and cyclization (**D** to **5**) leading to final fused pyrroles **5**. We reasoned that

dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

Scheme 3. Reasonable Mechanism for the Selective Formation of 4 and 5



such a divergence in reaction pathways would be caused by the different acidity of *N*-substituted amino acids **2h**−**2j**. Compared with acidity of acetic acid and *N*-substituted amino acids **2h**, enaminones **2i**, **2j** possess stronger acidity due to field effect of its amino group,[25] which favors protonation of imines through intramolecular proton transfer (**C** to **C**′). This would prevent isomerization to form enamine intermediate **A**. Further investigations regarding acid-controlled regioselectivity are in progress in our laboratory.

In conclusion, we have developed a three-component domino reaction (arylglyoxal monohydrates, enaminones and aromatic amines) as an alternative method for divergent synthesis of fused pyrroles with different substituted patterns by varying *N*-substituted enaminone substrate. The former reaction proceeds by domino [3 + 2] heterocyclization obtaining fused pyrroles **4a**−**4y** in good yields through allylic amination, showing that the synthetic route allows us to build blocks of pyrrole derivatives with a wide diversity of substituents. The latter gave the different substituted patterns on the fused pyrrole frameworks **5a**−**5o** through intermolecular *N*-arylation. Features of this strategy include the mild condition, convenient one-pot operation, short reaction periods of 15−32 min, and excellent regio- and chemoselectivities.

EXPERIMENTAL SECTION

General Methods. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured by infrared detector during microwave heating.

Example for the synthesis of **4a**: 7-(4-Chlorophenylamino)-1-(4-bromophenyl)-6,7-dihydro-6,6-dimethyl-2-*p*-tolyl-1*H*-indol-4(5*H*)-one (**4a**).

Microwave Heating. Typically, 2,2-dihydroxy-1-*p*-tolylethanone (**1a**, 1 mmol, 0.166 g, 1.0 equiv) was introduced in a 10-mL Initiator reaction vial, and 3-(4-bromophenylamino)-5,5-dimethylcyclohex-2-enone (**2a**, 1.0 mmol, 0.294 g, 1.0 equiv) and 4-chlorobenzenamine (**3a**, 1.0 mmol, 0.127 g, 1.0 equiv) as well as acetic acid (1.5 mL) were then successively added. Subsequently, the reaction vial was closed and then prestirred for 10 s. The mixture was irradiated (time, 16 min; temperature, 80 °C; absorption level, high; fixed hold time) until TLC (petroleum ether/acetone 3:1) revealed that conversion of the starting material **1a** was complete. The reaction mixture was then cooled to room temperature and then diluted with cold water (20 mL). The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, mixtures of petroleum ether/acetone, 7:1, v/v) to afford the desired pure fused pyrroles **4a** as a white solid (0.453 g, yield 85%, mp 206−207 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, ArH), 7.12−6.92 (m, 8H, ArH), 6.82 (s, 1H, ArH), 6.68 (s, 1H, ArH), 6.26 (d, J = 7.2 Hz, 2H, ArH), 3.99 (s, 1H, NH), 3.96 (s, 1H, CH), 2.77 (d, J = 17.2 Hz, 1H, CH_2), 2.26 (s, 3H), 2.18 (d, J = 17.2 Hz, 1H, CH_2), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 145.7, 144.8, 137.8, 137.5, 136.1, 132.6, 129.2, 129.1, 128.3, 122.7, 122.1, 119.8, 113.7, 105.1, 55.3, 47.8, 40.3, 27.0, 26.7, 21.2; IR (KBr, ν, cm^{-1}) 3303, 1652, 1597, 1491, 1453, 1281, 1215, 1076, 818, 808; HRMS (ESI) m/z calcd for $C_{29}H_{26}BrClN_2NaO$, 555.0809 [M + Na]$^+$, found 555.0794.

7-(4-Bromophenylamino)-1-(4-chlorophenyl)-6,7-dihydro-6,6-dimethyl-2-*p*-tolyl-1*H*-indol-4(5*H*)-one (4b). A white solid: 0.448 g, yield 84%; mp 234−235 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.02 − 6.89 (m, 7H, ArH), 6.69 (s, 1H, ArH), 6.22 (d, J = 8.0 Hz, 2H, ArH), 4.00 (d, J = 9.2 Hz, 1H, NH), 3.92 (d, J = 9.2 Hz, 1H, CH), 2.77 (d, J = 17.2 Hz, 1H, CH_2), 2.27−2.17(m, 4H, CH_2, 1H, CH_3, 3H), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 146.2, 144.9, 137.8, 135.5, 134.6, 131.8, 129.5, 129.1, 128.2, 128.2, 119.7, 114.1, 108.9, 105.0, 55.1, 47.7, 40.2, 26.9, 26.6, 21.1; IR (KBr, ν, cm^{-1}) 3305, 1652, 1587, 1511, 1491, 1452, 1249, 1195, 1070, 818, 806; HRMS (ESI) m/z calcd for $C_{29}H_{26}BrClN_2NaO$, 555.0809 [M + Na]$^+$, found 555.0835.

7-(4-Nitrophenylamino)-1-(4-chlorophenyl)-6,7-dihydro-6,6-dimethyl-2-*p*-tolyl-1*H*-indol-4(5*H*)-one (4c). A yellow solid: 0.413 g, yield 83%; mp 206−207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 2H, ArH), 7.08 (s, 1H, ArH), 6.99 (d, J = 8.0 Hz, 3H, ArH), 6.93 (d, J = 8.0 Hz, 3H, ArH), 6.84 (s, 1H, ArH), 6.71 (s, 1H, ArH), 6.32 (d, J = 8.8 Hz, 2H, ArH), 4.64 (d, J = 9.6 Hz, 1H, NH), 4.21 (d, J = 9.6 Hz, 1H, CH), 2.74 (d, J = 17.2 Hz, 1H, CH_2), 2.32−2.27(m, 4H, CH_2, 1H, CH_3, 3H), 1.21 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 153.8, 143.1, 137.0, 136.8, 135.7, 135.4, 133.1, 129.0, 128.1, 128.0, 119.7, 104.1, 52.8, 47.9, 26.1, 25.2, 20.6; IR (KBr, ν, cm^{-1}) 3293, 1656, 1592, 1494, 1455, 1322, 1307, 1266, 1191, 1111, 828, 754; HRMS (ESI) m/z calcd for $C_{29}H_{26}ClN_3NaO_3$, 522.1554 [M + Na]$^+$, found 522.1569.

6,7-Dihydro-6,6-dimethyl-1-phenyl-7-(phenylamino)-2-*p*-tolyl-1*H*-indol-4(5*H*)-one (4d). A light yellow solid: 0.315 g, yield 75%; mp 224−225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.13 (m, 4H, ArH), 7.10−6.79 (m, 8H, ArH), 6.76 (s, 1H, ArH), 6.22 (d, J = 8.4 Hz, 2H, ArH), 4.02 (s, 1H, NH), 3.58 (s, 1H, CH), 2.82 (d, J =

dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

17.2 Hz, 1H, CH_2), 2.26−2.23 (m, 4H, CH_2, 1H and CH_3, 3H), 1.15 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 145.8, 144.6, 134.3, 131.2, 129.6, 128.3, 127.3, 126.8, 112.7, 105.4, 55.3, 47.7, 40.2, 26.8, 26.7, 20.3; IR (KBr, ν, cm^{-1}) 3312, 1659, 1600, 1492, 1462, 1253, 1189, 1064, 957, 822, 794; HRMS (ESI) m/z calcd for $C_{29}H_{28}N_2NaO$, 443.2093 $[M + Na]^+$, found 443.2105.

7-(4-Bromophenylamino)-6,7-dihydro-6,6-dimethyl-1-phenyl-2-*p*-tolyl-1*H*-indol-4(5*H*)-one (4e). A white solid: 0.404 g, yield 81%; mp 203−204 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.24 (m, 2H, ArH), 7.06 (d, J = 8.4 Hz, 3H, ArH), 6.95 (s, 6H, ArH), 6.72 (s, 1H, ArH), 6.16 (d, J = 8.4 Hz, 2H, ArH), 4.01 (d, J = 9.2 Hz, 1H, NH), 3.81 (d, J = 9.2 Hz, 1H, CH), 2.80 (d, J = 9.2 Hz, 1H, CH_2), 2.25−2.17 (m, 4H, CH_2,1H and CH_3, 3H), 1.15 (s, 3H, CH_3), 1.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 147.4, 144.7, 136.6, 136.5, 136.5, 130.8, 128.8, 128.5, 128.2, 127.8, 119.2, 113.7, 105.7, 104.0, 53.1, 47.5, 26.1, 26.0, 20.6; IR (KBr, ν, cm^{-1}) 3316, 1658, 1591, 1519, 1489, 1462, 1282, 1215, 810, 700; HRMS (ESI) m/z calcd for $C_{29}H_{27}BrN_2NaO$, 521.1998 $[M + Na]^+$, found 521.1245.

7-(4-Bromophenylamino)-1-(4-chlorophenyl)-2-(4-fluorophenyl)-6,7-dihydro-6,6-dimethyl-1*H*-indol-4(5*H*)-one (4f). A yellow solid: 0.452 g, yield 84%; mp 235−236 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, ArH), 7.13−7.00 (m, 5H, ArH), 6.90−6.79 (m, 3H, ArH), 6.69 (s, 1H, ArH), 6.25 (d, J = 8.0 Hz, 2H, ArH), 4.01 (d, J = 8.0 Hz, 1H, NH), 3.82 (d, J = 8.4 Hz, 1H, CH), 2.77 (d, J = 17.2 Hz, 1H, CH_2), 2.24 (d, J = 17.2 Hz, 1H, CH_2), 1.15 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 162.1 (J_{CF}^1 = 246.7 Hz), 145.5, 145.0, 136.6, 135.7, 132.6 (J_{CF}^4 = 2.5 Hz), 130.1 (J_{CF}^3 = 8.2 Hz), 129.0, 122.8, 122.1, 119.7, 115.5 (J_{CF}^2 = 21.5 Hz), 113.6, 105.4, 55.2, 47.7, 40.2, 26.9, 26.5; IR (KBr, ν, cm^{-1}) 3325, 1659, 1594, 1490, 1455, 1214, 1157, 1015, 818, 804; HRMS (ESI) m/z calcd for$C_{28}H_{23}BrClFN_2NaO$, 559.0558 $[M + Na]^+$, found 559.0565.

7-(4-Bromophenylamino)-2-(4-chlorophenyl)-6,7-dihydro-6,6-dimethyl-1-*p*-tolyl-1*H*-indol-4(5*H*)-one (4g). A light yellow solid: 0.426 g, yield 80%; mp 220−221 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 7.6 Hz, 3H, ArH), 7.05 (d, J = 8.0 Hz, 2H, ArH), 6.98 (d, J = 7.6 Hz, 3H,), 6.75−6.71 (m, 3H, ArH), 6.18 (d, J = 8.0 Hz, 2H, ArH), 4.00 (s, 1H, NH), 3.93 (s, 1H, CH), 2.77 (d, J = 17.2 Hz, 1H, CH_2), 2.28 (s, 3H, CH_3), 2.21 (d, J = 17.2 Hz, 1H, CH_2), 1.15 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 146.4, 145.6, 139.0, 136.4, 134.0, 133.2, 131.6, 130.1, 129.3, 128.5, 119.5, 114.3, 108.7, 105.4, 55.2, 47.8, 40.2, 26.9, 26.6, 21.2; IR (KBr, ν, cm^{-1}) 3360, 1654, 1588, 1515, 1488, 1460, 1216, 822, 813, 746; HRMS (ESI) m/z calcd for $C_{29}H_{26}BrClN_2NaO$, 555.0809 $[M + Na]^+$, found 555.0815.

7-(4-Chlorophenylamino)-1,2-bis(4-bromophenyl)-6,7-dihydro-6,6-dimethyl-1*H*-indol-4(5*H*)-one (4h). Pale white solid: 0.520 g, yield 87%; mp 222−223 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H, ArH), 7.31 (d, J = 8.4 Hz, 2H, ArH), 7.26 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H, ArH), 6.99 (d, J = 8.4 Hz, 2H, ArH), 6.91 (d, J = 8.0 Hz, 3H, ArH), 6.79 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.25−6.19 (m, 2H, ArH), 4.01 (d, J = 6.8 Hz, 1H, NH), 3.76 (d, J = 7.2 Hz, 1H, CH), 2.77 (d, J = 17.2 Hz, 1H,CH_2), 2.25 (d, J = 17.2 Hz, 1H, CH_2), 1.14 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 145.6, 145.5, 136.4, 135.7, 132.8, 131.9, 131.7, 130.1, 129.7, 129.1, 123.0, 122.2, 121.8, 119.9, 114.2, 113.7, 105.9, 55.2, 47.7, 40.2, 26.9, 26.5; IR (KBr, ν, cm^{-1}) 3344, 1658, 1597, 1491, 1448, 1253, 1192, 1073, 1012, 813; HRMS (ESI) m/z calcd for $C_{28}H_{23}Br_2ClN_2NaO$, 618.9757 $[M + Na]^+$, found 618.9764.

7-(4-Chlorophenylamino)-1-(4-bromophenyl)-6,7-dihydro-6,6-dimethyl-2-phenyl-1*H*-indol-4(5*H*)-one (4i). A white solid: 0.424 g, yield 82%; mp 247−248 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, ArH), 7.18−7.05 (m, 6H, ArH), 6.99 (d, J = 8.0 Hz, 2H, ArH), 6.82 (s, 2H, ArH), 6.73 (s, 1H, ArH), 6.26 (d, J = 8.0 Hz, 2H, ArH),4.01 (s, 1H, NH), 3.91 (s, 1H, CH), 2.78 (d, J = 17.2 Hz, 1H, CH_2), 2.23 (d, J = 17.2 Hz, 1H, CH_2), 1.15 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 145.7, 145.1, 137.7, 136.1, 132.6, 131.2, 129.1, 128.5, 128.4, 127.6, 122.8, 122.2, 119.9, 113.7, 105.6, 55.3, 47.8, 40.3, 27.0, 26.7; IR (KBr, ν, cm^{-1}) 3328, 1656, 1597, 1512, 1491, 1459, 1247, 1194, 819, 763; HRMS (ESI) m/z calcd for $C_{28}H_{24}BrClN_2NaO$, 541.0652 $[M + Na]^+$, found 541.0653.

7-(4-Nitrophenylamino)-1-(4-chlorophenyl)-6,7-dihydro-6,6-dimethyl-2-phenyl-1*H*-indol-4(5*H*)-one (4j). A yellow solid: 0.418 g, yield 86%; mp 283−284 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 2H, ArH), 7.28 (s, 1H, ArH), 7.19 (s, 3H, ArH), 7.05−7.04 (m, 3H, ArH), 6.93−6.85 (m, 2H, ArH), 6.74 (s, 1H, ArH), 6.34 (d, J = 8.8 Hz, 2H, ArH), 4.76 (d, J = 9.6 Hz, 1H, NH), 4.22 (d, J = 9.6 Hz, 1H, CH), 2.75 (d, J = 17.2 Hz, 1H, CH_2), 2.30 (d, J = 17.2 Hz, 1H, CH_2), 1.21 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 170.7, 161.7, 150.3, 137.9, 137.8, 126.5, 107.3, 89.4, 75.2, 48.8, 40.7, 32.9, 27.5; IR (KBr, ν, cm^{-1}) 3321, 1648, 1595, 1504, 1495, 1313, 1270, 1112, 832, 763; HRMS (ESI) m/z calcd for $C_{28}H_{24}ClN_3NaO_3$, 508.1396 $[M + Na]^+$, found 508.1400.

7-(4-Bromophenylamino)-1-(4-chlorophenyl)-6,7-dihydro-2-(4-methoxyphenyl)-6,6-dimethyl-1*H*-indol-4(5*H*)-one (4k). A light yellow solid: 0.438 g, yield 80%; mp 206−207 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.8 Hz, 2H, ArH), 6.97 (d, J = 8.8 Hz, 6H, ArH), 6.71 (d, J = 8.8 Hz, 2H, ArH), 6.66 (s, 1H, ArH), 6.21 (d, J = 8.8 Hz, 2H, ArH), 4.00 (d, J = 9.6 Hz, 1H, NH), 3.81 (d, J = 9.6 Hz, 1H, CH), 3.74 (s, 3H, CH_3), 2.77 (d, J = 17.2 Hz, 1H, CH_2), 2.24 (d, J = 17.2 Hz, 1H, CH_2), 1.15 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 146.2, 145.1, 137.7, 135.4, 134.7, 131.8, 131.1, 129.5, 128.4, 128.3, 127.5, 119.7, 114.1, 108.9, 105.4, 55.1, 47.6, 40.2, 26.8, 26.6; IR (KBr, ν, cm^{-1}) 3309, 1656, 1597, 1557, 1518, 1492, 1460, 1249, 1177, 1110, 1070, 817, 775; HRMS (ESI) m/z calcd for $C_{29}H_{26}BrClN_2NaO_2$, 571.0758 $[M + Na]^+$, found 571.0763.

7-(*p*-Tolylamino)-1-(4-chlorophenyl)-6,7-dihydro-2-(4-methoxyphenyl)-6,6-dimethyl-1*H*-indol-4(5*H*)-one (4l). A white solid: mp 0.379 g, yield 78%; mp205−206 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H, ArH), 7.03−6.80 (m, 7H, ArH),), 6.70 (d, J = 8.4 Hz, 2H, ArH),), 6.66 (s, 1H, ArH),), 6.25 (d, J = 8.4 Hz, 2H, ArH), 4.00 (s, 1H, NH), 3.75 (s, 1H, CH), 3.73 (s, 3H, CH_3), 2.82 (d, J = 17.2 Hz,1H, CH_2), 2.23−2.19 (m, 4H, CH_2, 1H, CH_3, 3H), 1.14 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 158.8, 145.4, 144.8, 137.2, 135.5, 134.2, 129.6, 123.7, 119.4, 113.7, 112.7, 104.5, 55.3, 55.1, 47.7, 40.2, 26.8, 26.7, 20.3; IR (KBr, ν, cm^{-1}) 3345, 1658, 1613, 1517, 1455, 1408, 1291, 1215, 1177, 1089, 1048, 1024, 851; HRMS (ESI) m/z calcd for $C_{30}H_{29}ClN_2NaO_2$, 507.1809 $[M + Na]^+$, found 507.1797.

7-(4-Chlorophenylamino)-6,7-dihydro-2-(4-methoxyphenyl)-6,6-dimethyl-1-phenyl-1*H*-indol-4(5*H*)-one (4m). A light yellow solid: 0.389 g, yield 83%; mp 207−208 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H, ArH), 7.25−7.21 (m, 1H, ArH), 7.08 (s, 1H, ArH), 6.98−6.92 (m, 6H, ArH), 6.69−6.67 (m, 3H, ArH), 6.22 (d, J = 8.8 Hz, 2H, ArH), 4.00 (d, J = 6.4 Hz, 1H, NH), 3.88 (d, J = 7.2 Hz, 1H, CH), 3.72 (s, 3H, CH_3), 2.80 (d, J = 17.2 Hz, 1H, CH_2), 2.22 (d, J = 17.2 Hz, 1H, CH_2), 1.15 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 144.8, 143.8, 138.5, 137.6, 134.4, 131.6, 129.8, 129.2, 128.3, 128.2, 127.3, 122.4, 121.4, 114.3, 105.6, 45.2, 33.2, 28.4, 21.1; IR (KBr, ν, cm^{-1}) 3309, 1656, 1597, 1557, 1518, 1492, 1460, 1249, 1177, 1110, 1070, 817, 775. HRMS (ESI) m/z calcd for $C_{29}H_{27}ClN_2NaO_2$, 493.1653 $[M + Na]^+$, found 493.1632.

7-(4-Chlorophenylamino)-1-(3,4-dichlorophenyl)-6,7-dihydro-2-(4-methoxyphenyl)-6,6-dimethyl-1*H*-indol-4(5*H*)-one (4n). A white solid: 0.457 g, yield 85%; mp 228−229 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13−6.83 (m, 6H, ArH), 6.79−6.55 (m, 4H, ArH), 6.33−6.27 (m, 2H, ArH), 4.06 (s, 1H, NH), 3.98 (s, 1H, CH), 3.75 (s, 3H, CH_3), 2.76 (d, J = 16.4 Hz, 1H, CH_2), 2.23 (d, J = 16.4 Hz, 1H, CH_2), 1.18 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 159.1, 145.9, 144.4, 138.9, 137.6, 131.8, 129.6, 128.8, 123.1, 120.0, 113.8, 109.3, 104.8, 55.2, 47.9, 40.1, 29.9, 26.3; IR (KBr, ν, cm^{-1}) 3307, 1651, 1615, 1594, 1492, 1452, 1296, 1251, 1177, 1130, 1074, 1034, 838, 819; HRMS (ESI) m/z calcd for $C_{29}H_{25}Cl_3N_2NaO_2$ 563.0843 $[M + Na]^+$, found 563.0837.

7-(4-Nitrophenylamino)-1-(4-bromophenyl)-2-(4-chlorophenyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (4o). A yellow solid: 0.438 g, yield 82%; mp 288−289 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.6 Hz, 2H, ArH), 7.62 (d, J = 8.0 Hz, 1H, NH), 7.35−7.32 (m, 5H, ArH), 7.13−7.10 (m, 3H, ArH), 6.78 (s, 1H, ArH), 6.51

dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

(d, J = 8.8 Hz, 2H, ArH), 4.83−4.81 (m, 1H, CH), 2.69−2.65 (m, 1H, CH_2), 2.44−2.26 (m, 2H, CH_2), 2.11 (d, J = 10.6 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 152.4, 143.2, 136.1, 135.7, 135.4, 132.3, 128.5, 125.9, 121.8, 121.4, 105.6, 43.7, 33.6, 28.8; IR (KBr, ν, cm^{-1}) 3280, 1651, 1599, 1541, 1477, 1457, 1315, 1113, 1092, 1011, 833, 752; HRMS (ESI) m/z calcd for $C_{26}H_{18}BrClN_3O_3$, 534.0214 $[M - H]^-$, found 534.0227.

7-(3-Chlorophenylamino)-2-(4-bromophenyl)-1-(4-chlorophenyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (4p). A white solid: 0.44 g, yield 84%; mp 245−246 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 3H, ArH), 7.24 (s, 2H, ArH), 7.06 (t, J = 8.0 Hz, 1H, ArH), 6.93 (d, J = 8.4 Hz, 3H, ArH), 6.78 (s, 1H, ArH), 6.71 (d, J = 8.8 Hz, 1H, ArH), 6.48 (s, 1H, ArH), 6.39 (dd, J = 8.0, 2.0 Hz, 1H, ArH), 4.47 (s, 1H, NH), 4.16 (d, J = 8.4 Hz, 1H, CH), 2.78 (m, 1H, CH_2), 2.49 (m, 1H, CH_2), 2.43−2.34 (m, 1H, CH_2), 2.23 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 158.9, 146.0, 144.5, 135.4, 134.5, 131.8, 129.6, 123.5, 119.6, 113.8, 108.9, 104.5, 55.2, 55.0, 47.6, 40.2, 26.8, 26.6; IR (KBr, ν, cm^{-1}) 3327, 1651, 1598, 1517, 1495, 1459. 1181, 1093, 1011, 833, 806, 759; HRMS (ESI) m/z calcd for $C_{26}H_{19}BrCl_2N_2NaO$, 548.9922 $[M + Na]^+$, found 548.9934.

7-(4-Nitrophenylamino)-1-(4-bromophenyl)-6,7-dihydro-2-phenyl-1*H*-indol-4(5*H*)-one (4q). A white solid: 0.395 g, yield 79%; mp 226−227 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.8 Hz, 2H, ArH), 7.64 (d, J = 8.0 Hz, 1H, NH), 7.43−7.23 (m, 7H, ArH), 7.11(d, J = 7.2 Hz, 2H, ArH), 6.73 (s, 1H, ArH), 6.52 (d, J = 8.8 Hz, 2H, ArH), 4.83−4.81 (m, 1H, CH), 2.74−2.67 (m, 1H, CH_2), 2.39−2.31 (m, 2H, CH_2), 2.12−2.09 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 152.8, 142.9, 136.8, 136.1, 135.5, 133.1, 131.0, 129.6, 128.4, 128.2, 127.5, 126.0, 121.4, 105.1, 43.7, 33.6, 28.8; IR (KBr, ν, cm^{-1}) 3298, 1643, 1598,1533, 1493, 1478, 1461, 1312, 1203, 1111, 831, 761; HRMS (ESI) m/z calcd for $C_{26}H_{19}BrN_3O_3$, 502.0583 $[M - H]^-$, found 502.0594.

7-(*p*-Tolylamino)-1-(4-chlorophenyl)-6,7-dihydro-2-phenyl-1*H*-indol-4(5*H*)-one (4r). A white solid: 0.361 g, yield 85%; mp 245−246 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.20 (m, 6H, ArH), 7.09 (s, 3H, ArH), 6.98 (d, J = 8.0 Hz, 2H, ArH), 6.79 (s, 1H, ArH), 6.47 (d, J = 8.0 Hz, 2H, ArH), 4.47 (s, 1H, NH), 4.04 (s, 1H, CH), 2.84−2.75 (m, 1H, CH_2), 2.46 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.18−2.11 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 144.3, 143.6, 137.5, 135.9, 134.3, 131.4, 130.1, 129.5, 128.5, 127.6, 121.9, 114.0, 106.2, 45.4, 33.1, 28.1, 20.5; IR (KBr, ν, cm^{-1}) 3357, 1653, 1616, 1519, 1304, 1214, 1090, 842, 733, 696; HRMS (ESI) m/z calcd for $C_{27}H_{22}ClN_2O$, 425.1415 $[M - H]^-$, found 425.1417.

7-(4-Nitrophenylamino)-1-(4-chlorophenyl)-6,7-dihydro-2-phenyl-1*H*-indol-4(5*H*)-one (4s). A yellow solid: 0.371 g, yield 81%; mp 274−276 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.8 Hz, 2H, ArH), 7.65 (d, J = 8.0 Hz, 1H, NH), 7.30−7.23 (m, 7H, ArH), 7.12−7.11 (m, 2H, ArH), 6.73 (s, 1H, ArH), 6.52 (d, J = 8.8, 2H, ArH), 4.83−4.81 (m, 1H, CH), 2.74−2.68 (m, 1H, CH_2), 2.39−2.30 (m, 2H, CH_2), 2.13−2.08 (m, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.0, 152.8, 142.9, 136.8, 136.2, 136.0, 131.0, 129.9, 128.4, 127.5, 125.9, 121.6, 121.4, 105.1, 43.7, 33.6, 28.8; IR (KBr, ν, cm^{-1}) 3301, 1644, 1598, 1496, 1460, 1312, 1204, 1110, 831, 760; HRMS (ESI) m/z calcd for $C_{26}H_{20}ClN_3NaO_3$, 480.1085 $[M + Na]^+$, found 480.1099.

3-(7-(4-Bromophenylamino)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-*p*-tolylindol-1-yl)propanoic acid (4t). White solid: 0.376 g, yield 76%; mp 205−206 °C; 1H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.32 (d, J = 7.6 Hz, 2H, ArH), 7.25 (d, J = 7.6 Hz, 2H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 6.84 (d, J = 8.4 Hz, 2H, ArH), 6.34 (s, 1H, ArH), 6.31 (s, 1H, NH), 4.79 (d, J = 10.0 Hz, 1H, CH), 4.10−3.97 (m, 2H, CH_2), 2.81 (d, J = 16.4 Hz, 1H, CH_2), 2.34 (m, 4H, CH_3, 1H and CH_2, 1H), 2.27−2.19 (m, 1H, CH_2), 1.95 (d, J = 16.4 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.3, 171.4, 147.7, 143.0, 137.5, 135.7, 131.5, 129.4, 129.0, 128.6, 118.8, 113.7, 106.0, 104.6, 56.0, 52.0, 47.4, 34.3, 26.3, 20.7, 18.5; IR (KBr, ν, cm^{-1}) 3294, 1705, 1650, 1589, 1527, 1487, 1467, 1451, 1319, 1279, 1191, 1069, 814, 790; HRMS (ESI) m/z calcd for $C_{26}H_{26}BrN_2O_3$, 495.1105 $[M - H]^-$, found 495.1096.

3-(7-(4-Fluorophenylamino)-2-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxoindol-1-yl)propanoic acid (4u). White solid: 0.388 g, yield 85%; mp 204−205 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H, COOH), 8.03 (d, J = 8.0 Hz, 2H), 7.58−7.52 (m, 4H, ArH), 7.41 (s, 1H, ArH), 7.36 (s, 2H, ArH), 6.45 (d, J = 7.2 Hz, 1H, NH), 4.66 (d, J = 9.2 Hz, 1H, CH), 2.97−2.90 (m, 1H, CH_2), 2.64−2.62 (m, 2H, CH_2), 2.00 (d, J = 16.0 Hz, 1H, CH_2), 1.75 (d, J = 17.2 Hz, 1H, CH_2), 1.64 (d, J = 16.0 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ193.4, 174.1, 168.1 (J_{CF}^1 = 240.5 Hz), 140.4, 137.7, 134.8 (J_{CF}^4 = 1.7 Hz), 133.8, 131.8, 130.7, 130.1 (J_{CF}^3 = 7.8 Hz), 129.3, 129.0, 126.9, 116.0 (J_{CF}^2 = 21.6 Hz), 105.7, 55.7, 49.7, 37.5, 36.7, 33.9, 29.1, 28.0; IR (KBr, ν, cm^{-1}) 3417, 3091, 1753, 1692, 1588, 1564, 1496, 1441, 1402, 1354, 1290, 1188, 11117, 1090, 1003, 832, 819; HRMS (ESI) m/z calcd for $C_{25}H_{23}ClFN_2O_3$, 453.1376 $[M - H]^-$, found 453.1396.

3-(7-(4-Chlorophenylamino)-2-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxoindol-1-yl)propanoic acid (4v). White solid: 0.348 g, yield 67%; mp 202−203 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H, COOH), 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 7.08 (d, J = 8.4 Hz, 2H, ArH), 6.88 (d, J = 8.4 Hz, 2H, ArH), 6.41 (s, 1H, ArH), 6.30 (d, J = 9.6 Hz, 1H, NH), 4.79 (d, J = 9.6 Hz, 1H, CH), 4.11−3.99 (m, 2H, CH_2), 2.82 (d, J = 16.4 Hz, 1H, CH_2), 2.41−2.35 (m, 1H, CH_2), 2.28−2.18 (m, 1H, CH_2), 1.96 (d, J = 16.4 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.3, 171.4, 147.3, 143.7, 134.4, 131.7, 131.1, 130.7, 128.7, 121.4, 119.0, 118.7, 113.1, 105.4, 56.0, 47.4, 34.4, 26.2, 18.5; IR (KBr, ν, cm^{-1}) 3291, 1710, 1651, 1595, 1528, 1488, 1454, 1409, 1385, 1317, 1279, 1230, 1190, 1074, 1010, 832, 815; HRMS (ESI) m/z calcd for $C_{25}H_{23}BrClN_2O_3$, 515.0555 $[M - H]^-$, found 515.0556.

3-(7-(4-Chlorophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-6,6-dimethyl-4-oxoindol-1-yl)propanoic acid (4w). White solid: 0.402 g, yield 86%; mp 197−198 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.36 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.00 (d, J = 8.8 Hz, 2H, ArH), 6.87 (d, J = 8.8 Hz, 2H, ArH), 6.32−6.28 (m, 2H, ArH, 1H and NH, 1H), 4.78 (d, J = 10.0 Hz, 1H, CH), 4.10−3.93 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 2.82 (d, J = 16.4 Hz, 1H, CH_2), 2.41−2.32 (m, 1H, CH_2), 2.28−2.18 (m, 1H, CH_2), 1.94 (d, J = 16.4 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.4, 171.6, 159.0, 146.2, 143.5, 135.4, 130.2, 129.5, 124.2, 123.8, 118.6, 114.2, 111.8, 104.4, 55.1, 52.3, 47.5, 34.4, 26.5), 20.0; IR (KBr, ν, cm^{-1}) 3414, 3305, 1709, 1649, 1595, 1527, 1490, 1446, 1409, 1249, 1175, 1110, 1038, 838; HRMS (ESI) m/z calcd for $C_{26}H_{26}ClN_2O_4$, 465.1576 $[M - H]^-$, found 465.1555.

3-(7-(*p*-Tolylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-6,6-dimethyl-4-oxoindol-1-yl)propanoic acid (4x). White solid: 0.291 g, yield 65%; mp 206−208 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H, COOH), 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.00 (d, J = 8.4 Hz, 2H, ArH), 6.89 (d, J = 8.0 Hz, 2H, ArH), 6.76 (d, J = 8.0 Hz, 2H, ArH), 6.27 (s, 1H, ArH), 5.87 (d, J = 10.0 Hz, 1H, NH), 4.75 (d, J = 9.6 Hz, 1H, CH), 4.06−3.97 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 2.85 (d, J = 16.4 Hz, 1H, CH_2), 2.44−2.35 (m, 1H, CH_2), 2.28−2.19 (m, 1H, CH_2), 2.14 (s, 3H, CH_3), 1.92 (d, J = 16.4 Hz, 1H, CH_2), 1.08 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.4, 171.5, 159.0, 146.2, 143.5, 135.4, 130.2, 129.5, 124.2, 123.8, 118.6, 114.2, 111.8, 104.4, 55.1, 52.3, 47.5, 34.4, 26.5, 20.0; IR (KBr, ν, cm^{-1}) 3414, 3370, 1721, 1616, 1521, 1494, 1475, 1303, 1280, 1251, 1215, 1186, 1032, 817, 804; HRMS (ESI) m/z calcd for $C_{27}H_{29}N_2O_4$, 445.2122 $[M - H]^-$, found 445.2109.

3-(7-(4-Bromophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-6,6-dimethyl-4-oxoindol-1-yl)propanoic acid (4y). Pale white solid: 0.423 g, yield 83%; mp 202−203 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.36 (d, J = 7.6 Hz, 2H, ArH), 7.19 (d, J = 7.6 Hz, 2H, ArH), 7.00 (d, J = 7.6 Hz, 2H, ArH), 6.84 (d, J = 7.6 Hz, 2H, ArH), 6.32 (d, J = 9.6 Hz, 1H, NH), 6.28 (s, 1H, ArH), 4.79 (d, J = 9.2 Hz, 1H, CH), 4.05−4.00 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 2.82 (d, J = 16.0 Hz, 1H, CH_2), 2.42−2.20 (m, 2H, CH_2), 1.94 (d, J = 16.0 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.3, 171.5, 159.0,

dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

147.7, 142.8, 135.6, 130.2, 124.1, 118.7, 114.2, 113.7, 106.0, 104.4, 55.1, 52.0, 47.4, 34.3, 26.3; IR (KBr, ν, cm^{-1}) 3302, 1707, 1648, 1589, 1468, 1409, 1294, 1248, 1038, 838, 814; HRMS (ESI) m/z calcd for $C_{26}H_{26}BrN_2O_4$, 511.1054 $[M - H]^-$, found 511.1037.

2-(3-(4-Chlorophenylamino)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-*p*-tolylindol-1-yl)acetic acid (5a). Pale white solid: 0.385 g, yield 88%; mp 215−215.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H, COOH), 7.21−7.14 (m, 3H, ArH, 2H and NH, 1H), 7.10 (d, J = 7.6 Hz, 2H, ArH), 6.96 (d, J = 8.4 Hz, 2H, ArH), 6.43 (d, J = 8.4 Hz, 2H, ArH), 4.59 (s, 2H, CH_2), 2.67 (s, 2H, CH_2), 2.29 (s, 3H), 2.22 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 169.7, 147.2, 142.5, 137.2, 129.1, 126.9, 119.7, 119.3, 114.3, 113.9, 52.1, 46.0, 35.1, 34.7, 28.2, 20.7; IR (KBr, ν, cm^{-1}) 3551, 3412, 3300, 1717, 1613, 1471, 1402, 1344, 1270, 1099, 823; HRMS (ESI) m/z calcd for $C_{25}H_{24}ClN_2O_3$, 435.1470 $[M - H]^-$, found 435.1468.

2-(3-(4-Bromophenylamino)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-*p*-tolylindol-1-yl)acetic acid (5b). Pale white solid: 0.393 g, yield 82%; mp 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H, COOH), 7.17 (s, 3H, ArH, 2H and NH, 1H), 7.12 − 7.05 (m, 4H, ArH), 6.39 (d, J = 7.6 Hz, 2H, ArH), 4.59 (s, 2H, CH_2), 2.67 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.21 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.5, 169.7, 147.7, 142.5, 137.2, 130.8, 129.4, 129.1, 126.8, 119.4, 114.8, 113.9, 106.6, 52.1, 46.0, 35.1, 34.7, 28.2, 20.8; IR (KBr, ν, cm^{-1}) 3552, 3479, 3414, 3300, 1717, 1611, 1487, 1470, 1402, 1354, 1270, 1171, 1099, 1052, 985, 821; HRMS (ESI) m/z calcd for $C_{25}H_{24}BrN_2O_3$, 481.0948 $[M - H]^-$, found 481.0969.

2-(3-(4-Fluorophenylamino)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-*p*-tolylindol-1-yl)acetic acid (5c). Pale white solid: 0.317 g, yield 75%; mp 205−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H, COOH), 7.21−7.14 (m, 3H, ArH, 2H and NH, 1H), 7.10 (d, J = 8.0 Hz, 2H, ArH), 6.95 (d, J = 8.8 Hz, 2H, ArH), 6.42 (d, J = 8.8 Hz, 2H, ArH), 4.59 (s, 2H, CH_2), 2.67 (s, 2H, CH_2), 2.28 (s, 3H), 2.21 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 168.8, 153.7 (J_{CF}^1 = 241.1 Hz), 143.3 (J_{CF}^4 = 2.4 Hz), 142.4, 136.1, 128.5, 128.2, 126.8, 126.2, 120.3, 113.7, 113.6 (J_{CF}^2 = 22.5 Hz), 113.2 (J_{CF}^3 = 8.1 Hz), 52.1, 46.0, 35.1, 34.7, 28.1, 20.7; IR (KBr, ν, cm^{-1}) 3553, 3478, 3414, 3301, 1718, 1616, 1471, 1344, 1270, 1099, 1053, 823; HRMS (ESI) m/z calcd for $C_{25}H_{24}FN_2O_3$, 419.1765 $[M - H]^-$, found 419.1759.

2-(3-(4-Bromophenylamino)-2-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxoindol-1-yl)acetic acid (5d). White solid: 0.337 g, yield 67%; mp 201−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.28−7.20 (m, 3H, ArH, 2H and NH, 1H), 7.08 (d, J = 8.0 Hz, 2H, ArH), 6.39 (d, J = 8.0 Hz, 2H, ArH), 4.64 (s, 2H, CH_2), 2.68 (s, 2H, CH_2), 2.22 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 169.6 147.4, 143.0, 132.6, 131.2 130.9, 128.7, 128.6, 120.2, 114.9, 113.9, 107.0, 52.1, 46.0, 35.1, 34.7, 28.1; IR (KBr, ν, cm^{-1}) 3552, 3479, 3414, 3304, 1718, 1613, 1488, 1470, 1400, 1345, 1268, 1097, 834, 820; HRMS (ESI) m/z calcd for $C_{24}H_{21}BrClN_2O_3$, 501.0398 $[M - H]^-$, found 501.0433.

2-(3-(4-Chlorophenylamino)-2-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxoindol-1-yl)acetic acid (5e). White solid: 0.313 g, yield 62%; mp 199−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H, COOH), 7.59 (d, J = 7.8 Hz, 2H, ArH), 7.25 (s, 1H, NH), 7.16 (d, J = 8.0 Hz, 2H, ArH), 6.97 (d, J = 8.0 Hz, 2H, ArH), 6.43 (d, J = 8.0 Hz, 2H, ArH), 4.64 (s, 2H, CH_2), 2.68 (s, 2H, CH_2), 2.22 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 169.6, 146.9, 143.0, 131.5, 131.4, 129.1, 128.1, 127.9, 121.2, 120.4, 119.6, 114.4, 113.9, 52.1, 46.1, 35.1, 34.7, 28.1; IR (KBr, ν, cm^{-1}) 3552, 3478, 3414, 3302, 1719, 1613, 1529, 1470, 1398, 1344, 1268, 1096, 1015, 832; HRMS (ESI) m/z calcd for $C_{24}H_{21}BrClN_2O_3$, 501.0398 $[M - H]^-$, found 501.0430.

2-(3-(4-Bromophenylamino)-2-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxoindol-1-yl)acetic acid (5f). White solid: 0.430 g, yield 79%; mp 212−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H, COOH), 7.59 (d, J = 7.6 Hz, 2H, ArH), 7.27 (s, 1H, NH), 7.16 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 7.6 Hz, 2H, ArH), 6.38 (d, J = 7.6 Hz, 2H, ArH), 4.64 (s, 2H, CH_2), 2.68 (s, 2H, CH_2), 2.22 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.5, 169.6, 147.3, 143.0, 131.5, 130.9, 129.1, 128.0, 121.2, 120.2, 114.9, 113.9, 107.0, 52.1, 46.1, 35.1 34.7, 28.1; IR (KBr, ν, cm^{-1}) 3551, 3477, 3414, 3301, 1717, 1614, 1487, 1470, 1386, 1344, 1268, 1170, 1096, 1014, 832, 820; HRMS (ESI) m/z calcd for $C_{24}H_{21}Br_2N_2O_3$, 544.9895 $[M - H]^-$, found 544.9860.

2-(3-(4-Chlorophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-6,6-dimethyl-4-oxoindol-1-yl)acetic acid (5g). White solid: 0.296 g, yield 65%; mp 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H, NH), 7.15 (d, J = 8.4 Hz, 2H, ArH), 6.87 (d, J = 8.4 Hz, 4H, ArH), 6.50 (d, J = 8.4 Hz, 2H, ArH), 4.49 (s, 2H, CH_2), 3.78 (s, 3H), 2.63 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 1.15 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.8, 169.5, 158.7, 144.8, 141.3, 130.7, 127.6, 126.1, 122.0, 121.2, 121.1, 115.3, 113.7, 112.7, 54.7, 51.8, 45.5, 35.3, 34.7, 28.2; IR (KBr, ν, cm^{-1}) 3551, 3434, 3298, 1714, 1604, 1492, 1474, 1354, 1253, 1172, 1100, 1053, 1031, 822; HRMS (ESI) m/z calcd for $C_{25}H_{24}ClN_2O_4$, 451.1419 $[M - H]^-$, found 451.1402.

2-(3-(4-Bromophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-6,6-dimethyl-4-oxoindol-1-yl)acetic acid (5h). White solid: 0.312 g, yield 63%; mp 208−208.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H, COOH), 7.13 (d, J = 8.8 Hz, 3H, ArH, 1H and NH, 1H), 7.05 (d, J = 8.4 Hz, 2H, ArH), 6.93 (d, J = 8.4 Hz, 2H, ArH), 6.40 (d, J = 8.4 Hz, 2H, ArH), 4.56 (s, 2H, CH_2), 3.75 (s, 3H), 2.66 (s, 2H, CH_2), 2.21 (s, 2H, CH_2), 1.09 (s, 6H, CH_3); IR (KBr, ν, cm^{-1}) 3530, 3449, 3299, 1714, 1603, 1570, 1509, 1487, 1344, 1253, 1173, 1098, 1029, 836, 819; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 174.7, 163.9, 149.8, 146.3, 135.9, 135.7, 130.3, 127.3, 126.8, 121.4, 119.0, 117.7, 114.4, 60.0, 57.0, 50.7, 40.6, 40.0, 33.5; HRMS (ESI) m/z calcd for $C_{25}H_{24}BrN_2O_4$, 497.0897 $[M - H]^-$, found 497.0888.

2-(3-(4-Chlorophenylamino)-4,5,6,7-tetrahydro-4-oxo-2-*p*-tolylindol-1-yl)acetic acid (5i). Pale yellow solid: 0.291 g, yield 71%; mp 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H, COOH), 7.19 (d, J = 7.2 Hz, 2H, ArH), 7.14 (s, 1H, NH), 7.09 (d, J = 7.2 Hz, 2H, ArH), 6.95 (d, J = 8.0 Hz, 2H, ArH), 6.44 (d, J = 8.4 Hz, 2H, ArH), 4.60 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.04 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.1, 169.7, 147.1, 143.5, 137.2, 129.4, 129.2, 128.9, 128.0, 126.9, 120.0, 119.3, 114.9, 114.4, 46.0, 38.1, 22.8, 21.4, 20.7; IR (KBr, ν, cm^{-1}) 3551, 3477, 3414, 3235, 1750, 1637, 1600, 1492, 1385, 1238, 1097, 983, 819; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2O_3$, 407.1157 $[M - H]^-$, found 407.1165.

2-(3-(4-Fluorophenylamino)-4,5,6,7-tetrahydro-4-oxo-2-*p*-tolylindol-1-yl)acetic acid (5j). Pale yellow solid: 0.259 g, yield 66%; mp 219−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H, COOH), 7.17 (d, J = 7.2 Hz, 2H, ArH), 7.09 (d, J = 7.2 Hz, 2H, ArH), 6.90 (s, 1H, NH), 6.78−6.74 (m, 2H, ArH), 6.45−6.43 (m, 2H, ArH), 4.60 (s, 2H, CH_2), 2.76 (s, 2H, CH_2), 2.31 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.04 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.4, 169.7, 154.6 (J_{CF}^1 = 230.3 Hz), 144.2 (J_{CF}^4 = 1.4 Hz), 143.3, 137.1, 129.4, 129.1, 127.8, 127.2, 121.2, 114.6, 114.5 (J_{CF}^2 = 21.9 Hz), 114.1 (J_{CF}^3 = 7.3 Hz), 46.0, 38.0, 22.9, 21.4, 20.8; IR (KBr, ν, cm^{-1}) 3524, 3438, 3378, 1740, 1642, 1599, 1507, 1467, 1416, 1219, 1098, 1023, 824; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN_2O_3$, 391.1452 $[M - H]^-$, found 391.1467.

2-(3-(4-Chlorophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-4-oxoindol-1-yl)acetic acid (5k). Pale white solid: 0.381 g, yield 89%; mp 205−205.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H, COOH), 7.13 (d, J = 8.8 Hz, 3H, ArH, 1H and NH, 1H), 6.97−6.93 (m, 4H, ArH), 6.45 (d, J = 8.0 Hz, 2H, ArH), 4.60 (s, 2H, CH_2), 3.74 (s, 3H, CH_3), 2.77−2.75 (m, 2H, CH_2), 2.35−2.26 (m, 2H, CH_2), 2.09−2.00 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.2, 169.7, 158.9, 147.1, 143.3, 130.9, 128.7, 128.0, 121.9, 119.8, 119.3, 114.9, 114.4, 114.0, 55.0, 45.9, 38.1, 22.9, 21.4; IR (KBr, ν, cm^{-1}) 3524, 3414, 3372, 1738, 1642, 1493, 1246, 1097, 1021, 833, 809; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2O_4$, 423.1106 $[M - H]^-$, found 423.1100.

dx.doi.org/10.1021/jo301323r | J. Org. Chem. 2012, 77, 7497−7505

2-(3-(4-Bromophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-4-oxoindol-1-yl)acetic acid (5l). Yellow solid: 0.407 g, yield 87%; mp 193−194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H, COOH), 7.13 (s, 3H, ArH, 1H and NH, 1H), 7.07 (d, J = 8.0 Hz, 2H, ArH), 6.94 (d, J = 7.6 Hz, 2H, ArH), 6.41 (d, J = 8.0 Hz, 2H, ArH), 4.59 (s, 2H, CH_2), 3.74 (s, 3H, CH_3), 2.76 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 2.04 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.2, 172.0, 169.7, 158.9, 147.6, 143.3, 130.9, 130.8, 128.9, 121.9, 119.6, 115.0, 114.9, 114.0, 106.8, 55.0, 46.0, 38.1, 22.9, 21.4, 21.0; IR (KBr, ν, cm^{-1}) 3551, 3413, 3372, 1737, 1644, 1491, 1384, 1246, 1021, 825; HRMS (ESI) m/z calcd for $C_{23}H_{20}BrN_2O_4$, 469.0584 [M − H]$^-$, found 469.0567.

2-(3-(*p*-Tolylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-4-oxoindol-1-yl)acetic acid (5m). Pale white solid: 0.304 g, yield 75%; mp 216−217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H, COOH), 7.15 (d, J = 8.8 Hz, 2H, ArH), 6.92 (d, J = 8.8 Hz, 2H, ArH), 6.74 (d, J = 8.0 Hz, 3H, ArH, 1H and NH, 1H), 6.38 (d, J = 8.0 Hz, 2H, ArH), 4.59 (s, 2H, CH_2), 3.73 (s, 3H, CH_3), 2.77−2.74 (m, 2H, CH_2), 2.34−2.27 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.07−1.98 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.7, 169.8, 158.7, 145.1, 142.9, 130.9, 128.7, 127.2, 124.9, 122.4, 121.4, 114.4, 114.0, 113.6, 55.0, 45.9, 38.0, 22.9, 21.4, 20.0; IR (KBr, ν, cm^{-1}) 3554, 3413, 3374, 1740, 1647, 1615, 1514, 1490, 1414, 1245, 1218, 1021, 836, 809; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_4$, 403.1652 [M − H]$^-$, found 403.1656.

2-(3-(4-Fluorophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-4-oxoindol-1-yl)acetic acid (5n). Pale white solid: 0.301 g, yield 74%; mp 218−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H, COOH), 7.13 (d, J = 8.0 Hz, 2H, ArH), 6.93 (d, J = 8.0 Hz, 2H, ArH), 6.89 (s, 1H, NH), 6.79−6.75 (m, 2H, ArH), 6.45−6.43 (m, 2H, ArH), 4.59 (s, 2H, CH_2), 3.73 (s, 3H, CH_3), 2.76 (s, 2H, CH_2), 2.31 (s, 2H, CH_2), 2.04 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.5, 169.7, 158.8, 154.6 (J_{CF}^1 = 230.0 Hz), 144.2 (J_{CF}^4 = 1.3 Hz), 144.2, 143.1, 130.9, 127.6, 121.1, 114.6 (J_{CF}^2 = 21.9 Hz), 114.5, 114.2 (J_{CF}^3 = 8.1 Hz), 114.1, 55.0, 45.9, 38.0, 22.9, 21.4; IR (KBr, ν, cm^{-1}) 3554, 3414, 3370, 1731, 1687, 1583, 1556, 1494, 1460, 1089, 1010, 983, 814; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN_2O_4$, 407.1402 [M − H]$^-$, found 407.1400.

2-(3-(3-Bromophenylamino)-4,5,6,7-tetrahydro-2-(4-methoxyphenyl)-4-oxoindol-1-yl)acetic acid (5o). Pale yellow solid: 0.397 g, yield 85%; mp 218−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H, COOH), 7.25 (s, 1H, NH), 7.13 (d, J = 8.8 Hz, 2H, ArH), 6.95 (d, J = 8.8 Hz, 2H, ArH), 6.90−6.86 (m, 1H, ArH), 6.61−6.58 (m, 2H, ArH), 6.46−6.41 (m, 1H, ArH), 4.60 (s, 2H, CH_2), 3.74 (s, 3H, CH_3), 2.33−2.30 (m, 2H, CH_2), 2.35−2.28 (m, 2H, CH_2), 2.08−2.03 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.2, 169.7, 158.9, 149.8, 143.3, 130.9, 130.1, 129.0, 121.9, 121.8, 119.2, 118.4, 115.2, 114.8, 114.1, 112.0, 55.1, 46.0, 38.1, 22.9, 21.4; IR (KBr, ν, cm^{-1}) 3552, 3475, 3388, 1747, 1650, 1597, 1573, 1422, 1240, 1177, 1101, 1024, 985, 845, 812; HRMS (ESI) m/z calcd for $C_{23}H_{20}BrN_2O_4$, 469.0584 [M − H]$^-$, found 469.0567.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all pure products and X-ray crystal data (CIF) for **4f** and **5a**. 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 are grateful for financial support from the NSFC (No. 20928001, 21072163, 21002083, and 21102124), PAPD of Jiangsu Higher Education Institutions, Robert A. Welch Foundation (D-1361), NIH (R21DA031860-01), the NSF of Jiangsu Education Committee (11KJB150016), and Jiangsu Science and Technology Support Program (No. BE2011045).

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