A Facile Method for the Synthesis of 3-(Aminomethylene)oxindoles from Isatylidene Malononitriles and α-Azido Ketones

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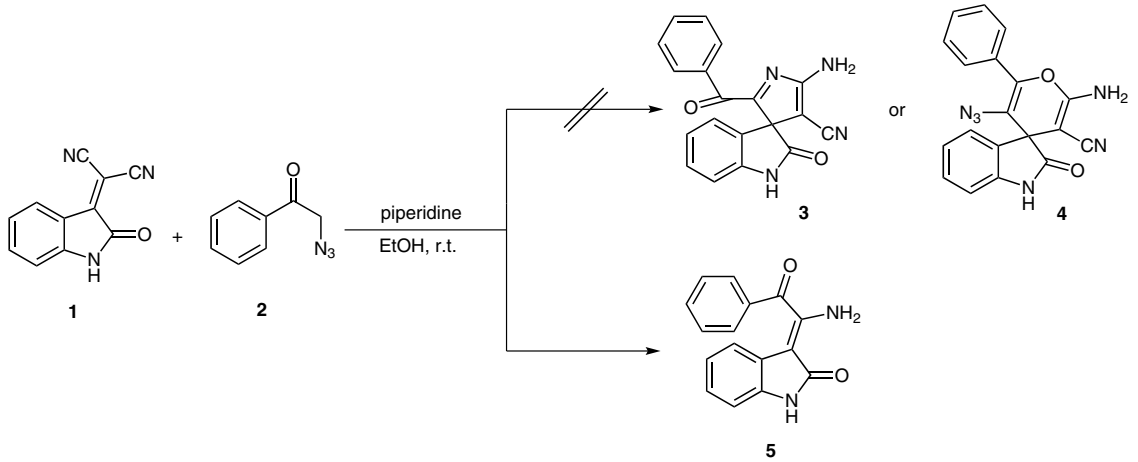
Abstract: A simple one-pot synthesis of 3-(aminomethylene)oxindoles was achieved by the reaction of α-azido ketones and isatylidene malononitriles via Michael addition followed by the conversion of azides to amines. All the synthesized 3-(aminomethylene)oxindoles exhibited good diastereoselectivity.

Key words: isatylidene malononitriles, azido ketones, oxindoles, 3-(aminomethylene)oxindoles, one-pot synthesis

α-Azido ketones constitute an important class of synthetically useful azides that exhibit double reactivity in C–C bond formation. The electrophilic carbonyl function of α-azido ketone acts as an electrophile for the attack of carbanions leading to the formation of synthetically important 2-azido alcohols. On the other hand, the active methylene group of α-azido ketones facilitates the controlled generation of carbanions followed by trapping with various carbon electrophiles that results in the formation of aldol-type products.[1]

Marco and co-workers demonstrated that the reaction of α-azido ketones with highly stabilized Michael acceptors such as arylidene malononitriles leads to the formation of polyfunctionalized pyrroles via sequential 1,4-conjugate addition followed by deprotonation which induced the formation of an anion by a loss of nitrogen and intramolecular nucleophilic attack to the cyano function.[2] And also it was anticipated that α-azido ketones having a good electron-withdrawing azido moiety would provide 2-amino-4*H*-pyrans on reaction with arylidene malononitriles via Michael addition followed by O-ring closure.[3] Inspired by these observations, we envisioned that treatment of α-azido ketones with isatylidene malononitriles in the presence of base would form azide moiety bearing fused spiro[4*H*-pyranoxindole] heterocycles via Michael addition followed by O-ring closure[4] or would lead to oxospiro[indoline-3,3′-pyrrole] heterocycles via Michael addition followed by N-ring closure (Scheme 1).[2] Quite surprisingly, when we carried out the reaction of α-azido ketone **2** with isatylidene malononitrile **1** in the presence of piperidine, we observed an unexpected domino process leading to functionalized 3-(aminomethylene)oxindole derivative **5**, instead of the anticipated spiroxindole derivatives **3** and **4**.

3-(Aminomethylene)oxindoles are well known to serve as useful building blocks in total syntheses of natural products,[5] and additionally these oxindoles have been identified as protein kinase inhibitors.[6] Although several methods have been developed recently for the synthesis of 3-(aminomethylene)oxindole derivatives including palladium-catalyzed cyclization of α,β-acetylenic amides,[7] reaction of 2-alkynylaryl isocyanates with amides[8] and stereoselective synthesis of 3-(aminomethylene)oxindoles via Ugi-carbopalladative cyclization–Buchwald reaction pathways,[9] the synthesis of 3-aminomethylene



Scheme 1 Reaction of α-azido ketone with isatylidene malononitrile

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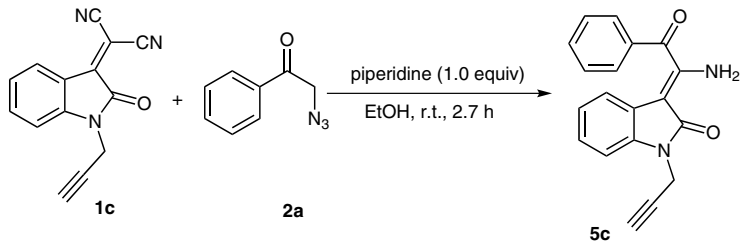


Scheme 2 Synthesis of 3-(aminomethylene)oxindole **5c**

Table 1 Effect of the Different Solvents and Bases on the Time and Yield of Reaction[a]

Entry	Solvent	Base	Time (h)	Yield (%)
1	EtOH	K_2CO_3	24	–
2	EtOH	NaOMe	24	–
3	EtOH	NaOEt	24	–
4	EtOH	DABCO	16	12
5	EtOH	piperidine	2.7	67
6	EtOH	pyrrolidine	5	40
7	EtOH	Et_3N	24	8
8	H_2O	piperidine	24	–
9	MeOH	piperidine	8	30
10	MeCN	piperidine	24	trace
11	toluene	piperidine	24	–
12	DMF	piperidine	24	–

[a] All the reactions were conducted at r.t.

oxindoles from readily available starting materials such as isatylidene malononitriles and azido ketones has not been yet documented. Based upon the above considerations and in continuation of our efforts on developing new strategies towards spiroxindoles using isatylidene malononitriles as electrophiles,[10] herein we wish to report a simple one-pot method for the synthesis of 3-(aminomethylene)oxindole derivatives.

Initially we examined the reaction of α-azido ketone **2a** (1.25 mmol) with isatylidene malononitrile **1c** (1.0 mmol) in ethanol in the presence of catalytic amount (30 mol%) of piperidine at room temperature for five hours after which time we obtained the product in 35% yield. Enhancement in the yield of the product to 67% was achieved by using equimolar amount of piperidine (Scheme 2). Further the reaction was conducted in the presence of various bases (Table 1, entries 1–7). Out of all bases screened, pyrrolidine and piperidine were found to be suitable for this transformation (Table 1, entries 5 and 6). To find out the effect of solvent on the yield of the reaction, different solvents were examined (Table 1, entries 8–12). Maximum yield of the product was achieved when ethanol was used as the solvent (Table 1, entry 5). The product **5c** was isolated as a single diastereomer by column chromatography and the structure was established by spectroscopic analysis. In the IR spectrum of **5c**, the peaks at 3407 and 3285 cm^{-1} were diagnostic of the primary amine group. In the ^1H NMR spectrum, the NH_2 protons were observed at δ = 8.64 and 8.99 ppm as two singlets. In the ^{13}C NMR spectrum, carbon attached to amino group resonated at δ = 155.5 ppm. The mass spectrum of **5c** displayed the molecular ion $[M^+ + H]$ peak at $m/z = 303$. Further the stereochemistry of **5c** was confirmed as *Z*-selectivity based on its single crystal X-ray diffraction analysis (Figure 1).[11]

Since α-azido ketones and isatylidene malononitriles are readily available, the domino approach to 3-aminomethylene oxindoles is highly attractive. Therefore we extended the substrate scope to various isatylidene malononitriles and α-azido ketones using the optimized conditions (Scheme 3, Table 2).[12] It is noteworthy that all 3-(aminomethylene)oxindoles showed excellent diastereoselectivity as established by ^1H NMR spectroscopy.

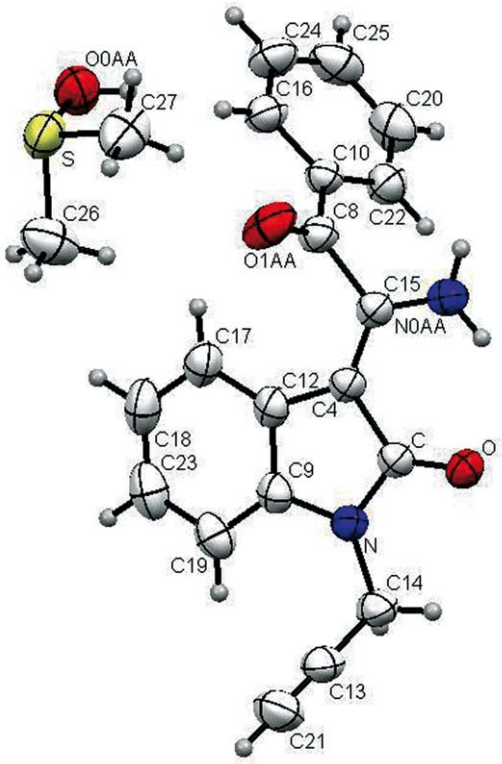
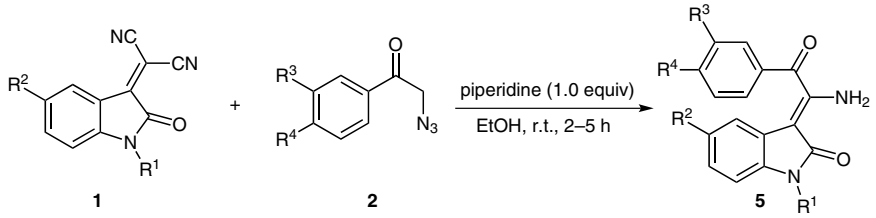
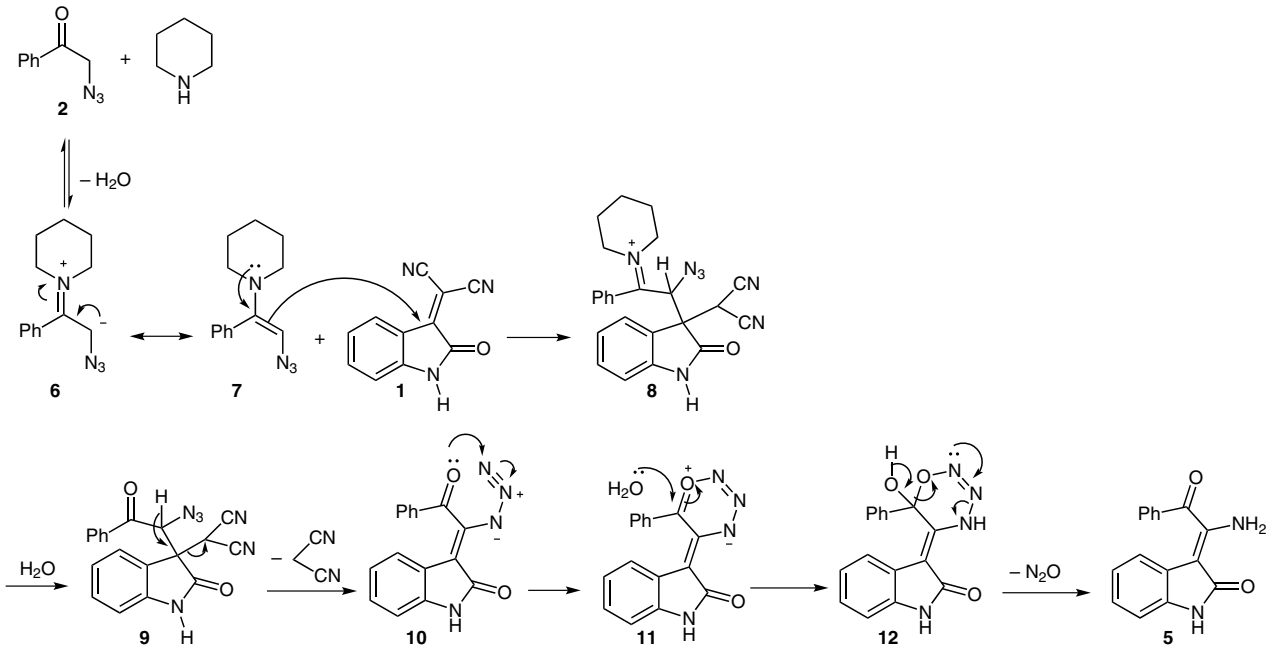


Figure 1 ORTEP diagram of compound **5c** with DMSO solvate



Scheme 3 Synthesis of 3-(Aminomethylene)oxindoles **5a**–**n**



Scheme 4 Plausible mechanism for the formation of **5**

To account for the formation of products, a plausible mechanism is depicted in Scheme 4. Initially piperidine reacts with α-azido ketone **2** to form enamine **7**, which undergoes Michael addition with isatylidene malononitrile **1** to form adduct **9**. Elimination of malononitrile from the adduct **9** results in the formation of vinyl azide **10**. Intramolecular cyclization of vinyl azide **10** may take place to form a oxatriazine **11**,[13] which transforms to intermediate **12** by the addition of water. Finally the intermediate **12** rearranges to form product **5**.

Table 2 Synthesis of 3-(Aminomethylene)oxindoles **5a**–**n** from Isatylidene Malononitriles and α-Azido Ketones

Entry	Isatylidene malononitrile **1**		Azido ketone **2**		Product **5**	Time (h)	Yield (%)[a]
	R^1	R^2	R^3	R^4			
1	H	H	H	H	**5a**	2.0	65
2	allyl	H	H	H	**5b**	2.5	60
3	propargyl	H	H	H	**5c**	2.7	67
4	CH_2COOEt	H	H	H	**5d**	2.4	70
5	benzyl	H	H	H	**5e**	3.0	65
6	Me	H	H	H	**5f**	3.5	59
7	H	Me	H	H	**5g**	4.5	61
8	H	Cl	H	H	**5h**	4.2	62
9	propargyl	H	C_4H_4		**5i**	5.0	56
10	allyl	H	C_4H_4		**5j**	4.5	52

Table 2 Synthesis of 3-(Aminomethylene)oxindoles **5a–n** from Isatylidene Malononitriles and α-Azido Ketones (continued)

Entry	Isatylidene malononitrile **1**		Azido ketone **2**		Product **5**	Time (h)	Yield (%)[a]
	R^1	R^2	R^3	R^4			
11	H	H	H	Cl	**5k**	3.9	50
12	CH_2COOEt	H	H	Cl	**5l**	3.2	55
13	allyl	H	H	Cl	**5m**	3.8	51
14	propargyl	H	H	Cl	**5n**	3.1	64

[a] Isolated yield after column chromatography.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) Crystallographic data for compound **5c** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication number CCDC 840032. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or email: deposit@ccdc.cam.ac.uk].

(12) **General Procedure for the Synthesis of Oxyindolyl Enaminone**: To a stirred solution of isatylidene malononitrile **1** (1.0 mmol) and α-azido ketone **2** (1.25 mmol) in EtOH (5 mL), was added piperidine (1.0 mmol). Stirring was continued at r.t. for appropriate times as mentioned in Table 2. After the reaction was complete as indicated by TLC, solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–PE, 25:75). **(*Z*)-3-(1-Amino-2-oxo-2-phenylethylidene)indolin-2-one (5a)**: brown solid; mp 246–248 °C. IR (KBr): 3413, 3260, 2925, 1665, 1616, 1461, 1324, 1210, 1005, 783, 724, 669, 581, 513 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ = 6.45 (d, *J* = 7.65 Hz, 1 H, ArH), 6.52 (t, *J* = 7.65 Hz, 1 H, ArH), 6.75–6.78 (m, 2 H, ArH), 7.42 (d, *J* = 7.65 Hz, 2 H, ArH), 7.65 (t, *J* = 7.65 Hz, 1 H, ArH), 7.72 (br s, 1 H, D_2O exchangeable, NH), 7.99 (d, *J* = 7.65 Hz, 2 H, ArH), 9.01 (br s, 1 H, D_2O exchangeable, NH), 9.81 (s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 94.2, 109.4, 117.9, 120.4, 122.9, 123.6, 129.3, 130.1, 134.0, 135.1, 136.8, 154.5, 171.1, 192.0. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.82; H, 4.56; N, 10.62. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{12}N_2O_2$: 265.0972 $[M + H]^+$; found: 265.0977. **(*Z*)-3-(1-Amino-2-oxo-2-phenylethylidene)-1-(prop-2-ynyl)indolin-2-one (5c)**: orange solid; mp 220–222 °C. IR (KBr): 3407, 3285, 2931, 1665, 1616, 1464, 1352, 724, 679, 583 cm. ^1H NMR (500 MHz, DMSO-d_6): δ = 3.18 (s, 1 H, ≡CH), 4.62 (s, 2 H, CH_2), 6.46 (d, *J* = 7.65 Hz, 1 H, ArH), 6.68 (t, *J* = 7.65 Hz, 1 H, ArH), 6.96 (t, *J* = 7.65 Hz, 1 H, ArH), 7.00 (d, *J* = 7.65 Hz, 1 H, ArH), 7.59 (t, *J* = 7.65 Hz, 2 H, ArH), 7.73 (t, *J* = 7.65 Hz, 1 H, ArH), 8.00 (d, *J* = 7.65 Hz, 2 H, ArH), 8.64 (br s, 1 H, D_2O exchangeable, NH), 8.99

(br s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.0, 73.9, 78.9, 91.4, 108.6, 117.0, 121.1, 121.9, 123.4, 129.6, 129.7, 130.1, 133.5, 135.5, 155.5, 167.2, 191.5. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.44; H, 4.63; N, 9.23. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{14}N_2O_2$: 303.1128 $[M + H]^+$; found: 303.1142.

(*Z*)-Ethyl 2-[3-(1-Amino-2-oxo-2-phenylethylidene)-2-oxoindolin-1-yl]acetate (5d): pale orange solid; mp 230–232 °C. IR (KBr): 3404, 3294, 2924, 1714, 1668, 1624, 1496, 1365, 728, 588 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, *J* = 6.05 Hz, 3 H, Me), 4.12 (q, *J* = 7.65 Hz, 2 H, CH_2), 4.63 (s, 2 H, CH_2), 6.46 (d, *J* = 7.65 Hz, 1 H, ArH), 6.66 (t, *J* = 5.35 Hz, 1 H, ArH), 6.91 (t, *J* = 6.10 Hz, 2 H, ArH), 7.60 (t, *J* = 7.65 Hz, 2 H, ArH), 7.74 (t, *J* = 7.65 Hz, 1 H, ArH), 8.00 (d, *J* = 2 H, ArH), 8.61 (br s, 1 H, D_2O exchangeable, NH), 8.90 (br s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.6, 41.0, 61.5, 92.0, 108.7, 117.4, 121.3, 122.3, 123.8, 130.1, 134.0, 135.9, 137.4, 155.7, 168.5, 169.0, 192.0. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.52; H, 5.16; N, 8.06. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{18}N_2O_4$: 351.1339 $[M + H]^+$; found: 351.1345.

(*Z*)-3-(1-Amino-2-oxo-2-phenylethylidene)-1-benzylindolin-2-one (5e): brown solid; mp 233–235 °C. IR (KBr): 3410, 3281, 3057, 1663, 1619, 1464, 741, 700, 600 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 5.00 (s, 2 H, CH_2), 6.46 (d, *J* = 8.4 Hz, 1 H, ArH), 6.62 (t, *J* = 3.85 Hz, 1 H, ArH), 6.84 (d, *J* = 7.65 Hz, 2 H, ArH), 7.27–7.37 (m, 5 H, ArH), 7.59 (t, *J* = 7.65 Hz, 2 H, ArH), 7.73 (t, *J* = 7.65 Hz, 1 H, ArH), 8.02 (d, *J* = 7.65 Hz, 2 H, ArH), 8.61 (br s, 1 H, D_2O exchangeable, NH), 9.00 (br s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 42.6, 92.1, 109.0, 117.4, 121.2, 122.4, 123.8, 127.5, 127.7, 129.1, 130.1, 130.2, 134.0, 135.9, 137.9, 137.9, 155.7, 168.6, 192.1. Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.89; H, 5.18; N, 7.92. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{18}N_2O_2$: 355.1441 $[M + H]^+$; found: 355.1457.

(*Z*)-3-(1-Amino-2-oxo-2-phenylethylidene)-5-methylindolin-2-one (5g): orange solid; mp 210–212 °C. IR (KBr): 3423, 3154, 1665, 1618, 1481, 1326, 791, 718, 671, 587 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.94 (s, 3 H, Me), 6.20 (s, 1 H, ArH), 6.65–6.68 (m, 2 H, ArH), 7.58 (t, *J* = 7.65 Hz, 2 H, ArH), 7.72 (t, *J* = 7.65 Hz, 1 H, ArH), 7.98 (d, *J* = 7.65 Hz, 2 H, ArH), 8.33 (br s, 1 H, D_2O exchangeable, NH), 9.01 (br s, 1 H, D_2O exchangeable, NH), 10.32 (s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.5, 93.3, 109.4, 118.2, 123.2, 124.4, 128.9, 130.0, 130.1, 134.1, 134.9, 135.8, 154.9, 170.8, 192.2. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.41; H, 5.11; N, 10.03. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_2O_2$: 279.1128 $[M + H]^+$; found: 279.1133.

(*Z*)-3-[1-Amino-2-(naphthalen-2-yl)-2-oxoethylidene]-1-(prop-2-ynyl)indolin-2-one (5i): bright orange solid; mp 246–248 °C. IR (KBr): 3410, 3297, 3054, 2931, 1669, 1619, 1468, 1357, 1278, 1183, 669, 582 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.23 (t, *J* = 2.3 Hz, 1 H, ≡C*H*), 4.63 (d, *J* = 2.3 Hz, 2 H, CH_2), 5.61 (br s, 1 H, D_2O exchangeable, NH), 6.69–6.74 (m, 2 H, ArH), 7.00–7.05 (m, 2 H, ArH), 7.53 (t, *J* = 8.05 Hz, 1 H, ArH), 7.63 (t, *J* = 8.05 Hz, 1 H, ArH), 7.86–7.94 (m, 3 H, ArH), 8.14 (d, *J* = 8.55 Hz, 1 H, ArH), 8.57 (s, 1 H, ArH), 9.1 (br s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, $CDCl_3$-d_6): δ = 28.7, 71.9, 77.7, 95.6, 108.6, 119.0, 121.8, 121.9, 123.8, 124.5, 127.4, 128.0, 129.6, 129.9, 130.2, 132.5, 134.0, 136.6, 137.1, 153.4, 168.5, 191.7. Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.43; H, 4.63; N, 7.91. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{16}N_2O_2$: 353.1285 $[M + H]^+$; found: 353.1290.

(*Z*)-3-[1-Amino-2-(4-chlorophenyl)-2-oxoethylidene]-indolin-2-one (5k): orange solid; mp 236–238 °C. IR (KBr): 3317, 3158, 2925, 2854, 1664, 1614, 1469, 1359, 1279, 1182, 785, 749, 477 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 6.38 (d, *J* = 7.65 Hz, 1 H, ArH), 6.59 (t, *J* = 7.65 Hz, 1 H, ArH), 6.79 (d, *J* = 7.65 Hz, 1 H, ArH), 6.85 (t, *J* = 7.65 Hz, 1 H, ArH), 7.65 (d, *J* = 8.45 Hz, 2 H, ArH), 7.99 (d, *J* = 8.45 Hz, 2 H, ArH), 8.38 (br s, 1 H, D_2O exchangeable, NH), 9.02 (br s, 1 H, D_2O exchangeable, NH), 10.47 (s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 79.6, 93.4, 109.7, 117.5, 120.6, 123.9, 130.3, 131.9, 132.8, 137.1, 140.8, 154.4, 170.6, 191.1. Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.39; H, 3.67; N, 9.32.

(*Z*)-Ethyl 2-{3-[1-Amino-2-(4-chlorophenyl)-2-oxoethylidene]-2-oxoindolin-1-yl}acetate (5l): bright orange solid; mp 221–223 °C. IR (KBr): 3347, 3194, 2925, 1743, 1663, 1613, 1469, 1368, 1275, 1174, 1092, 1016, 754, 593, 539 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, *J* = 7.3 Hz, 3 H, Me), 4.12 (q, *J* = 6.85 Hz, 2 H, CH_2), 4.63 (s, 2 H, CH_2), 6.45 (d, *J* = 7.65 Hz, 1 H, ArH), 6.68 (t, *J* = 7.65 Hz, 1 H, ArH), 6.89–6.93 (m, 2 H, ArH), 7.67 (d, *J* = 8.4 Hz, 2 H, ArH), 8.0 (d, *J* = 7.6 Hz, 2 H, ArH), 8.59 (br s, 1 H, D_2O exchangeable, NH), 8.94 (br s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 14.6, 41.0, 61.5, 92.0, 108.7, 117.4, 121.4, 122.1, 123.9, 130.3, 131.9, 132.7, 137.5, 140.9, 155.0, 169.0, 191.0. Anal. Calcd for $C_{20}H_{17}ClN_2O_4$: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.48; H, 4.51; N, 7.21. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{17}ClN_2O_4$: 385.0950 $[M + H]^+$; found: 385.0955.

(13) McEwen, W. E.; Conrad, W. E.; VanderWerf, C. A. *J. Am. Chem. Soc.* **1952**, *74*, 1168.

