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One-pot synthesis of highly substituted indolines

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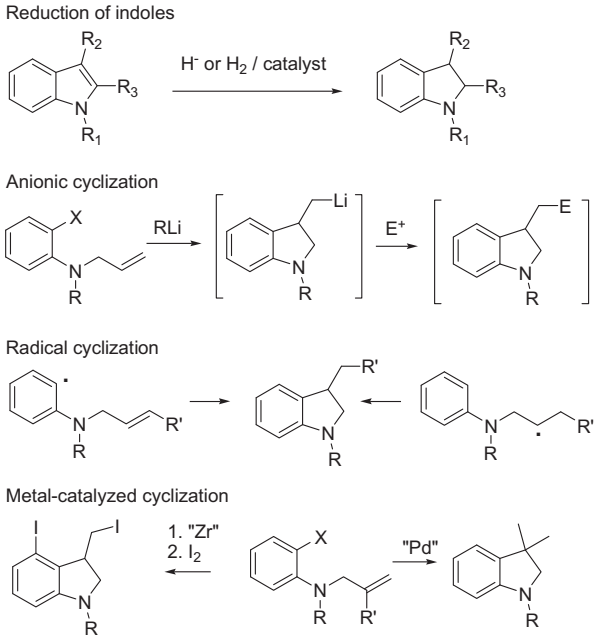
ABSTRACT

A general and convenient one-pot synthesis of highly substituted indolines from arylhydrazines and aldehydes is reported. This synthesis allows introduction of substitution at essentially all positions of the indoline nucleus to achieve significant diversity in this biologically important template.

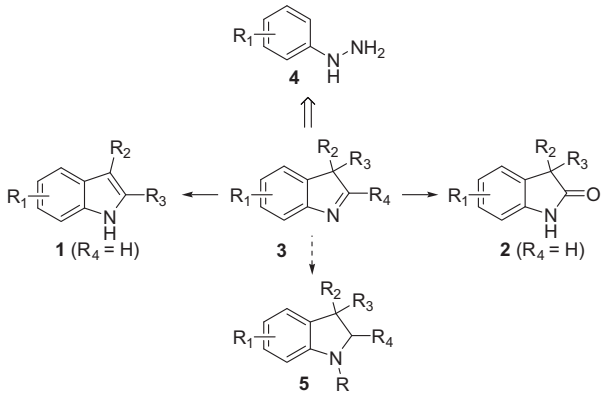
1. Introduction

Indolines are common structural elements in many biologically active compounds and natural products.[1–5] A great number of methods have been developed for synthesis of this important class of compounds. These (Scheme 1) include reduction of indoles,[6–18] anionic,[19–23] radical,[24–26] and metal-mediated[27–30] intramolecular cyclizations, as well as several other approaches.[31–33]



Scheme 1. Selected existing syntheses of indolines.

As part of our efforts in developing therapeutic agents for CNS diseases, we desired a convenient and versatile synthesis of 3,3-disubstituted indolines with potential substitution at alternate positions of the scaffold. We recently reported the synthesis of indoles **1**[34] and oxindoles **2**[35] from indolenines **3**, which could be readily synthesized from arylhydrazines **4** (Scheme 2). To further extend the utility of the indolenine template, we report herein a general and convenient one-pot synthesis of 3,3-disubstituted indolines **5**, which allows introduction of substitution at essentially any position of the molecule. Although sporadic synthesis of indolines from their corresponding indolenines have been previously reported,[36–41] the examples were generally limited to 3,3-dimethylindolines and the synthesis required isolation of relatively instable indolenines.



Scheme 2. Synthetic utility of indolenines.

2. Results and discussion

One critical requirement for a one-pot synthesis for a multi-step chemical transformation is that the solvent system is

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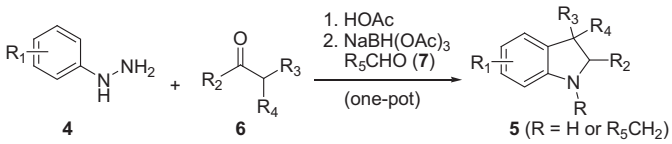
Table 1
One-pot synthesis of 3,3-disubstituted indolines from arylhydrazines[a]



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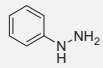
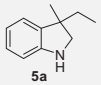
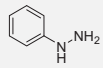
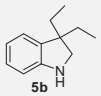
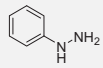
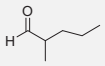
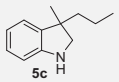
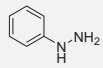
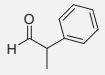
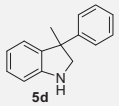
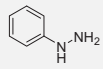
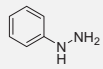
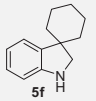
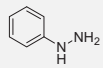
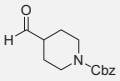
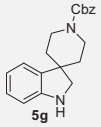
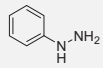
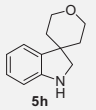
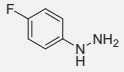
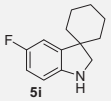
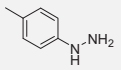
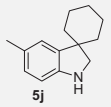
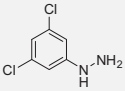
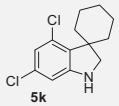
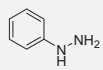
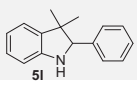
1			—	 5a	59
2			—	 5b	58
3			—	 5c	63
4			—	 5d	73
5			—	 5e	0
6			—	 5f	73
7			—	 5g	50
8			—	 5h	49
9			—	 5i	47
10			—	 5j	56
11			—	 5k	77
12			—	 5l	66

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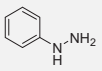
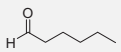
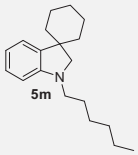
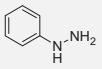
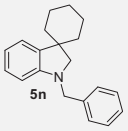
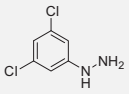
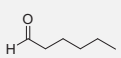
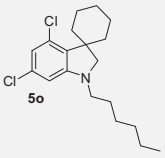
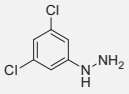
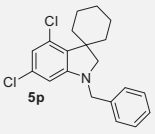
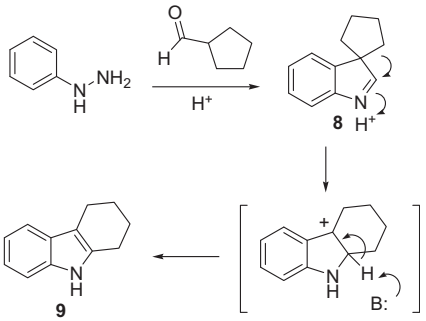
13					55
14					44
15					63
16					60

[a] Reaction conditions: 1. **4** (3.57 mmol), **6** (3.57 mmol) in AcOH (11.9 mL), 60–80 °C, 1-3 h; 2. $NaBH(OAc)_3$ (4.64 mmol, 1.3 equiv) or $NaBH(OAc)_3$ (8.20 mmol, 2.3 equiv) and aldehyde **7** (3.57 mmol).
[b] All hydrazines used were HCl salts except phenylhydrazine.
[c] Isolated yield after chromatography.

compatible with all the reactions in the synthetic sequence. In our efforts to develop a one-pot synthesis of indolines **5** from arylhydrazines **4**, composed of a Fischer indole reaction, indolenine **3** C=N bond reduction, and final reductive amination with a suitable aldehyde, we chose acetic acid as the solvent system because we have previously demonstrated the utility of this solvent for indolenine formation.[34,35] Furthermore, acetic acid has been commonly used as a catalyst for imine reduction and reductive amination with mild reducing agents such as $NaBH_3CN$ and $NaBH(OAc)_3$.[42] For our purposes we chose the less toxic reducing agent $NaBH(OAc)_3$ for indolenine reduction and reductive amination. Although initially it was our concern that $NaBH(OAc)_3$ may decompose in acetic acid solvent, we envisioned that C=N bond reduction and reductive amination could be significantly accelerated in acetic acid and therefore may successfully compete with the decomposition.

To explore the feasibility, scope and limitations of this one-pot approach, a number of arylhydrazines **4**, α-branched aldehydes **6** (for indolenine formation), and aldehydes **7** (for reductive amination) were utilized and the results are summarized in Table 1. In almost all cases, the indolenine formation went smoothly in neat acetic acid. In general, the reaction was complete in several hours at 80 °C with free arylhydrazines and at 60 °C with arylhydrazine HCl salts, where progress of the reactions was best monitored by LC–MS. The one exception that we encountered to this general process was in the case of cyclopentane carboxaldehyde (entry 5). The reaction intermediate, the indolenine **8** quickly rearranged to the indole product **9** (Scheme 3), presumably due to the ring constrain of cyclopentane. In all other examples investigated, the indolenine reduction went smoothly at temperatures below 20 °C as soon as the addition of $NaBH(OAc)_3$ was complete. In practice, the reaction mixture was diluted (2–3 times) with 1,2-dichloroethane before the reduction due to the high freezing point of acetic acid (16.2 °C).



Scheme 3. Rearrangement of spiroindolenines.

To further demonstrate that introduction of substitution at the 1-position could also be carried out in this one-pot procedure, hexanal or benzaldehyde was added after the initial indolenine formation followed by addition of $NaBH(OAc)_3$ and the desired products were isolated in good yields (entries 13–16).

3. Conclusion

We have developed a convenient and general one-pot synthesis of 3,3-disubstituted indolines from arylhydrazines via Fischer indole synthesis followed by indolenine reduction and reductive amination. This synthesis allows introduction of substitution at essentially all positions of the indole nucleus to achieve significant diversity in this biologically important template.

4. Experimental

4.1. General

All solvents and reagents were obtained commercially and used as received. ^1H and ^{13}C NMR spectra were recorded on a Varian

instrument in the cited deuterated solvents. Chemical shifts are given in ppm, and coupling constants are in Hertz. All final compounds were purified by flash chromatography using 220–400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25-nm thickness) plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol. Mass spectra were recorded on either a Finnigan or a Hewlett–Packard spectrometer. LC–MS was run on an Agilent system with a Hewlett–Packard mass spectrometer.

4.2. General procedure for one-pot synthesis of indolines

4.2.1. Synthesis of N1-unsubstituted indolines. A mixture of arylhydrazine **4** or its HCl salt (3.57 mmol) and α,α-branched aldehyde **6** (3.57 mmol) in AcOH (11.9 mL) was stirred at 60–80 °C for 1–3 h (in general, 80 °C for free hydrazines and 60 °C for hydrazine HCl salts). The reaction was ideally monitored by LC–MS. Upon completion, the reaction mixture was cooled with cold water and diluted with 1,2-dichloroethane (11.9 mL) followed by treatment with $NaBH(OAc)_3$ (4.64 mmol, 1.3 equiv) in portions with cooling in cold water and was then stirred for 10 min followed by 20 min at room temperature. The reaction mixture was concentrated to dryness and extracted with EtOAc and washed with Na_2CO_3. The organic layer was dried over Na_2SO_4 and purified by chromatography with EtOAc/hexanes or CH_2Cl_2/hexanes to provide the indoline products.

4.2.2. Synthesis of N1-unsubstituted indolines. The same procedure was followed except aldehyde **7** (3.57 mmol) was added before $NaBH(OAc)_3$ (8.20 mmol, 2.3 equiv) reduction.

4.3. Characterization of compounds 5a–5p

*4.3.1. 3-Ethyl-3-methylindoline (**5a**).* Yield 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 (t, *J*=7.5 Hz, 3H) 1.13 (s, 3H) 1.44–1.55 (m, 2H) 3.04 (dd, *J*=8.9 and 2.2 Hz, 2H) 3.04 (dd, *J*=8.9 and 1.6 Hz, 2H) 5.3 (s, 1H) 6.42 (d, *J*=7.6 Hz, 1H) 6.48 (dt, *J*=7.3 and 1.0 Hz, 1H) 6.83–6.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 9.6, 26.0, 33.2, 45.3, 58.9, 109.1, 117.3, 122.8, 127.6, 137.1, 152.2. HRMS Calcd for $(M+H)^+$: $C_{11}H_{16}N^+$: 162.1277, Found: 162.1278.

*4.3.2. 3,3-Diethylindoline (**5b**).* Yield 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.70 (t, *J*=7.5 Hz, 6H) 1.43–1.60 (m, 4H) 3.16 (d, *J*=1.7 Hz, 2H) 5.28 (s, 1H) 6.41 (d, *J*=7.7 Hz, 1H) 6.46 (dt, *J*=7.3 and 0.9 Hz, 1H) 6.82–6.87 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 9.3, 31.0, 49.1, 56.5, 109.0, 117.0, 123.5, 127.6, 135.0, 152.9. HRMS Calcd for $(M+H)^+$: $C_{12}H_{18}N^+$: 176.1434, Found: 176.1435.

*4.3.3. 3-Methyl-3-propylindoline (**5c**).* Yield 63%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (t, *J*=7.3 Hz, 3H) 1.00–1.12 (m, 1H) 1.14 (s, 3H) 1.22–1.30 (m, 1H) 1.36–1.52 (m, 2H) 3.04 (dd, *J*=8.9 and 2.3 Hz, 1H) 3.21 (dd, *J*=8.9 and 1.9 Hz, 1H) 5.31 (s, 1H) 6.41 (d, *J*=7.7 Hz, 1H) (dt, *J*=7.4 and 1.1 Hz, 1H) 6.82–6.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 15.3, 18.2, 26.5, 43.4, 45.1, 59.3, 109.1, 117.3, 122.7, 127.5, 137.4, 152.1. HRMS Calcd for $(M+H)^+$: $C_{12}H_{18}N^+$: 176.1434, Found: 176.1437.

*4.3.4. 3-Methyl-3-phenylindoline (**5d**).* Yield 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (s, 3H) 3.42 (d, *J*=8.9 Hz, 1H) 3.56 (d, *J*=9.0 Hz, 1H) 5.51 (s, 1H) 6.53–6.57 (m, 2H) 6.86 (dd, *J*=7.9 and 1.0 Hz, 1H) 6.93 (dt, *J*=7.5 and 1.3 Hz, 1H) 7.10–7.15 (m, 1H) 7.20–7.28 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 27.1, 49.6, 63.4, 109.8, 117.9, 124.1, 126.5, 126.8, 128.0, 128.7, 137.1, 148.8, 152.2. HRMS Calcd for $(M+H)^+$: $C_{15}H_{16}N^+$: 210.1277, Found: 210.1281.

*4.3.5. Spiro[cyclohexane-1,3′-indoline] (**5f**).* Yield 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25–1.65 (m, 10H) 3.22 (d, *J*=2.1 Hz, 2H) 5.35 (s, 1H) 6.40 (d, *J*=7.7 Hz, 1H) 6.47 (dt, *J*=7.4 and 1.0 Hz, 1H) 6.83 (dt, *J*=7.6 and 1.3 Hz, 1H) 6.91 (d, *J*=7.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 23.3, 26.0, 36.8, 46.0, 56.7, 109.2, 117.3, 122.6, 127.7, 138.4, 151.9. HRMS Calcd for $(M+H)^+$: $C_{13}H_{17}N^+$: 188.1434, Found: 188.1437.

*4.3.6. Benzyl spiro[indoline-3,4′-piperidine]-1′-carboxylate (**5g**).* Yield 50%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52–1.66 (m, 4H) 2.85–3.10 (m, 4H) 3.27 (s, 1H) 3.92 (d, *J*=13.7 Hz, 2H) 5.05 (s, 2H) 6.44–6.51 (m, 2H) 6.87 (dt, *J*=7.7 and 1.1 Hz, 1H) 6.94 (d, *J*=7.3 Hz, 1H) 7.26–7.36 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 35.8, 41.5, 44.4, 55.7, 66.9, 109.5, 117.7, 122.9, 128.1, 128.2, 128.5, 129.0, 136.7, 137.7, 151.9, 155.2. HRMS Calcd for $(M+H)^+$: $C_{20}H_{23}N_2O_2^+$: 323.1754, Found: 323.1758.

4.4. 2′,3′,5′,6′-Tetrahydrospiro[indoline-3,4′-pyran] (5h)

Yield 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (dd, *J*=13.2 and 1.7 Hz, 2H) 1.75 (dt, *J*=13.0 and 4.6 Hz, 2H) 3.40–3.51 (m, 2H) 3.74–3.78 (m, 2H) 5.44 (s, 1H) 6.44 (d, *J*=7.8 Hz, 1H) 6.50 (dt, *J*=7.4 and 1.0 Hz, 1H) 6.86 (dt, *J*=7.7 and 1.3 Hz, 1H) 6.96 (d, *J*=7.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 36.9, 43.7, 56.2, 64.8, 109.3, 117.5, 122.9, 128.0, 137.0, 152.0. HRMS Calcd for $(M+H)^+$: $C_{12}H_{16}NO^+$: 190.1226, Found: 190.1227.

*4.4.1. 5′-Fluorospiro[cyclohexane-1,3′-indoline] (**5i**).* Yield 47%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17–1.69 (m, 10H) 3.26 (d, *J*=10.7 Hz, 2H) 5.26 (s, 1H) 6.36 (dd, *J*=8.3 and 4.4 Hz, 1H) 6.64 (dt, *J*=9.6 and 2.4 Hz, 1H) 6.78 (dd, *J*=8.8 and 2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 23.2, 25.8, 36.3, 46.4, 57.1, 109.2, 109.3, 110.1, 110.3, 113.4, 113.6, 140.4, 140.4, 148.2, 155.0, 157.3. HRMS Calcd for $(M+H)^+$: $C_{13}H_{17}FN^+$: 206.1340, Found: 206.1342.

*4.4.2. 5′-Methylspiro[cyclohexane-1,3′-indoline] (**5j**).* Yield 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21–1.58 (m, 10H) 2.12 (s, 3H), 3.20 (s, 2H) 5.12 (s, 1H) 6.33 (d, *J*=7.5 Hz, 1H) 6.65 (d, *J*=7.2 Hz, 1H) 6.73 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 21.3, 23.4, 26.0, 36.8, 46.0, 56.9, 109.2, 123.4, 125.9, 128.0, 138.7, 149.6. HRMS Calcd for $(M+H)^+$: $C_{14}H_{20}N^+$: 202.1590, Found: 202.1593.

*4.4.3. 4′,6′-Dichlorospiro[cyclohexane-1,3′-indoline] (**5k**).* Yield 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08–1.33 (m, 3H) 1.47–1.58 (m, 5H) 2.05 (dt, *J*=13.1 and 3.5 Hz, 2H) 3.36 (d, *J*=1.1 Hz, 2H) 6.15 (s, 1H) 6.34 (d, *J*=1.7 Hz, 1H) 6.40 (d, *J*=1.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 22.7, 25.6, 33.4, 47.9, 56.4, 107.1, 116.8, 130.4, 131.3, 133.3, 155.2. HRMS Calcd for $(M+H)^+$: $C_{13}H_{16}Cl_2N^+$: 256.0660, Found: 256.0659.

*4.4.4. 3,3-Dimethyl-2-phenylindoline (**5l**).* Yield 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.65 (S, 3H) 1.45 (S, 3H) 4.53 (d, *J*=2.1 Hz, 1H) 6.49 (d, *J*=1.7 Hz, 1H) 6.56 (d, *J*=1.7 Hz, 1H) 6.69 (d, *J*=1.4 Hz, 1H) 7.27–7.36 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 22.4, 26.1, 46.8, 73.9, 107.6, 117.6, 128.1, 128.3, 128.7, 130.6, 131.6, 133.4, 139.5, 154.1. HRMS Calcd for $(M+H)^+$: $C_{16}H_{16}Cl_2N^+$: 292.0654, Found: 292.0658.

*4.4.5. 1′-Hexylspiro[cyclohexane-1,3′-indoline] (**5m**).* Yield 55%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (t, *J*=7.0 Hz, 3H) 1.10–1.70 (m, 18H) 2.98 (t, *J*=7.2 Hz, 2H) 3.13 (s, 2H), 6.35 (d, *J*=7.5 Hz, 1H) 6.48 (dt, *J*=7.4 and 0.8 Hz, 1H) 6.80–6.92 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 14.5, 22.8, 23.3, 25.9, 26.9, 27.0, 31.7, 36.8, 44.6, 48.4, 62.5, 107.1, 117.3, 122.5, 128.0, 139.0, 151.8. HRMS Calcd for $(M+H)^+$: $C_{19}H_{30}N^+$: 272.2373, Found: 272.2376.

*4.4.6. 1′-Benzylspiro[cyclohexane-1,3′-indoline] (**5n**).* Yield 44%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21–1.29 (m, 3H) 1.46–1.57 (m,

7H) 3.13 (s, 2H) 4.25 (s, 2H) 6.46 (d, J=7.9 Hz, 2H) 6.53 (t, J=7.3 Hz, 2H) 6.89–7.0 (m, 2H) 7.19–7.31 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 23.3, 25.9, 36.7, 44.7, 52.4, 62.9, 107.4, 117.7, 122.7, 127.6, 128.0, 128.3, 129.0, 139.0, 139.1, 151.5. HRMS Calcd for $(M+H)^+$: $C_{20}H_{24}N^+$: 278.1903, Found: 278.1907.

*4.4.7. 4′,6′-Dichloro-1′-hexylspiro[cyclohexane-1,3′-indoline] (**5o**).* Yield 63%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 (t, J=7.0 Hz, 3H) 1.10–1.70 (m, 14H) 2.08 (dt, J=13.2 and 4.0 Hz, 2H) 2.45–2.46 (m, 2H) 3.06 (d, J=7.2 Hz, 2H) 3.27 (s, 2H), 6.36 (d, J=1.7 Hz, 1H) 6.41 (d, J=1.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 14.5, 22.6, 22.7, 25.6, 26.5, 26.7, 31.7, 33.4, 46.4, 46.9, 61.7, 105.1, 116.5, 130.2, 131.8, 133.9, 154.4. HRMS Calcd for $(M+H)^+$: $C_{19}H_{28}Cl_2N^+$: 340.1593, Found: 340.1599.

*4.4.8. 1′-Benzyl-4′,6′-dichlorospiro[cyclohexane-1,3′-indoline] (**5p**).* Yield 60%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11–1.25 (m, 3H) 1.47–1.57 (m, 5H) 2.06–2.13 (m, 2H) 3.32 (s, 2H) 4.35 (s, 2H) 6.48 (dd, J=8.8 and 1.7 Hz, 2H) 7.20–7.32 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 22.6, 25.5, 33.4, 46.6, 50.8, 62.2, 105.5, 117.0, 127.8, 128.1, 129.2, 130.3, 131.8, 133.9, 138.0, 154.2. HRMS Calcd for $(M+H)^+$: $C_{20}H_{22}Cl_2N^+$: 346.1124, Found: 346.1129.

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