Synthesis of 3,3-Disubstituted Indoline-2-thiones Catalysed by *N*-Heterocyclic Carbene

Hideo Ikota,[a] Takayuki Ishida,[a] Chihiro Tsukano,[a] and Yoshiji Takemoto[a]

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

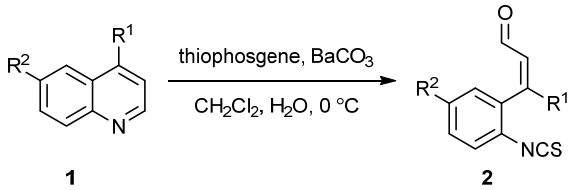
E-mail: takemoto@pharm.kyoto-u.ac.jp

Tel: 075-753-4528; Fax: 075-753-4569

Supplementary Information

General. Unless otherwise noted, all reactions were performed under argon atmosphere. Analytical thin-layer chromatography was performed with Merck Silica gel 60 and Merck 25 DC-Alufolein. Flash silica gel column chromatography was performed with Kanto Silica gel 60 N (spherical, neutral, 40-100 μm) or Fuji Silysia NH silica gel. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-ECA500 KP at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00 ppm), DMSO (δ 2.50 ppm), and acetone (δ 2.05 ppm). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); dd (double doublet); ddd (double double doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-ECA500 KP at 125 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0 ppm), DMSO-d_6 (δ 39.5 ppm), and acetone-d_6 (δ 206.3 ppm). Infrared spectra were recorded on FT/IR-4100 Fourier-transform infrared ATR attenuated total resonance (JASCO). Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on JEOL JMS-700 (FAB+). X-ray crystallographic data were recorded on RIGAKU R-AXIS RAPID.

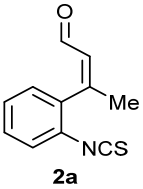
Typical Procedure for Preparation of Isothiocyanate-enal (2)



1 **2**

Typical procedure: To a solution of quinoline **1** (10.0 mmol, 1.00 equiv.) and barium carbonate (10.0 mmol, 1.00 equiv.) in 10 mL of CH_2Cl_2 and 10 mL of H_2O at 0 °C was added thiophosgene (10.0 mmol, 1.00 equiv.). After 40 min, the suspension was filtered through a pad of Celite and the filter cake was wash with CH_2Cl_2. The filterate was extracted with CH_2Cl_2 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 9/1 to 8/2) to give the enal **2**.

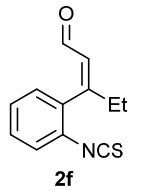
(*Z*)-3-(2-isothiocyanatophenyl)but-2-enal (2a)



2a

Using a typical procedure, from **1a** (1.31 mL, 10.0 mmol), **2a** (1.62 g, 80%) was obtained as an yellow oil; ^{1}H NMR ($CDCl_3$, δ); 9.30 (1H, d, J = 8.6 Hz), 7.42-7.38 (1H, m), 7.35-7.31 (2H, m), 7.24-7.23 (1H, m), 6.22 (1H, dd, J = 8.3, 1.4 Hz), 2.30 (3H, d, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$, δ): 191.7, 157.7, 137.2, 135.0, 130.7, 129.5, 129.2, 128.7, 127.1, 126.7, 25.8; IR (ATR): 2056, 1679 cm^{-1}; HRMS (MH^+) calcd for $C_{11}H_{10}NOS$: 204.0483. Found: 204.0481.

(*Z*)-3-(2-isothiocyanatophenyl)pent-2-enal (2f)

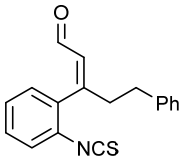


2f

Using a typical procedure, from **1f** (96.0 mg, 442 μmol), **2f** (72.6 mg, 66%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.32 (1H, d, J = 8.3 Hz), 7.41-7.37 (1H, m), 7.34-7.30 (2H, m), 7.20 (1H, d, J = 6.9 Hz), 6.21 (1H, d, J = 8.0 Hz), 2.58 (2H, q, J = 7.2 Hz), 1.15 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, δ): 192.3, 163.4, 137.4, 134.9, 129.63, 129.58, 129.3, 129.1, 127.1, 126.6, 32.3, 11.4; IR (ATR): 2060, 1678

cm^{-1}; HRMS (MH$^+$) calcd for $C_{12}H_{12}NOS$: 218.0640. Found: 218.0644.

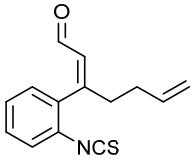
(*Z*)-3-(2-isothiocyanatophenyl)-5-phenylpent-2-enal (2g)



2g

Using a typical procedure, from **1g** (201 mg, 862 μmol), **2g** (176 mg, 70%) was obtained as an orange oil; ^{1}H NMR ($CDCl_3$, δ): 9.31 (1H, d, *J* = 8.0 Hz), 7.39-7.36 (1H, m), 7.33-7.24 (4H, m), 7.19 (1H, d, *J* = 7.4 Hz), 7.18-7.13 (3H, m), 6.23 (1H, d, *J* = 8.0 Hz), 2.91-2.84 (2H, m), 2.84-2.77 (2H, m); ^{13}C NMR ($CDCl_3$, δ): 192.1, 161.0, 139.9, 137.6, 134.3, 130.2, 129.83, 129.77, 129.4, 128.5, 128.2, 127.1, 126.8, 126.3, 40.6, 33.2; IR (ATR): 2062, 1677 cm^{-1}; HRMS (MH$^+$) calcd for $C_{18}H_{16}NOS$: 294.0953. Found: 294.0955.

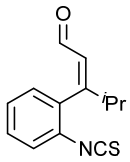
(*Z*)-3-(2-isothiocyanatophenyl)hepta-2,6-dienal (2h)



2h

Using a typical procedure, from **1h** (178 mg, 971 μmol), **2h** (157 mg, 67%) was obtained as an orange oil; ^{1}H NMR ($CDCl_3$, δ): 9.31 (1H, d, *J* = 8.0 Hz), 7.42-7.38 (1H, m), 7.35-7.31 (2H, m), 7.22-7.19 (1H, m), 6.22 (1H, d, *J* = 8.0 Hz), 5.83-5.75 (1H, m), 5.08-5.01 (2H, m), 2.67 (2H, t, *J* = 7.3 Hz), 2.29-2.21 (2H, m); ^{13}C NMR ($CDCl_3$, δ): 192.0, 160.9, 137.5, 136.3, 134.3, 130.3, 129.8, 129.7, 129.3, 127.0, 126.8, 116.0, 38.3, 30.9; IR (ATR): 2064, 1677 cm^{-1}; HRMS (MH$^+$) calcd for $C_{14}H_{13}NOS$: 243.0718. Found: 243.0710.

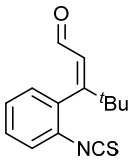
(*Z*)-3-(2-isothiocyanatophenyl)-4-methylpent-2-enal (2i)



2i

Using a typical procedure, from **1i** (47.3 mg, 276 μmol), **2i** (50.5 mg, 79%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.29 (1H, d, *J* = 8.0 Hz), 7.41-7.37 (1H, m), 7.35-7.30 (2H, m), 7.17 (1H, d, *J* = 8.0 Hz), 6.21 (1H, d, *J* = 8.0 Hz), 2.78-2.70 (1H, m), 1.21 (3H, d, *J* = 6.9 Hz), 1.14 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, δ): 192.8, 167.5, 136.9, 134.8, 129.9, 129.54, 129.49, 127.9, 126.9, 126.5, 36.7, 20.8, 20.4; IR (ATR): 2070, 1680 cm^{-1}; HRMS (MH$^+$) calcd for $C_{13}H_{14}NOS$: 232.0796. Found: 232.0793.

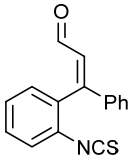
(*Z*)-3-(2-isothiocyanatophenyl)-4,4-dimethylpent-2-enal (2j)



2j

Using a typical procedure, from **1j** (150 mg, 810 μmol), **2j** (156 mg, 78%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.13 (1H, d, *J* = 8.0 Hz), 7.41-7.36 (1H, m), 7.35-7.29 (2H, m), 7.18-7.15 (1H, m), 6.31 (1H, d, *J* = 8.0 Hz), 1.21 (9H, s); ^{13}C NMR ($CDCl_3$, δ): 193.3, 169.6, 136.5, 133.9, 130.2, 130.1, 129.2, 128.5, 126.6, 126.2, 38.1, 28.8; IR (ATR): 2075, 1673 cm^{-1}; HRMS (MH$^+$) calcd for $C_{14}H_{16}NOS$: 246.0953. Found: 246. 0955.

(*Z*)-3-(2-isothiocyanatophenyl)-3-phenylacrylaldehyde (2k)

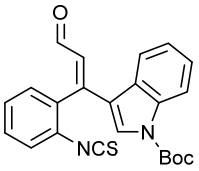


2k

Using a typical procedure, from **1k** (216 mg, 1.05 mmol), **2k** (209 mg, 75%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.45 (1H, d, *J* = 8.0 Hz), 7.51-7.43 (2H, m), 7.43-7.38 (3H, m), 7.38-7.33 (4H, m), 6.75 (1H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, δ): 192.2, 157.4, 137.4, 136.8, 133.3, 131.8, 130.9, 130.5,

130.3, 128.9, 128.3, 127.4, 127.0, 126.7; IR (ATR): 2064, 1667 cm^{-1}; HRMS (MH^+) calcd for $C_{16}H_{12}NOS$: 266.0640. Found: 266.0644.

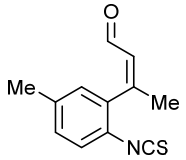
tert-butyl (_Z_)-3-(1-(2-isothiocyanatophenyl)-3-oxoprop-1-en-1-yl)-1_H_-indole-1-carboxylate (2l)



2l

Using a typical procedure, from **1l** (243 mg, 706 μmol), **2l** (225 mg, 79%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.47 (1H, d, *J* = 8.0 Hz), 8.16 (1H, d, *J* = 8.6 Hz), 7.64 (1H, d, *J* = 7.7 Hz), 7.50 (1H, dd, *J* = 7.3, 7.3 Hz), 7.46 (1H, s), 7.44-7.38 (3H, m), 7.35 (1H, d, *J* = 8.0 Hz), 7.30 (1H, dd, *J* = 7.7, 7.7 Hz), 6.93 (1H, d, *J* = 8.0 Hz), 1.66 (9H, s); ^{13}C NMR ($CDCl_3$, δ): 191.9, 150.8, 149.0, 137.9, 136.4, 133.7, 131.4, 130.8, 130.3, 129.1, 127.3, 127.1, 127.0, 126.5, 125.4, 123.8, 120.7, 120.0, 115.6, 85.1, 28.0; IR (ATR): 2979, 2056, 1735, 1666, 1450 cm^{-1}; HRMS (MH^+) calcd for $C_{23}H_{21}N_2O_3S$: 405.1273. Found: 405.1268.

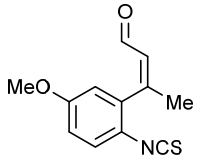
(_Z_)-3-(2-isothiocyanato-5-methylphenyl)but-2-enal (2m)



2m

Using a typical procedure, from **1m** (73.9 mg, 470 μmol), **2m** (46.3 mg, 45%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.32-9.30 (1H, m), 7.22-7.16 (2H, m), 7.03-7.00 (1H, m), 6.23-6.19 (1H, m), 2.37 (3H, s), 2.29 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 192.2, 158.3, 137.6, 136.9, 135.1, 131.1, 130.9, 130.4, 130.0, 126.7, 26.0, 21.1; IR (ATR); 2074, 1676 cm^{-1}: HRMS (MH^+) calcd for $C_{12}H_{12}NOS$: 218.0640. Found: 218.0635.

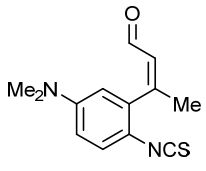
(_Z_)-3-(2-isothiocyanato-5-methoxyphenyl)but-2-enal (2n)



2n

Using a typical procedure, from **1n** (179 mg, 1.03 mmol), **2n** (92.7 mg, 39%) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, δ): 9.34 (1H, d, *J* = 8.3 Hz), 7.25 (1H, d, *J* = 8.9 Hz), 6.90 (1H, dd, *J* = 8.9, 2.9 Hz), 6.72 (1H, d, *J* = 2.9 Hz), 6.21 (1H, d, *J* = 8.3 Hz), 3.83 (3H, s), 2.30 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 192.0, 158.2, 157.8, 136.6, 136.3, 130.9, 128.1, 121,3, 114.9, 114.8, 55.7, 25.9; IR (ATR): 2066, 1679 cm^{-1}; HRMS (MH^+) calcd for $C_{12}H_{12}NO_2S$: 234.0589. Found: 234.0594.

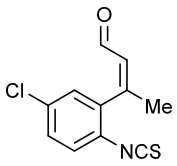
(_Z_)-3-(5-(dimethylamino)-2-isothiocyanatophenyl)but-2-enal (2o)



2o

Using a typical procedure, from **1o** (204 mg, 1.09 mmol), **2o** (39.2 mg, 15%) was obtained as an orange oil; ^{1}H NMR ($CDCl_3$, δ): 9.36 (1H, d, *J* = 8.3 Hz), 7.16 (1H, d, *J* = 8.9 Hz), 6.63 (1H, dd, *J* = 8.9, 2.9 Hz), 6.39 (1H, d, J = 2.9 Hz), 6.19 (1H, dd, *J* = 8.3, 1.4 Hz), 2.99 (6H, s), 2.30 (3H, d, *J* = 1.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 192.6, 159.3, 148.8, 136.3, 134.7, 130.7, 127.8, 116.2, 112.5, 111.8, 40.2, 26.0; IR (ATR): 2120, 1681 cm^{-1}; HRMS (MH^+) calcd for $C_{13}H_{15}N_2OS$: 247.0905. Found: 247.0909.

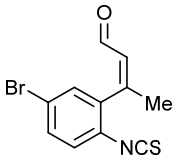
(*Z*)-3-(5-chloro-2-isothiocyanatophenyl)but-2-enal (2p)



2p

Using a typical procedure, from **1p** (178 mg, 1.00 mmol), **2p** (162 mg, 68%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 9.33 (1H, d, J = 8.3 Hz), 7.36 (1H, dd, J = 8.6, 2.3 Hz), 7.26 (1H, d, J = 8.6 Hz), 7.22 (1H, d, J = 2.3 Hz), 6.23 (1H, d, J = 8.3 Hz), 2.29 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 191.4, 156.2, 138.9, 136.7, 133.0, 131.4, 130.0, 129.3, 128.0, 127.9, 25.9; IR (ATR): 2045, 1682 cm^{-1}; HRMS (MH^+) calcd for $C_{11}H_9{}^{35}ClNOS$: 238.0093. Found: 238.0099.

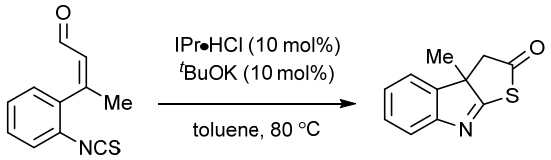
(*Z*)-3-(5-bromo-2-isothiocyanatophenyl)but-2-enal (2q)



2q

Using a typical procedure, from **1q** (222 mg, 1.00 mmol), **2q** (153 mg, 54%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 9.33 (1H, d, J = 8.3 Hz), 7.51 (1H, dd, J = 8.6, 2.3 Hz), 7.37 (1H, d, J = 2.3 Hz), 7.19 (1H, d, J = 8.6 Hz), 6.23 (1H, dd, J = 8.3 Hz), 2.29 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 191.4, 156.1, 139.0, 136.9, 132.8, 132.1, 131.4, 128.4, 128.2, 120.7, 25.9; IR (ATR): 2042, 1683 cm^{-1}; HRMS (MH^+) calcd for $C_{11}H_9{}^{79}BrNOS$: 281.9588. Found: 281.9594.

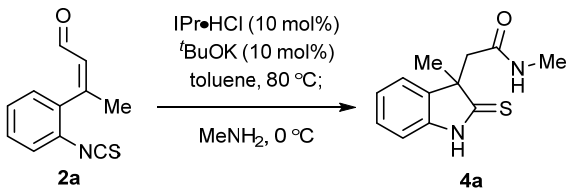
Synthesis of 3a-methyl-3,3a-dihydro-2*H*-thieno[2,3-b]indol-2-one (3a)



2a **3a**

To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (7.5 mg, 22.1 μmol) in 1 mL of toluene at ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 22.1 μL, 22.1 μmol). After 15 min, enal **2a** (45.0 mg, 221 μmol) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to 80 °C and stirred for additional 3 h. The resulting mixture was gradually cooled to ambient temperature and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/$CHCl_3$ = 5/5 to 0/10) to give the indolenine **3a** (7.0 mg, 16%) as an yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 7.65 (1H, dd, J = 8.2, 1.0 Hz), 7.43-7.40 (2H, m), 7.27-7.23 (1H, m), 3.10 (1H, d, J = 15.8 Hz), 2.56 (1H, d, J = 15.8 Hz), 1.47 (3H, d, J = 0.6 Hz); ^{13}C NMR ($CDCl_3$, δ): 201.9, 187.2, 156.0, 141.5, 128. 9, 125.6, 122.9, 120.7, 61.7, 52.0, 26.0; IR (ATR): 3369, 1248, 1192, 997, 793, 747 cm^{-1}; HRMS (MH^+) calcd for $C_{11}H_{10}NOS$: 204.0483. Found: 204.0480.

Synthesis of 3-methyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4a)

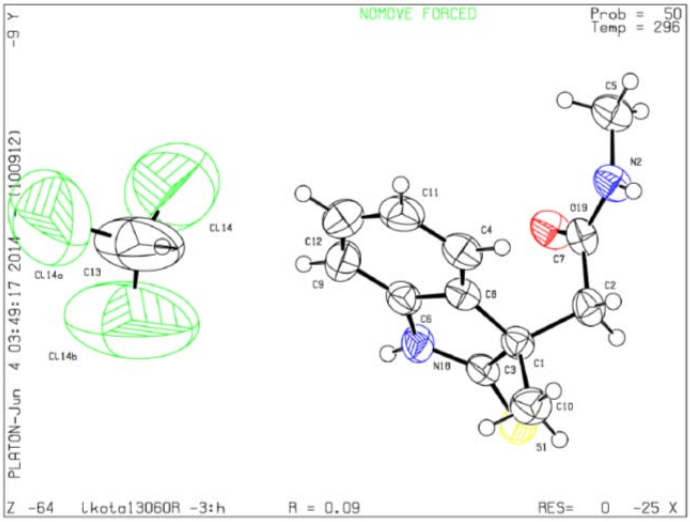


2a **4a**

To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (85.1 mg, 0.20 mmol) in 10 mL of toluene at ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 200 μL, 0.20 mmol). After 15 min, enal **2a**

(407 mg, 2.00 mmol) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to 80 °C and stirred for additional 3 h. The reaction mixture was gradually cooled to 0 °C and $MeNH_2$ (2.0 M sol. in THF, 2.0 mL, 4.00 mmol) was added. After additional 10 min, the reaction mixture was concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 4/6 to 2/8) to give the indoline-2-thione **4a** (354 mg, 75%) as an yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 9.83 (1H, s), 7.36 (1H, d, J = 7.4 Hz), 7.25-7.22 (1H, m), 7.15 (1H, dd, J = 7.4, 7.4 Hz), 6.99 (1H, d, J = 7.7 Hz), 5.62 (1H, s), 2.98 (1H, d, J = 14.3 Hz), 2.86 (1H, d, J = 14.3 Hz), 2.59 (3H, d, J = 4.9 Hz), 1.45 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 211.8, 169.3, 141.6, 138.0, 128.1, 124.1, 123.7, 110.3, 57.3, 46.2, 28.3, 26.1; IR (ATR): 3343, 3063, 1637, 1544, 1473 cm^{-1}; HRMS (MH^+) calcd for $C_{12}H_{15}N_2OS$: 235.0905. Found: 235.0907.

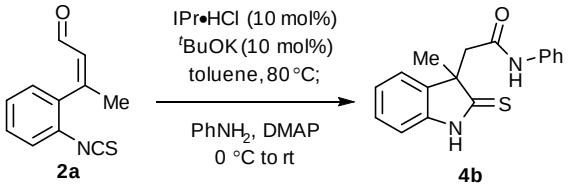
The X-ray structure of compound 4a (ORTEP)



Thermal ellipsoids are shown at the 50% probability level.

The crystallographic data reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-992277. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html. (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB21EZ, U.K.; fax +44 1223 336033; or deposit@ccdc.camac.uk).

Synthesis of 3-methyl-3-(2-(*N*-phenylamino)-2-oxoethyl)-indoline-2-thione (4b)

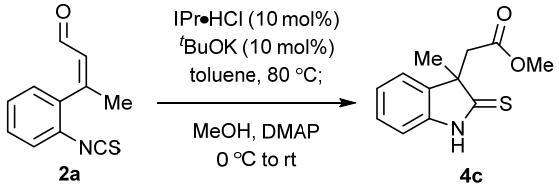


2a **4b**

To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (17.0 mg, 40.0 μmol) in 2 mL of toluene at ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 40.0 μL, 40.0 μmol). After 15 min, enal **2a** (81.3 mg, 400 μmol) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to

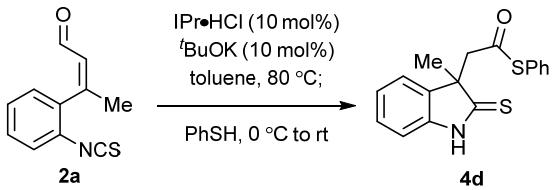
80 °C and stirred for additional 3 h. The reaction mixture was gradually cooled to 0 °C and aniline (74.5 mg, 800 μmol) and *N*,*N*-dimethyl-4-aminopyridine (48.9 mg, 400 μmol) were added. After additional 15 min, the reaction mixture was warmed to ambient temperature. After additional 9 h, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 8/2 to 7/3 to 6/4) to give the indoline-2-thione **4b** (74.1 mg, 62%) as an yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.37 (1H, s), 7.76 (1H, s), 7.37 (1H, d, *J* = 7.4 Hz), 7.27-7.24 (2H, m), 7.19-7.15 (3H, m), 7.13-7.10 (1H, m), 7.00 (1H, dd, *J* = 7.3, 7.3 Hz), 6.93 (1H, d, *J* = 7.4 Hz), 3.17 (1H, d, *J* = 14.3 Hz), 2.98 (1H, d, *J* = 14.3 Hz), 1.47 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 211.2, 167.1, 141.5, 137.7, 137.4, 128.8, 128.2, 124.3, 124.2, 123.6, 119.9, 110.7, 57.6, 47.0, 28.4; IR (ATR): 3309, 1671, 1469 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{17}N_2OS$: 297.1062. Found: 297.1059.

Synthesis of 3-methyl-3-(2-methoxy-2-oxoethyl)-indoline-2-thione (4c)



To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (17.0 mg, 40.0 μmol) in 2 mL of toluene at ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 40.0 μL, 40.0 μmol). After 15 min, enal **2a** (81.3 mg, 400 μmol) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to 80 °C and stirred for additional 3 h. The reaction mixture was gradually cooled to 0 °C and MeOH (5.0 mL) and *N*,*N*-dimethyl-4-aminopyridine (48.9 mg, 400 μmol) were added. After additional 15 min, the reaction mixture was warmed to ambient temperature. After additional 9 h, the reaction mixture was quenched with saturated aq. $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 8/2 to 7/3) to give the indoline-2-thione **4c** (55.4 mg, 59%) as an yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 9.93 (1H, s), 7.28-7.25 (2H, m), 7.13 (1H, dd, *J* = 7.6, 7.6 Hz), 7.02 (1H, d, *J* = 8.0 Hz), 3.47 (3H, s), 3.20 (1H, d, *J* = 16.6 Hz), 3.00 (1H, d, *J* = 16.6 Hz), 1.43 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 211.3, 170.1, 142.3, 137.8, 127.9, 123.6, 122.6, 110.4, 55.9, 51.4, 43.6, 27.7; IR (ATR): 1733, 1150, 1014 cm^{-1}; HRMS (MH^+) calcd for $C_{12}H_{14}NO_2S$: 236.0746. Found: 236.0746.

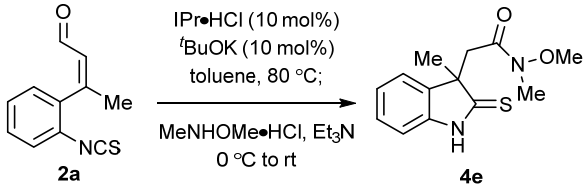
Synthesis of 3-methyl-3-(2-thiophenyl-2-oxoethyl)-indoline-2-thione (4d)



To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (17.0 mg, 40.0 μmol) in 2 mL of toluene at

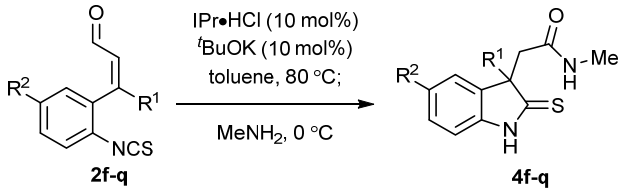
ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 40.0 μL, 40.0 μmol). After 15 min, enal **2a** (81.3 mg, 400 μmol) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to 80 °C and stirred for additional 3 h. The reaction mixture was gradually cooled to 0 °C and PhSH (49.1 μL, 480 μmol) was added. After additional 15 min, the reaction mixture was warmed to ambient temperature. After additional 6 h, the reaction mixture was quenched with water. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 8/2 to 7/3) to give the indoline-2-thione **4d** (59.5 mg, 48%) as an yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.33 (1H, s), 7.30-7.25 (4H, m), 7.22-7.17 (3H, m), 7.11 (1H, dd, *J* = 7.3, 7.3 Hz), 6.94 (1H, d, *J* = 7.7 Hz), 3.49 (1H, d, *J* = 16.0 Hz), 3.36 (1H, d, *J* = 16.3 Hz), 1.44 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 210.8, 193.5, 142.1, 137.3, 134.3, 129.3, 129.0, 128.2, 127.1, 123.8, 123.3, 110.5, 56.7, 52.3, 27.8; IR (ATR): 1698, 1197 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{16}NOS_2$: 314.0673. Found: 314.0673.

Synthesis of 3-methyl-3-(2-(methoxy(methyl)amino-2-oxoethyl)-indoline-2-thione (4e)



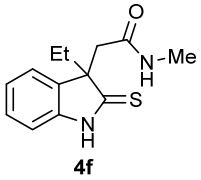
To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (17.0 mg, 40.0 μmol) in 2 mL of toluene at ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 40.0 μL, 40.0 μmol). After 15 min, enal **2a** (81.3 mg, 400 μmol) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to 80 °C and stirred for additional 3 h. The reaction mixture was gradually cooled to 0 °C and *N*,*O*-dimethylhydroxylamine hydrochloride (78.0 mg, 800 μmol) and triethylamine (223 μL, 1.60 mmol) were added. After additional 15 min, the reaction mixture was warmed to ambient temperature. After additional 10 h, the reaction mixture was quenched with water. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 6/4 to 5/5) to give the indoline-2-thione **4e** (53.1 mg, 50%) as an yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.09 (1H, s), 7.23-7.20 (2H, m), 7.10 (1H, t, *J* = 7.6 Hz), 6.97 (1H, d, *J* = 7.7 Hz), 3.71 (3H, s), 3.34 (1H, d, *J* = 16.9 Hz), 3.22 (1H, d, *J* = 16.9 Hz), 3.01 (3H, s), 1.43 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 212.1, 170.2, 142.5, 139.1, 127.6, 123.4, 122.2, 110.6, 61.1, 55.8, 41.6, 31.8, 28.5; IR (ATR): 2939, 1653, 1198, 1007 cm^{-1}; HRMS (MH^+) calcd for $C_{13}H_{17}N_2O_2S$: 265.1011. Found: 265.1004.

Typical Procedure for Preparation of 3,3-Disubstituted indoline-2-thione (4f-q)



Typical procedure: To a solution of 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (0.04 mmol, 0.100 equiv.) in 2 mL of toluene at ambient temperature was added potassium *tert*-butoxide (1.0 M sol. in THF, 0.100 equiv.). After 15 min, enal **2f-q** (0.4 mmol, 1.00 equiv.) was added to the reaction mixture. After additional 5 min, the reaction mixture was warmed to 80 °C and stirred for additional 3 h. The reaction mixture was gradually cooled to 0 °C and $MeNH_2$ (2.0 M sol. in THF, 2.00 equiv.) was added. After additional 10 min, the reaction mixture was concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/AcOEt = 2/8 to 0/10) to give the corresponding indoline-2-thione **4f-q**.

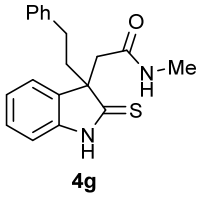
3-ethyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4f)



4f

Using a typical procedure, from **2f** (96.0 mg, 442 μmol), **4f** (72.6 mg, 66%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 11.15 (1H, s), 7.33 (1H, d, *J* = 7.4 Hz), 7.20 (1H, dd, *J* = 7.4, 7.4 Hz), 7.11 (1H, t, *J* = 7.4, 7.4 Hz), 6.94 (1H, d, *J* = 7.7 Hz), 6.01 (1H, s), 3.01 (1H, d, *J* = 14.3 Hz), 2.93 (1H, d, *J* = 14.3 Hz), 2.54 (3H, d, *J* = 4.6 Hz), 1.99-1.95 (2H, m), 0.46 (3H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, δ): 210.0, 169.8, 143.0, 135.7, 128.0, 123.8, 123.7, 110.5, 62.1, 45.9, 34.6, 26.1, 7.6; IR (ATR): 3019, 1654, 1469 cm^{-1}; HRMS (MH^+) calcd for $C_{13}H_{17}N_2OS$: 249.1062. Found: 249.1057.

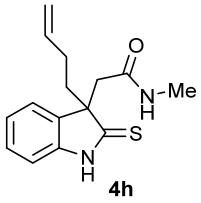
3-phenethyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4g)



4g

Using a typical procedure, from **2g** (175 mg, 596 μmol), **4g** (129 mg, 67%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 11.10 (1H, s), 7.38 (1H, d, *J* = 7.4 Hz), 7.24-7.09 (5H, m), 6.99-6.97 (3H, m), 5.91 (1H, s), 2.99 (1H, d, *J* = 14.0 Hz), 2.91 (1H, d, *J* = 14.0 Hz), 2.53 (3H, d, *J* = 4.6 Hz), 2.31-2.17 (3H, m), 1.80 (1H, td, *J* = 12.2, 4.0 Hz); ^{13}C NMR ($CDCl_3$, δ): 209.6, 169.5, 143.0, 141.1, 135.7, 128.3, 128.22, 128.21, 125.8, 124.0, 123.7, 110.7, 61.5, 46.3, 43.3, 29.6, 26.2; IR (ATR): 3026, 1651, 1468 cm^{-1}; HRMS (MH^+) calcd for $C_{19}H_{21}N_2OS$: 325.1374. Found: 325.1376.

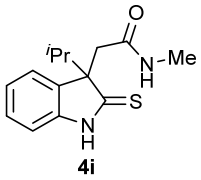
3-(4-butenyl)-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4h)



4h

Using a typical procedure, from **2h** (150 mg, 616 μmol), **4h** (131 mg, 78%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 11.15 (1H, s), 7.34 (1H, d, *J* = 7.4 Hz), 7.21 (1H, dd, *J* = 7.7, 7.7 Hz), 7.12 (1H, dd, *J* = 7.4, 7.4 Hz), 6.95 (1H, d, *J* = 7.7 Hz), 6.00 (1H, s), 5.64-5.56 (1H, m), 4.87-4.80 (2H, m), 3.00 (1H, d, *J* = 14.3 Hz), 2.93 (1H, d, *J* = 14.3 Hz), 2.55 (3H, d, *J* = 4.9 Hz), 2.07-2.00 (2H, m), 1.79-1.69 (1H, m), 1.37-1.29 (1H, m); ^{13}C NMR ($CDCl_3$, δ): 209.7, 169.6, 142.3, 137.2, 135.7, 128.1, 123.9, 123.7, 114.8, 110.7, 61.2, 46.2, 40.5, 27.5, 26.2; IR (ATR): 3313, 3079, 1652, 1469 cm^{-1}; HRMS (MH^+) calcd for $C_{15}H_{19}N_2OS$: 275.1218. Found: 275.1214.

3-isopropyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4i)

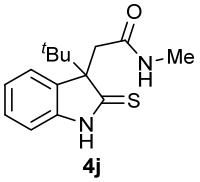


4i

Using a typical procedure, from **2i** (54.8 mg, 237 μmol), **4i** (42.0 mg, 68%) was obtained as a colorless amorphous; ^{1}H NMR ($CDCl_3$, δ): 9.94 (1H, s), 7.34 (1H, d, *J* = 7.4 Hz), 7.28-7.25 (1H,

m), 7.15 (1H, dd, *J* = 7.4, 7.4 Hz), 6.97 (1H, d, *J* = 8.0 Hz), 5.71 (1H, s), 3.08 (1H, d, *J* = 14.0 Hz), 2.98 (1H, d, *J* = 14.0 Hz), 2.53 (3H, d, *J* = 4.9 Hz), 2.24-2.19 (1H, m), 1.10 (3H, d, *J* = 6.9 Hz), 0.54 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, δ): 211.0, 169.7, 142.9, 134.4, 128.1, 124.7, 123.6, 110.2, 64.9, 44.1, 38.9, 26.1, 17.1, 16.5; IR (ATR): 3300, 3101, 1644, 1468 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{19}N_2OS$: 263.1218. Found: 263.1220.

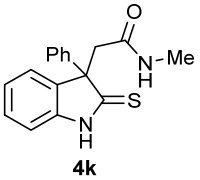
3-*tert*-butyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4j)



4j

Using a typical procedure, from **2j** (150 mg, 611 μmol), **4j** (58.5 mg, 35%) was obtained as a colorless amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.02 (1H, s), 7.36 (1H, d, *J* = 7.4 Hz), 7.23 (1H, dd, *J* = 7.7, 7.7 Hz), 7.09 (1H, dd, *J* = 7.6, 7.6 Hz), 6.92 (1H, d, *J* = 7.7 Hz), 5.76 (1H, s), 3.29 (1H, d, *J* = 13.7 Hz), 2.98 (1H, d, *J* = 13.7 Hz), 2.45 (3H, d, *J* = 4.9 Hz), 1.04 (9H, s); ^{13}C NMR ($CDCl_3$, δ): 210.7, 170.1, 142.7, 134.6, 128.1, 127.4, 122.8, 109.5, 67.1, 40.8, 37.7, 26.1, 25.1; IR (ATR): 3330, 2959, 1658, 1429 cm^{-1}; HRMS (MH^+) calcd for $C_{15}H_{21}N_2OS$: 277.1374. Found: 277.1375.

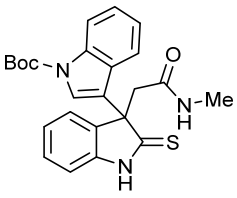
3-phenyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4k)



4k

Using a typical procedure, from **2k** (207 mg, 780 μmol), **4k** (206 mg, 89%) was obtained as a colorless amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.60 (1H, s), 7.28-7.20 (5H, m), 7.20-7.16 (2H, m), 7.11 (1H, dd, *J* = 7.4, 7.4 Hz), 6.97 (1H, d, *J* = 8.0 Hz), 5.87 (1H, s), 3.64 (1H, d, *J* = 14.0 Hz), 3.34 (1H, d, *J* = 14.0 Hz), 2.56 (3H, d, *J* = 4.6 Hz); ^{13}C NMR ($CDCl_3$, δ): 209.34, 169.5, 143.1, 140.8, 137.4, 128.5, 128.3, 127.5, 126.4, 124.9, 124.0, 111.0, 64.4, 45.0, 26.2; IR (ATR): 3263, 1666, 1436 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{17}N_2OS$: 297.1061. Found: 297.1067.

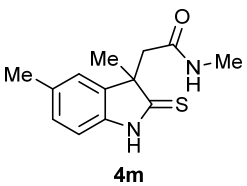
3-(*N*-Boc-indolyl)-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4l)



4l

Using a typical procedure, from **2l** (220 mg, 544 μmol), **4l** (142 mg, 60%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.61 (1H, s), 8.08-8.04 (1H, m), 7.73 (1H, s), 7.29-7.27 (1H, m), 7.19-7.16 (2H, m), 7.07 (2H, dd, *J* = 7.3, 7.3 Hz), 6.92 (1H, dd, *J* = 7.6. 7.6 Hz), 6.67 (1H, d, *J* = 8.0 Hz), 5.78 (1H, s), 3.57 (1H, d, *J* = 13.5 Hz), 3.40 (1H, d, *J* = 13.5 Hz), 2.59 (3H, d, *J* = 4.9 Hz), 1.68 (9H, s); ^{13}C NMR ($CDCl_3$, δ): 208.3, 168.6, 149.5, 142.9, 136.0, 135.7, 128.9, 127.6, 124.9, 124.5, 123.9, 122.6, 120.5, 119.6, 115.3, 110.7, 84.2, 60.5, 45.5, 28.2, 26.4; IR (ATR): 3277, 3087, 1729, 1651, 1447 cm^{-1}; HRMS (MH^+) calcd for $C_{24}H_{26}N_3O_3S$: 436.1694. Found: 436.1696.

3,5-dimethyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4m)

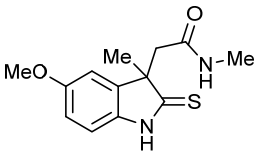


4m

Using a typical procedure, from **2m** (42.7 mg, 197 μmol), **4m** (35.6 mg, 73%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.60 (1H, s), 7.18 (1H, s), 7.02 (1H, d, *J* = 7.7 Hz), 6.87 (1H, d, *J* = 7.7 Hz), 5.84 (1H, s), 2.98 (1H, d, *J* = 14.3 Hz), 2.86 (1H, d, *J* = 14.3 Hz), 2.59 (3H, s), 2.32 (3H, s), 1.43 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 210.8, 169.6, 139.5, 138.2, 133.8, 128.5, 124.4, 110.2, 57.3, 46.0, 28.3, 26.1, 21.2; IR (ATR): 3018, 1654, 1474 cm^{-1}; HRMS (MH^+) calcd for

$C_{13}H_{17}N_2OS$: 249.1062. Found: 249.1060.

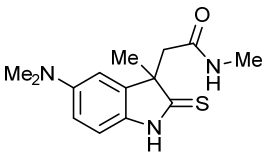
5-methoxy-3-methyl-3-(2-(*N*-methylamino)-2-oxoethyl)-indoline-2-thione (4n)



4n

Using a typical procedure, from **2n** (77.5 mg, 332 μmol), **4n** (65.5 mg, 75%) was obtained as a yellow amorphous; ^{1}H NMR ($CDCl_3$, δ): 10.69 (1H, s), 6.97 (1H, d, J = 2.3 Hz), 6.89 (1H, d, J = 8.6 Hz), 6.74 (1H, dd, J = 8.6, 2.3 Hz), 5.88 (1H, s), 3.77 (3H, s), 2.99 (1H, d, J = 14.3 Hz), 2.87 (1H, d, J = 14.3 Hz), 2.60 (3H, d, J = 4.9 Hz), 1.44 (3H, s); ^{13}C NMR ($CDCl_3$, δ): 210.0, 169.6, 157.2, 139.8, 135.5, 112.9, 111.0, 110.5, 57.5, 55.7, 45.9, 28.2, 26.2; IR (ATR): 3393, 1670, 1488 cm^{-1}; HRMS (MH^+) calcd for $C_{13}H_{17}N_2O_2S$: 265.1011. Found: 265.1005.

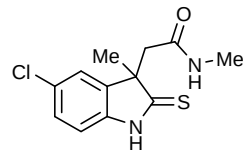
5-dimethylamino-3-methyl-3-(2-(N-methylamino)-2-oxoethyl)-indoline-2-thione (4o)



4o

Using a typical procedure, from **2o** (35.1 mg, 142 μmol), **4o** (17.2 mg, 44%) was obtained as a yellow amorphous; ^{1}H NMR (DMSO-d_6, δ): 12.26 (1H, s), 7.58 (1H, d, J = 4.6 Hz), 6.81 (1H, d, J = 8.6 Hz), 6.79 (1H, d, J = 2.3 Hz), 6.56 (1H, dd, J = 8.6, 2.3 Hz), 2.83 (6H, s), 2.75 (1H, d, J = 14.9 Hz), 2.53 (1H, d, J = 14.9 Hz), 2.40 (3H, d, J = 4.6 Hz), 1.25 (3H, s); ^{13}C NMR (DMSO-d_6, δ): 208.5, 169.0, 147.6, 140.3, 133.6, 111.2, 110.2, 109.1, 56.0, 44.1, 40.9, 27.6, 25.2; IR (ATR): 3486, 1699, 1490 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{20}N_3OS$: 278.1327. Found: 278.1331.

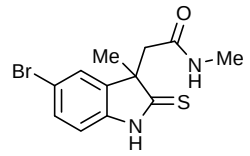
5-chloro-3-methyl-3-(2-(N-methylamino)-2-oxoethyl)-indoline-2-thione (4p)



4p

Using a typical procedure, from **2p** (80.0 mg, 337 μmol), **4p** (38.9 mg, 43%) was obtained as a yellow amorphous; ^{1}H NMR (acetone-d_6, δ): 11.47 (1H, s), 7.46 (1H, d, J = 2.0 Hz), 7.24 (1H, dd, J = 8.3, 2.0 Hz), 7.05 (1H, d, J = 8.3 Hz), 6.90 (1H, s), 2.96 (1H, d, J = 15.5 Hz), 2.83 (1H, d, J = 15.5 Hz), 2.52 (3H, d, J = 4.6 Hz), 1.35 (3H, s); ^{13}C NMR (acetone-d_6, δ): 213.4, 169.7, 143.0, 142.4, 129.0, 128.3, 124.7, 111.9, 57.4, 45.7, 28.2, 25.8; IR (ATR): 3187, 2970, 1651, 1459 cm^{-1}; HRMS (MH^+) calcd for $C_{12}H_{14}{}^{35}ClN_2OS$: 269.0515. Found: 269.0520.

5-bromo-3-methyl-3-(2-(N-methylamino)-2-oxoethyl)-indoline-2-thione (4q)



4q

Using a typical procedure, from **2q** (67.7 mg, 240 μmol), **4q** (20.0 mg, 27%) was obtained as a yellow amorphous; ^{1}H NMR (acetone-d_6, δ): 11.42 (1H, s), 7.56 (1H, d, J = 2.0 Hz), 7.36 (1H, dd, J = 8.3, 2.0 Hz), 6.97 (1H, d, J = 8.3 Hz), 6.85 (1H, s), 2.92 (1H, d, J = 15.5 Hz), 2.79 (1H, d, J = 15.5 Hz), 2.49 (3H, d, J = 4.9 Hz), 1.32 (3H, s); ^{13}C NMR (acetone-d_6, δ): 213.4, 169.7, 143.5, 142.8, 131.2, 127.5, 116.5, 112.4, 57.4, 45.7, 28.2, 25.8; IR (ATR): 3503, 1654, 1457 cm^{-1}; HRMS (MH^+) calcd for $C_{12}H_{14}{}^{79}BrN_2OS$:313.0010. Found: 313.0014.