

## Supporting information

# Synthesis of novel spiro [indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile derivatives in water using regioselective sequential three component reaction

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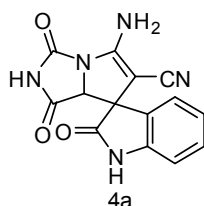
## 1. General information.

All Starting materials were purchased from Sigma Aldrich and used without further purification.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on 400 or 500 MHz for  $^1\text{H}$  and 100 or 125 MHz for  $^{13}\text{C}$  in DMSO- $d_6$ , Chemical shift values were reported in  $\delta$  values (ppm) downfield from tetramethylsilane. Infrared (IR) spectra were recorded on a Shimadzu Affinity 1, FTIR spectrometer. CHN analyses were carried out either on in an Elementar Vario EL III or Perkin-Elmer 2400 II elemental analyzers. Melting points were recorded by using SRS EZ-Melt automated melting point apparatus by capillary methods and uncorrected.

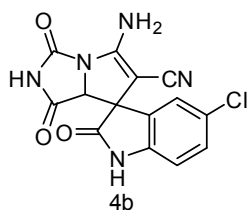
## 2. General procedure for the synthesis of spiro pyrrolizidine analogues.

A mixture of isatin (1 mmol), malononitrile (1 mmol) and  $\text{Et}_3\text{N}$  (0.2 mmol) was added in 5 ml water. The above mixture was stirred for 10 minutes at room temperature. Then, hydantion/2-thiohydantoin (1 mmol) was added to this stirred reaction mixture. After addition of this third component, the reaction mixture was stirred at 70 °C temperature and monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, filtered, and washed with ethyl acetate and hexane (3:1) mixture. The resultant product was found pure enough for characterization. In case of 2-thiohydantoin after completion of the reaction, the reaction mixture was cooled to room temperature, filtered. The resultant precipitate was added in a hot toluene and acetonitrile (3:1) mixture and filtered to get the pure desired product.

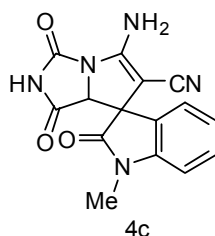
### 3. Spectral data of compounds.



**5'-amino-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4a):** Yield: 90%, Light brown solid, mp 263-265 °C; IR (KBr): 3375, 3260, 3205, 2755, 2193, 1799, 1741, 1662, 1624 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ = 11.67 (bs, 1H, NH), 10.60 (bs, 1H, NH), 7.76 (bs, 2H, NH<sub>2</sub>), 7.42 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.28 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.07 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.87 (d, *J* = 7.5 Hz, 1H, Ar-H), 5.11 (s, 1H, CH); <sup>13</sup>C NMR (125MHz, DMSO-d<sub>6</sub>): δ = 177.5, 171.4, 156.4, 155.7, 142.5, 129.5, 128.4, 124.4, 122.4, 116.6, 110.0, 68.7, 61.8, 56.4; Anal. Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub> (295.25): C, 56.95; H, 3.07; N, 23.72; Found: C, 56.99; H, 3.12; N, 23.78.

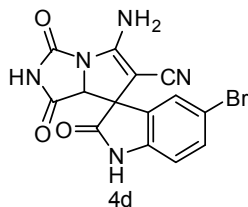


**5'-amino-5-chloro-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4b):** Yield: 78%, Light brown solid, mp 305-307 °C; IR (KBr): 3493, 3392, 3237, 2750, 2197, 1790, 1742, 1700, 1636, 1572 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 11.74 (bs, 1H, NH), 10.77 (bs, 1H, NH), 7.86 (bs, 2H, NH<sub>2</sub>), 7.58 (s, 1H, Ar-H), 7.33 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.88 (d, *J* = 7.2 Hz, 1H, Ar-H), 5.18 (s, 1H, CH); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ = 177.7, 171.6, 156.9, 156.0, 141.9, 130.8, 129.9, 126.9, 125.2, 116.9, 112.0, 68.8, 62.0, 57.1; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>ClN<sub>5</sub>O<sub>3</sub> (329.69): C, 51.00; H, 2.45; N, 21.24; Found: C, 51.07; H, 2.48; N, 21.30.

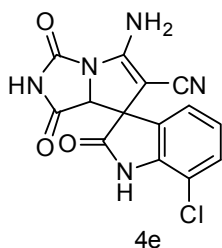


**5'-amino-1-methyl-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4c):** Yield: 70%, Light brown solid, mp 275-277 °C; IR (KBr): 3552, 3501, 3210, 2928, 2187, 1790, 1742, 1688, 1648 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ = 11.58 (bs, 1H, NH), 7.75 (bs, 2H, NH<sub>2</sub>), 7.42 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.33 (t, *J* = 7.5

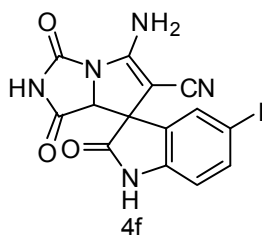
Hz, 1H, Ar-H), 7.10 (t,  $J = 7.5$  Hz, 1H, Ar-H), 7.01 (d,  $J = 7.5$  Hz, 1H, Ar-H), 5.07 (s, 1H, CH), 3.04 (s, 3H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (125MHz, DMSO-d<sub>6</sub>):  $\delta = 175.6, 171.1, 156.5, 155.6, 143.8, 129.7, 127.5, 124.1, 123.2, 116.6, 109.1, 68.7, 61.4, 56.0, 26.2$ ; Anal. Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub> (309.28): C, 58.25; H, 3.58; N, 22.64; Found: C, 58.20; H, 3.63; N, 22.71.



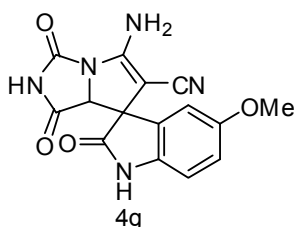
**5'-amino-5-bromo-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4d):** Yield: 72%, Light brown solid, mp 298-300 °C; IR (KBr): 3485, 3385, 3243, 3150, 2736, 2193, 1790, 1744, 1707, 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta = 11.70$  (bs, 1H, NH), 10.81 (bs, 1H, NH), 7.82 (bs, 2H, NH<sub>2</sub>), 7.66 (s, 1H, Ar-H), 7.52-7.46 (m, 1H, Ar-H), 6.90-6.85 (m, 1H, Ar-H), 5.15 (s, 1H, CH); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta = 177.6, 171.6, 156.9, 156.0, 142.3, 132.8, 131.2, 127.9, 116.3, 114.6, 112.5, 68.8, 62.0, 57.1$ ; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>BrN<sub>5</sub>O<sub>3</sub> (374.15): C, 44.94; H, 2.16; N, 18.72; Found: C, 44.99; H, 2.18; N, 18.79.



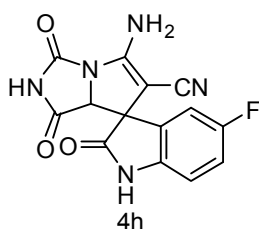
**5'-amino-7-chloro-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4e):** Yield: 70%, Light brown solid, mp 310-312 °C; IR (KBr): 3490, 3312, 3258, 3208, 3092, 2193, 1801, 1753, 1725, 1695, 1658 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta = 11.78$  (bs, 1H, NH), 11.14 (bs, 1H, NH), 7.88 (bs, 2H, NH<sub>2</sub>), 7.44 (d,  $J = 7.6$  Hz, 1H, Ar-H), 7.38 (d,  $J = 8.0$  Hz, 1H, Ar-H), 7.12 (t,  $J = 7.6$  Hz, 1H, Ar-H), 5.16 (s, 1H, CH); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta = 178.5, 172.2, 157.4, 156.5, 141.0, 131.1, 130.5, 124.7, 124.2, 117.4, 115.1, 69.5, 62.4, 58.1$ ; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>ClN<sub>5</sub>O<sub>3</sub> (329.69): C, 51.00; H, 2.45; N, 21.24; Found: C, 51.06; H, 2.50; N, 21.30.



**5'-amino-5-iodo-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4f):** Yield: 76%, Black colour solid, mp 254-256 °C; IR (KBr): 3240, 3092, 3186, 2952, 2873, 2201, 1733, 1605, 1461, 1436 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ = 11.70 (bs, 1H, NH), 10.73 (bs, 1H, NH), 7.88-7.79 (m, 3H, NH<sub>2</sub>, Ar-H), 7.62 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.79 (d, *J* = 8.0 Hz, 1H, Ar-H), 5.17 (s, 1H, CH); <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): δ = 176.9, 171.2, 156.5, 155.5, 142.3, 130.8, 120.9, 116.5, 114.5, 113.8, 112.4, 68.3, 61.5, 56.3 ; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>IN<sub>5</sub>O<sub>3</sub> (421.15): C, 39.93; H, 1.91; N, 16.63; Found: C, 39.88; H, 1.94; N, 16.68.

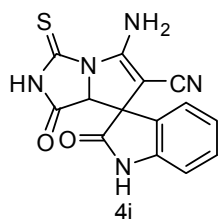


**5'-amino-5-methoxy-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4g):** Yield: 78%, Ash colour solid, mp 271-273 °C; IR (KBr): 3377, 3325, 3267, 2895, 2187, 1801, 1748, 1720, 1659, 1593 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 11.67 (bs, 1H, NH), 10.42 (bs, 1H, NH), 7.76 (bs, 2H, NH<sub>2</sub>), 7.10 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-H), 6.77 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.12 (s, 1H, CH), 3.73 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ = 177.8, 171.8, 156.8, 156.2, 155.9, 136.1, 130.1, 117.2, 114.8, 111.7, 110.9, 69.1, 62.6, 57.4, 55.9 ; Anal. Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>O<sub>4</sub> (325.28): C, 55.39; H, 3.41; N, 21.53; Found: C, 55.45; H, 3.44; N, 21.60.

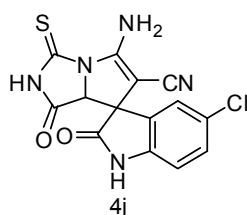


**5'-amino-5-fluoro-1',2,3'-trioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4h):** Yield: 70%, Blackish solid, mp 235-237 °C; IR (KBr): 3389, 3265, 3208, 3186, 2895, 2195, 1743, 1718, 1649, 1591 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 11.73 (bs, 1H, NH), 10.66 (bs, 1H, NH), 7.85 (bs, 2H, NH<sub>2</sub>), 7.44 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-H), 7.16-7.11 (m, 1H, Ar-H), 6.88 (dd, *J* = 8.4, 4.4 Hz, 1H, Ar-H), 5.16 (s, 1H, CH); <sup>13</sup>C NMR (100MHz, DMSO-d<sub>6</sub>): δ = 178.4, 172.1, 157.3, 156.5, 139.6, 130.9,

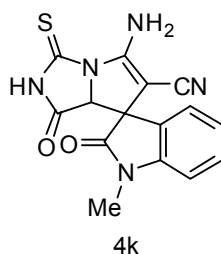
117.5, 117.0, 116.8, 113.5, 111.9, 69.3, 62.5, 57.7 ; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>FN<sub>5</sub>O<sub>3</sub> (313.24): C, 53.68; H, 2.57; N, 22.36; Found: C, 53.73; H, 2.61; N, 22.40.



**5'-amino-1',2-dioxo-3'-thioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4i):** Yield: 76%, Reddish brown solid, mp 285-287 °C; IR (KBr): 3460, 3325, 3280, 3150, 2900, 2183, 1769, 1699, 1630, 1574 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ = 12.81 (bs, 1H, NH), 10.80 (bs, 1H, NH), 7.87 (bs, 2H, NH<sub>2</sub>), 7.46-7.44 (m, 1H, Ar-H), 7.33-7.24 (m, 1H, Ar-H), 7.02-7.18 (m, 1H, Ar-H), 6.88-6.93 (m, 1H, Ar-H), 5.46 (s, 1H, CH) ; <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): δ = 183.2, 177.2, 171.9, 156.3, 143.1, 131.2, 127.8, 124.9, 123.0, 116.6, 110.8, 71.2, 64.6, 56.9 ; Anal. Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>5</sub>O<sub>2</sub>S (311.32): C, 54.01; H, 2.91; N, 22.50; Found: C, 54.05; H, 2.96; N, 22.56.

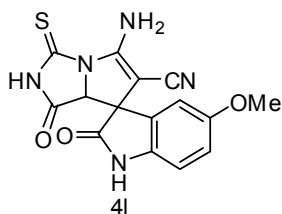


**5'-amino-5-chloro-1',2-dioxo-3'-thioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4j):** Yield: 68%, Reddish brown solid, mp 305-307 °C; IR (KBr): 3466, 3392, 3312, 3228, 2884, 2197, 1772, 1691, 1635, 1568 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ = 12.84 (bs, 1H, NH), 10.86 (bs, 1H, NH), 7.92 (bs, 2H, NH<sub>2</sub>), 7.62 (d, *J* = 2 Hz, 1H, Ar-H), 6.93-6.91 (m, 2H, Ar-H), 5.48 (s, 1H, CH); <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): δ = 183.2, 176.9, 171.7, 156.4, 141.4, 134.4, 130.3, 125.3, 122.2, 116.5, 112.2, 70.9, 64.1, 56.0; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>ClN<sub>5</sub>O<sub>2</sub>S (345.76): C, 48.63; H, 2.33; N, 20.25; Found: C, 48.67; H, 2.36; N, 20.28.

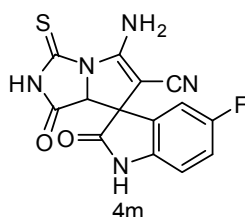


**5'-amino-1-methyl-1',2-dioxo-3'-thioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4k):** Yield: 70%, Reddish brown solid, mp 287-289 °C; IR (KBr): 3388, 3293, 3117, 2944, 2197, 1755, 1685, 1648, 1614, 1573 cm<sup>-1</sup>; <sup>1</sup>H

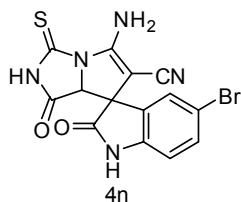
NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 12.84 (bs, 1H, NH), 7.92 (bs, 2H, NH<sub>2</sub>), 7.42 (t,  $J$  = 8.0 Hz, 1H, Ar-H), 7.19 (t,  $J$  = 7.6 Hz, 1H, Ar-H) 7.10 (d,  $J$  = 8.0 Hz, 2H, Ar-H), 5.45 (s, 1H, CH), 3.12 (s, 3H, NCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 183.6, 175.8, 172.1, 156.9, 144.9, 130.9, 127.4, 125.1, 124.2, 117.0, 110.2, 71.7, 64.4, 55.9, 27.2 ; Anal. Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>O<sub>2</sub>S (325.35): C, 55.38; H, 3.41; N, 21.53; Found: C, 55.32; H, 3.45; N, 21.60.



**5'-amino-5-methoxy-1',2-dioxo-3'-thioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4l):** Yield: 65%, Black solid, mp 266-268 °C; IR (KBr): 3309, 3285, 2951, 2191, 1770, 1694, 1637, 1578 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 12.81 (bs, 1H, NH), 10.53 (bs, 1H, NH), 7.86 (bs, 2H, NH<sub>2</sub>), 7.14 (s, 1H, Ar-H), 6.91-6.80 (m, 2H, Ar-H), 5.42 (s, 1H, CH), 3.75 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 183.6, 177.5, 172.3, 156.7, 156.3, 136.5, 129.5, 117.1, 115.4, 112.2, 111.6, 71.6, 65.1, 56.7, 56.4 ; Anal. Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>S (341.34): C, 52.78; H, 3.25; N, 20.52; Found: C, 52.73; H, 3.28; N, 20.58.

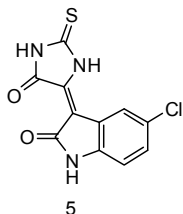


**5'-amino-5-fluoro-1',2-dioxo-3'-thioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4m):** Yield: 62%, Reddish brown solid, mp 302-304 °C; IR (KBr): 3412, 3281, 3197, 3088, 2878, 2183, 1771, 1688, 1573 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  = 12.81 (bs, 1H, NH), 10.73 (bs, 1H, NH), 7.89 (bs, 2H, NH<sub>2</sub>), 7.45-7.43 (m, 1H, Ar-H), 6.91-6.87 (m, 2H, Ar-H), 5.43 (s, 1H, CH); <sup>13</sup>C NMR (125 MHz, DMSO- $d_6$ ):  $\delta$  = 182.7, 178.4, 171.2, 155.9, 138.5, 133.6, 129.0, 121.1, 116.0, 112.3, 111.1, 70.4, 63.6, 55.7 ; Anal. Calcd for C<sub>14</sub>H<sub>8</sub>FN<sub>5</sub>O<sub>2</sub>S (329.31): C, 51.06; H, 2.45; N, 21.27; Found: C, 51.11; H, 2.41; N, 21.33.



**5'-amino-5-bromo-1',2-dioxo-3'-thioxo-1',2',3',7a'-tetrahydrospiro[indoline-3,7'-pyrrolo[1,2-c]imidazole]-6'-carbonitrile (4n):** Yield: 60%, Reddish brown solid, mp 311-

313 °C; IR (KBr): 3479, 3394, 3321, 3235, 2881, 2196, 1771, 1693, 1639, 1579  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 12.84 (bs, 1H, NH), 10.86 (bs, 1H, NH), 7.92 (bs, 2H,  $\text{NH}_2$ ), 7.63 (s, 1H, Ar-H), 6.93-6.91 (m, 2H, Ar-H), 5.48 (s, 1H, CH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 183.2, 178.9, 169.5, 156.4, 141.7, 133.1, 128.0, 122.6, 113.9, 112.5, 106.7, 70.9, 64.1, 55.9 ; Anal. Calcd for  $\text{C}_{14}\text{H}_8\text{BrN}_5\text{O}_2\text{S}$  (390.21): C, 43.09; H, 2.07; N, 17.95; Found: C, 43.13; H, 2.04; N, 17.88.



**5-chloro-3-(5-oxo-2-thioxoimidazolidin-4-ylidene)indolin-2-one (5):** Yield: 90%, Dark red solid, mp 113-115 °C; IR (KBr): 2955, 2950, 2923, 2853, 1608, 1464, 1377, 909, 721  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 13.05 (bs, 1H, NH), 11.46 (bs, 1H, NH), 11.32 (bs, 1H, NH), 8.55-8.40 (m, 1H, Ar-H), 7.40-7.30 (m, 1H, Ar-H), 7.10-6.90 (m, 1H, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 178.8, 169.9, 165.8, 139.9, 134.3, 130.4, 124.4, 123.4, 122.5, 114.9, 107.3 ; Anal. Calcd for  $\text{C}_{11}\text{H}_6\text{ClN}_3\text{O}_2\text{S}$  (279.70): C, 47.24; H, 2.16; N, 15.02; Found: C, 47.30; H, 2.11; N, 15.08.



#### 4. Copies of $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of compounds

