

# Supplementary Data

## **Synthesis of Barbiturate-Based Methionine Aminopeptidase-1 Inhibitors**

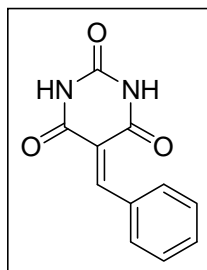
Manas K. Haldar,<sup>a</sup> Michael D. Scott,<sup>a</sup> Nitesh Sule,<sup>b</sup> D. K. Srivastava<sup>b,\*</sup> and Sanku Mallik<sup>a,\*</sup>

<sup>a</sup>*Department of Pharmaceutical Sciences and* <sup>b</sup>*Department of Chemistry, Biochemistry and Molecular Biology, North Dakota State University, Fargo, North Dakota 58105, USA*

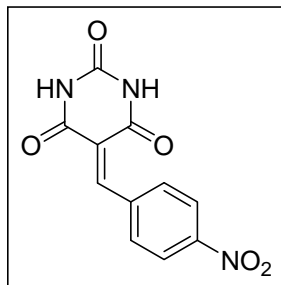
## Supplementary Data

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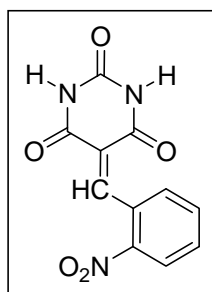
### Synthesis of the compounds:



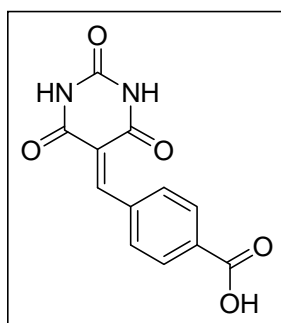
**Compound 1:** Hu, Y.; Chen, Z-C.; Le, Z-G.; Zheng, Q-G. *Synthetic Communications* **2004**, 34, 4521.



**Compound 2:** Reddy, C. S.; Nagaraj, A.; Jalapathi, P. *Indian J. Chem. B: Organic Chemistry Including Medicinal Chemistry* **2007**, 46, 660.



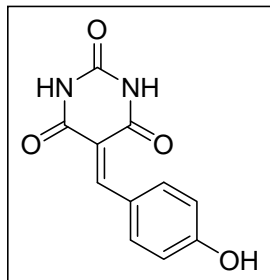
**Compound 3:** Hu, Y.; Chen, Z-C.; Le, Z-G.; Zheng, Q-G. *Synthetic Communications* **2004**, 34, 4521.



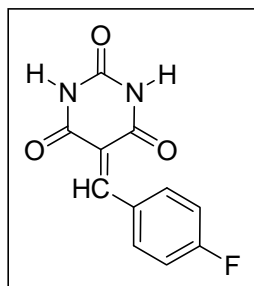
**Compound 4:** Gursu, E.; Ulusoy, N. *Acta Pharmaceutica Turcica* **1996**, 38, 107.

## Supplementary Data

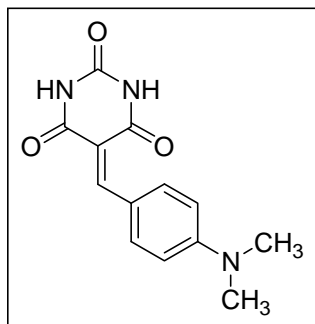
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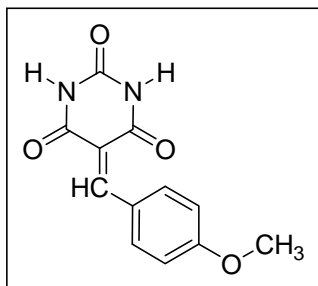
**Compound 5:** Kaupp, G.; Naimi-J., M. Reza; Schmeyers, J. *Tetrahedron* **2003**, *59*, 3753.



**Compound 6:** Alcerreca, G.; Sanabria, R.; Miranda, R.; Arroyo, G.; Tamariz, J.; Delgado, F. *Synthetic Communications* **2000**, *30*, 1295.

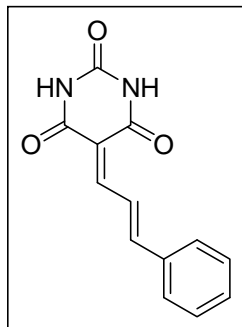


**Compound 7:** Reddy, C. S.; Nagaraj, A.; Jalapathi, P. *Indian J. Chem. B: Organic Chemistry Including Medicinal Chemistry* **2007**, *46*, 660.



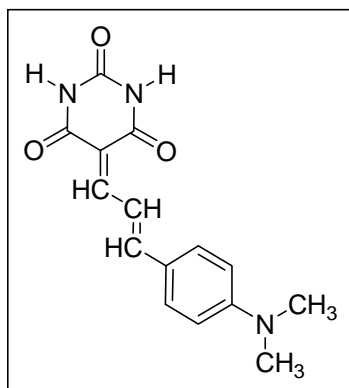
**Compound 8:** Alcerreca, G.; Sanabria, R.; Miranda, R.; Arroyo, G.; Tamariz, J.; Delgado, F. *Synthetic Communications* **2000**, *30*, 1295.

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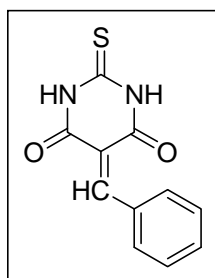
**Compound 9:** Li, J.-T.; Dai, H.-G.; Liu, D.; Li, T.-S. *Synthetic Communications* **2006**, *36*, 789.

**Compound 10:** A solution of 2-thiobarbituric acid (0.429 g, 3 mmol) in distilled water (20 mL)



was stirred for 10 minutes at room temperature. 4-Dimethylaminocinnamaldehyde (0.526 g, 3 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 80 °C for 4 hours. The formed precipitate was filtered and washed with water and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.710 g (83%); mp: 299-300°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.05 (s, 6 H) 6.79 (d, *J* = 9.1 Hz, 2 H) 7.54 (d, *J* = 8.8 Hz, 2 H) 7.62 (d, *J* = 14.8 Hz, 1 H) 7.97 (d, *J* = 12.4 Hz, 1 H) 8.15 - 8.29 (m, 1 H), 11.02 (d, *J* = 17.9 Hz, 2 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>; 133 MHz) δ

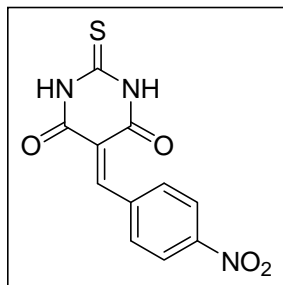
111.08, 112.77, 119.77, 123.40, 132.19, 151.14, 153.49, 156.17, 156.64, 164.04, 164.29.



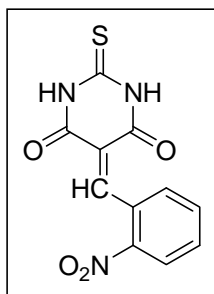
**Compound 11:** Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.-G. *Synthetic Communications* **2004**, *34*, 4521.

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**Compound 12:** A solution of 2-thiobarbituric acid (0.429 g, 3 mmol) in distilled water (20 mL)

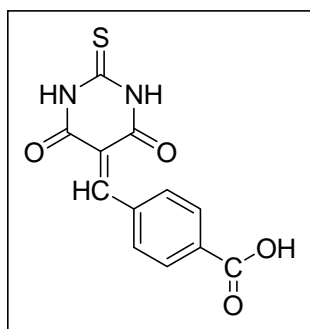


was stirred for 10 minutes at 65 °C. 4-Nitrobenzaldehyde (0.453 g, 3 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 100°C for 12 hours. The formed precipitate was filtered and washed with water and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate, however, after several recrystallizations we could get up to 92% pure sample. Yield: 0.832 g (81%) based on net product isolated, mp: 303-304°C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.05 (d, *J* = 8.8 Hz, 2 H) 8.23 (d, *J* = 9.2 Hz, 2 H) 8.30 (s, 1 H) 12.37 (s, 1 H) 12.51 (s, 1 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>; 100 MHz) δ 122.97, 123.38, 124.95, 133.22, 140.49, 148.89, 152.38, 159.76, 161.62, 179.49.



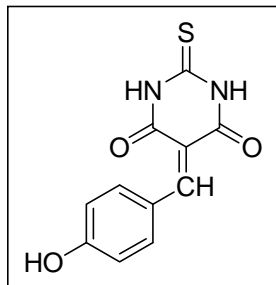
**Compound 13:** Wang, C.; Ma, J.-j.; Zhou, X.; Zang, X.-h.; Wang, Z.; Gao, Y.-j.; Cui, P.-l. *Synthetic Communications* **2005**, *35*, 2759.

**Compound 14:** A solution of 2-thiobarbituric acid (0.429 g, 3 mmol) in distilled water (20 mL)

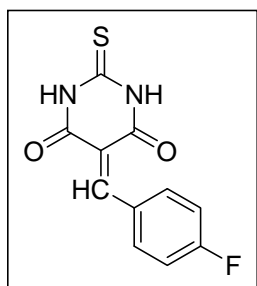


was stirred for 10 minutes at 65 °C. 4-Carboxybenzaldehyde (0.450 g, 3 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 80 °C for 1 hour. The formed precipitate was filtered and washed with water and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.191 g (23%), mp: 342-344°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.43 (q, *J* = 8.1 Hz, 1 H) 7.92 - 8.17 (m, 4 H) 8.31 (s, 1 H) 11.56 - 12.56 (m, 2 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>; 126 MHz) δ 126.55, 128.76, 129.37, 129.76, 138.80, 166.38, 167.23, 172.86.

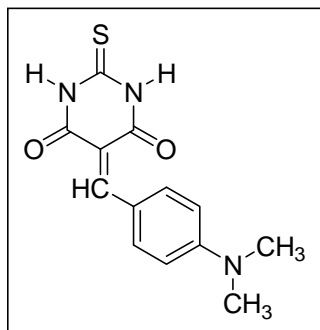
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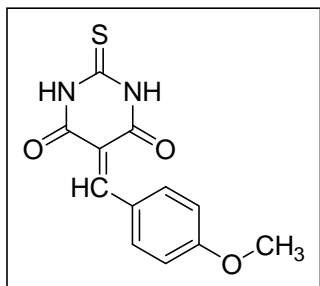
**Compound 15:** Lu, J.; Li, Y.; Bai, Y.; Tian, M. *Heterocycles* **2004**, 63, 583.



**Compound 16:** Shi, D.Q.; Chen, J.; Zhuang, Q.Y.; Wang, X.S.; Hu, H. W. *Chinese Chemical Letters* **2003**, 14, 1242.

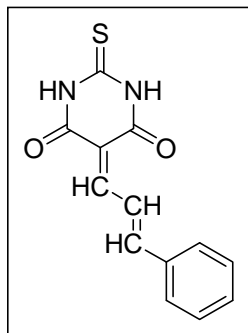


**Compound 17:** Wang, C.; Ma, J.-j.; Zhou, X.; Zang, X.-h.; Wang, Z.; Gao, Y.-j.; Cui, P.-l. *Synthetic Communications* **2005**, 35, 2759.



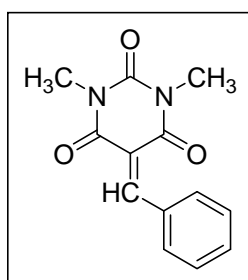
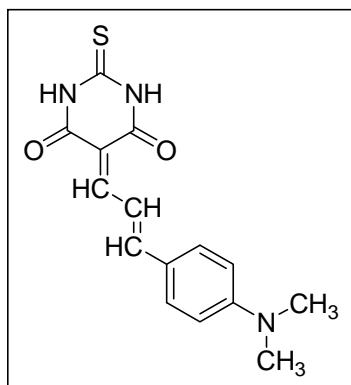
**Compound 18:** Wang, C.; Ma, J.-j.; Zhou, X.; Zang, X.-h.; Wang, Z.; Gao, Y.-j.; Cui, P.-l. *Synthetic Communications* **2005**, 35, 2759.

## Supplementary Data



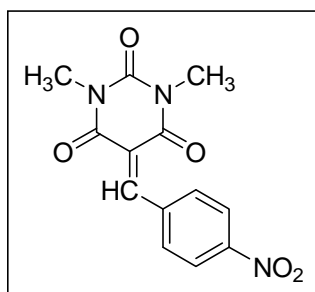
**Compound 19:** Wang, C.; Ma, J-j.; Zhou, X.; Zang, X-h.; Wang, Z.; Gao, Y-j.; Cui, P-l. *Synthetic Communications* **2005**, 35, 2759.

**Compound 20:** A solution of 2-thiobarbituric acid (0.429 g, 3 mmol) in distilled water (20 mL) was stirred for 10 minutes at 65 °C. 4-Dimethylaminocinnamaldehyde (0.526 g, 3 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 60 °C for 1 hour. The formed precipitate was filtered and washed with water and then dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.570 g (63%), mp: 292-293°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.09 (s, 6 H) 6.83 (d, *J* = 8.8 Hz, 2 H) 7.59 (d, *J* = 8.8 Hz, 2 H) 7.74 (d, *J* = 14.8 Hz, 1 H) 8.01 (d, *J* = 12.4 Hz, 1 H) 8.25 (m, 1 H) 12.13 (d, *J* = 12.4 Hz, 2 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>; 100 MHz) δ 39.47, 111.61, 121.22, 123.17, 130.41, 132.04, 152.18, 153.86, 156.28, 177.75, 193.17.



**Compound 21:** Deb, M. L.; Bhuyan, P. J. *Tetrahedron Letters* **2005**, 46, 6453.

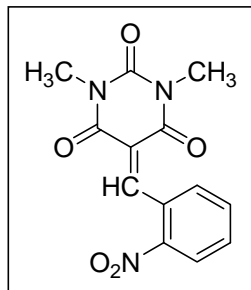
**Compound 22:** Solid 4-dimethylbarbituric acid (0.468 g, 3 mmol), 4-nitrobenzaldehyde (0.453 g, 3 mmol), and amidosulfonic acid (0.298 g) were ground for 10 minutes with a mortal and pestle. It was then placed in a desiccator for 2 hours. The ground mixture was then dissolved in DMSO and poured into 50 mL of distilled water. The formed precipitate was filtered, washed with boiling water and MeOH and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.486 g (56%), mp: 198-200 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.14 (s, 3 H) 3.24 (s, 3



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H) 7.98 (d,  $J = 8.2$  Hz, 2 H) 8.27 (d,  $J = 8.5$  Hz, 2 H) 8.42 (s, 1 H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ; 100 MHz)  $\delta$  27.83, 28.41, 121.89, 122.55, 131.73, 140.08, 147.93, 151.98, 159.73, 161.30.

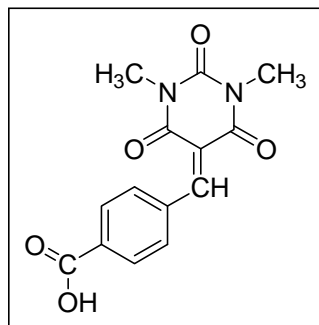
**Compound 23:** Solid 4-dimethylbarbituric acid (0.465 g, 3 mmol), 2-nitrobenzaldehyde (0.453 g, 3 mmol), and amidosulfonic acid (0.298 g) were ground for 10 minutes with a mortar and pestle.



It was then placed in a desiccator for 2 hours. The ground mixture was then dissolved in DMSO and poured into 50 mL of distilled water. The formed precipitate was filtered, washed with boiling water and MeOH and then dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.754 g (87%), mp: 159-161 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.06 (s, 3 H) 3.25 (s, 3 H) 7.52 (d,  $J = 7.7$  Hz, 1 H) 7.64 - 7.75 (m, 1 H) 7.76 - 7.87 (m, 1 H) 8.26 (d,  $J = 8.2$  Hz, 1 H) 8.71 (s, 1 H).

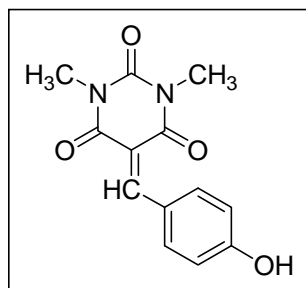
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz)  $\delta$  27.66, 28.28, 120.09, 123.89, 129.82, 129.91, 133.69, 146.08, 150.94, 153.37, 159.77, 161.01.

**Compound 24:** Solid 4-dimethylbarbituric Acid (0.465 g, 3 mmol), 4-carboxybenzaldehyde (0.448 g, 3 mmol) and amidosulfonic acid (0.298 g) were ground for 10 minutes with a mortar and pestle.



It was then placed in a desiccator for 2 hours. The ground mixture was then dissolved in DMSO and poured into 50 mL distilled water. The formed precipitate was filtered, washed with boiling water and MeOH and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.770 g (89%), mp: 303-306 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.16 (s, 3 H) 3.23 (s, 3 H) 7.96 (s, 4 H) 8.37 (s, 1 H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz)  $\delta$

27.86, 28.44, 120.55, 128.42, 131.52, 137.14, 153.68, 159.87, 161.63, 166.52.

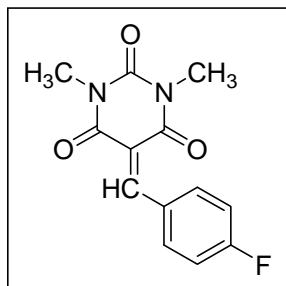


**Compound 25:** Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, 46, 6453.



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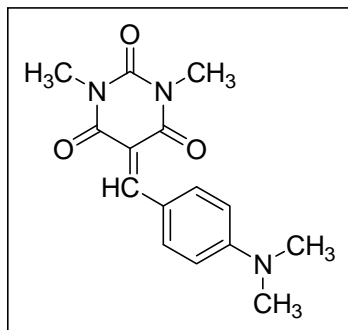
**Compound 26:** A solution of 4-dimethylbarbituric acid (0.468 g, 3 mmol) in distilled water (20



mL) was stirred for 10 minutes at room temperature. 4-Fluorobenzaldehyde (0.372 g, 3 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 80 °C for 1 hour. The formed precipitate was filtered and washed with water and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.684 g (87%), mp: 269-271°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.21 (d, *J* = 14.1 Hz, 6 H) 7.33 (t, *J* = 8.9 Hz, 2 H) 8.18 (dd, *J* = 8.5, 5.8 Hz, 2 H) 8.34 (s, 1 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100

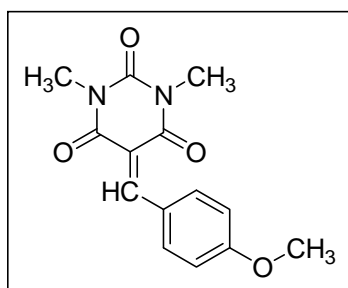
MHz) δ 27.86, 28.41, 114.92, 115.13, 118.41, 129.18, 135.82, 135.91, 150.91, 154.15, 161.97, 165.26.

**Compound 27:** Solid 4-dimethylbarbituric acid (0.465 g, 3 mmol), 4-dimethylaminobenzaldehyde



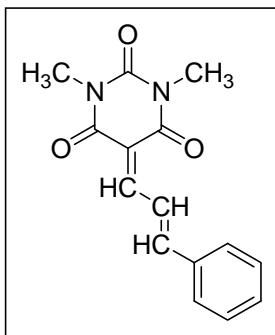
(0.453 g, 3 mmol), and amidosulfonic acid (0.298 g) was ground for 10 minutes with a mortar and pestle. It was then placed in a desiccator for 2 hours. The ground mixture was then dissolved in DMSO and poured into 50 mL distilled water. The formed precipitate was filtered, washed with boiling water and MeOH and dried in vacuum. Yield: 0.767g (89%); mp: 240-242°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.13 (s, 6 H) 3.21 (s, 6 H) 6.80 (d, *J* = 9.1 Hz, 2 H) 8.21 (s, 1 H) 8.41 (d, *J* = 9.1 Hz, 2 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz) δ

27.68, 28.30, 39.47, 101.00, 119.94, 131.31, 138.87, 151.25, 154.11, 156.18, 160.96, 163.02



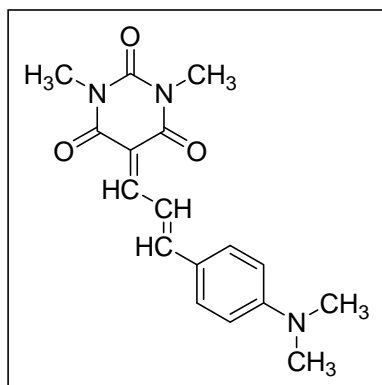
**Compound 28:** Jursic, B. S.; Stevens, E. D. *Tetrahedron Lett.* **2003**, 44, 2203.

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**Compound 29:** Jursic, B.S.; Stevens, E.D. *Tetrahedron Lett.* **2003**, *44*, 2203.

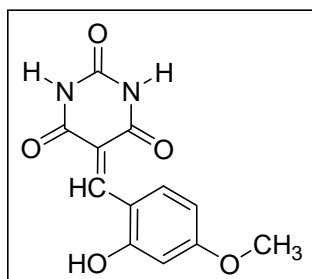
**Compound 30:** A solution of 4-dimethylbarbituric Acid (0.468 g, 3 mmol) in distilled water (20



mL) was stirred for 10 minutes at room temperature. 4-Dimethylaminocinnamaldehyde (0.526 g, 3 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 60 °C for 1 hour. The formed precipitate was filtered and washed with water and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.420 g (45%), mp: 253-255°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.07 (s, 6 H) 3.19 (s, 6 H) 6.80 (d, *J* = 8.8 Hz, 2 H) 7.57 (d, *J* = 8.8 Hz, 2 H) 7.67 (d, *J* = 15.1 Hz, 1 H) 8.04 (d, *J* = 12.4 Hz, 1 H) 8.20 - 8.33 (m, 1 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>,

100 MHz) δ 27.35, 27.92, 40.07, 109.89, 112.00, 119.16, 122.68, 131.50, 151.16, 152.87, 156.27, 165.36, 161.58, 162.05.

**Compound 31:** A solution of barbituric acid (0.122 g, 1 mmol) in distilled water (7 mL) was stirred for 10 minutes at room temperature. 2-Hydroxy-4-



methoxybenzaldehyde (0.164 g, 1 mmol) was added to the solution and stirred for 30 minutes at room temperature. The solution was then heated at 60 °C for 1 hour. The formed precipitate was filtered and washed with water and dried in vacuum. Recrystallization was performed in DMF and ethyl acetate/hexane. Yield: 0.219 g (87%), mp: 253-255°C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.82 (s, 3 H) 6.40 - 6.63

(m, 2 H) 7.96 (s, 1 H) 8.62 - 8.81 (m, 2 H) 10.90 - 11.12 (m, 2 H) 11.20 (s, 1 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 75 MHz) δ 55.57, 99.85, 106.29, 113.02, 113.32, 135.65, 149.44, 150.35, 162.46, 162.74, 164.43.