



## A concise synthesis of indolic enamides: coscinamide A, coscinamide B, and igzamide

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### ABSTRACT

A concise synthesis of indolic enamides coscinamide A, coscinamide B, and the brominated tryptamine derivative igzamide is described. Both *E*- and *Z*-isomers of these natural compounds were obtained during the thermally assisted dehydration reaction and were tested for antitumor activity. Coscinamide B was found to possess antitumor activity against DU145 with an  $IC_{50}$  of 7.6  $\mu\text{g/mL}$ .

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The 3-substituted indolic enamide moiety is found in a myriad of marine compounds isolated over the past 20 years. Both *E*- and *Z*-indolic enamides are found in nature. Representative examples of the former include coscinamides A, B, and C,<sup>1</sup> chondriamides A and B,<sup>2</sup> aspergillamide B,<sup>3</sup> while others such as igzamide<sup>4</sup>, terpeptin,<sup>5</sup> aspergillamide A<sup>3</sup>, and halocyamines A and B<sup>6</sup> comprise the latter. Coscinamides A and B were isolated from the marine sponge, *Coscinoderma* sp. and show partial cytoprotection against HIV in the NCI assay.<sup>1</sup> Igzamide was isolated from another marine sponge, *Plocamissa igzo* and displays weak cytotoxicity against the L1210 murine leukemia cell line.<sup>4</sup> Several methods for construction of these and other indolic enamides have been recently reported.<sup>7–12</sup> All methods require the use of protection either on the indole ring or elsewhere. Herein, we report a concise synthesis of indolic enamides coscinamide A, coscinamide B, and igzamide that is void of protecting groups (Fig. 1).

The synthesis begins with the preparation and reduction of indole-3-carbonyl nitrile **4**<sup>13</sup> (Scheme 1). Depending on the mode of reduction, either amino alcohol **5** or the amino ketone **6**<sup>14</sup> can be obtained in excellent yields. The use of  $\text{LiAlH}_4$ <sup>15</sup> produces the amino alcohol and hydrogenolysis affords the amino ketone. The direct introduction of the 6-bromo substituent was achieved by bromination of oxotryptamine **6** using molecular bromine. This resulted in a regioisomeric mixture of 5- and 6-brominated oxotryptamine derivatives from which **7** was obtained in pure form after flash chromatography.<sup>14</sup> Reduction of **7** with  $\text{NaBH}_4$  provided amino alcohol **8**.<sup>16</sup>

Conversion of amino alcohols **5** and **8** to their corresponding bis-3-indoleglyoxamides **9** and **10**<sup>17</sup> was achieved in good yields with 3-indoleglyoxylyl chloride (Scheme 2). With these precursors in hand, their transformation to *E*- and *Z*-indolic enamides under thermal dehydration conditions was investigated.

Using xylene as the solvent, dehydration of hydroxyl amide **9** took place at 130 °C giving both *E*- and *Z*-isomers of coscinamide B. From the crude reaction mixture, a 5:3 *E*:*Z* ratio of coscinamide B (**2**) and its *Z*-isomer (**11**)<sup>18</sup> was determined by NMR. Efforts to optimize the *Z*-isomer by shortening the reaction time were unsuccessful due to incomplete reaction. The combined yield for both isomers after chromatography was 69% in addition to 5% of recovered starting amide **9** (Scheme 3).

When (*Z*)-coscinamide B was maintained in  $\text{DMSO}-d_6$  at 45 °C for 2 d, 80% of the *Z*-isomer was converted to the natural *E*-configuration. This observation prompted us to investigate the use of a polar aprotic solvent for the dehydration in order to obtain a higher *E*/*Z* ratio. When hydroxyl amide **9** was heated at 130 °C in DMF, a 5:1 *E*:*Z* ratio of **2** and **11** was obtained in a combined yield of 90%.

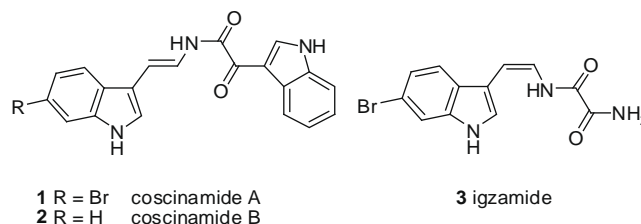
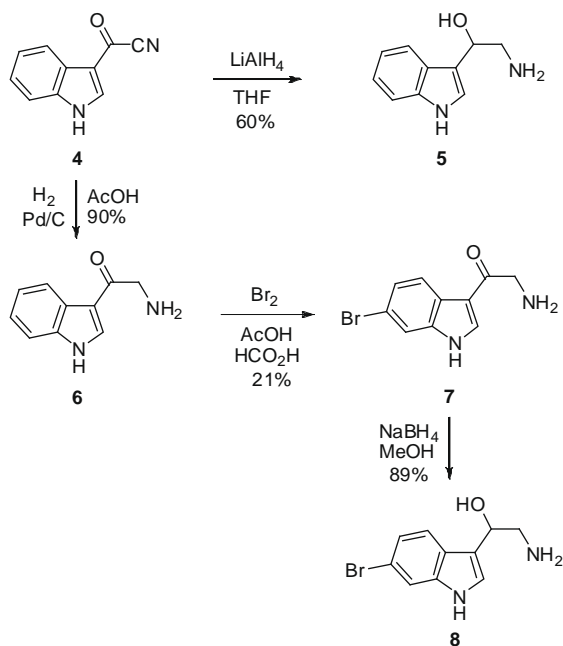
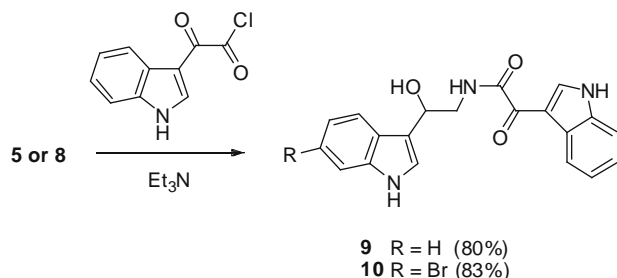
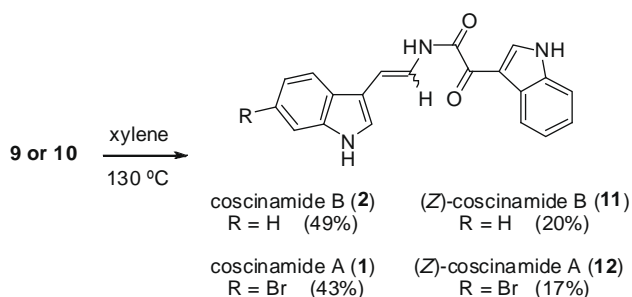


Figure 1. Structure of coscinamides A and B and igzamide.

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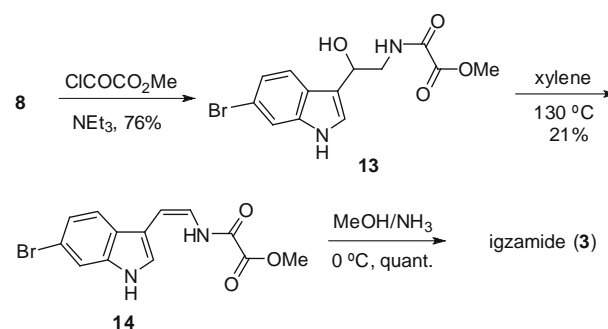
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Scheme 1. Synthesis of amino alcohols **5** and **8**.Scheme 2. Synthesis of amides **9** and **10**.

Scheme 3. Synthesis of coscinamides A and B and Z-isomers.

Similar results were seen with **10**. The thermally assisted dehydration of **10** in xylene yielded coscinamide A (**1**) along with its Z-isomer **12**<sup>19</sup> (Scheme 3) in a 5:3 ratio, respectively. The combined yield for both isomers after chromatography is approximately 70%. The corresponding reaction in DMF also provided similar results to that previously seen with coscinamide B. The *E:Z* ratio was approximately 5:1. These results indicate better selectivity for *E*-indolic enamides in DMF while the amount of *Z*-enamide isomers can be increased using a non-polar solvent such as xylene.

Based on the above observation, the synthesis of the *Z*-indolic enamide, igzamide was pursued (Scheme 4). Treatment of **8** and



Scheme 4. Synthesis of igzamide.

methyl chlorooxoacetate with Et<sub>3</sub>N in THF produced amide **13**<sup>20</sup> in 76% yield. Heating this compound in xylene at 130 °C yielded a separable mixture of *Z* and *E* enamides of **14** in a 3:2 ratio, respectively. Quantitative transformation of purified intermediate **14**<sup>21</sup> to igzamide was achieved with saturated ammonia methanol.<sup>7,22</sup>

Derivatives **9**–**14** and natural products **1**–**3** were evaluated for cytotoxicity (MTS assay) against DU145, a human prostate cancer cell line. Only coscinamide B (**2**) was found to possess in vitro anti-tumor activity with an IC<sub>50</sub> of 7.6 µg/mL. Igzamide (**3**), which was reported active against L1210 murine leukemia cell line, was inactive against DU145 at 9.2 µg/mL.

In conclusion, a concise synthesis of coscinamides A and B, and igzamide has been accomplished from readily available starting materials. Noteworthy is the absence of protecting groups which simplifies the procedure. Further application of this methodology to the synthesis of related indolic enamides and evaluation of their biological properties are in progress.

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## References and notes

- Bokesch, H. R.; Pannell, L. K.; McKee, T. C.; Boyd, M. R. *Tetrahedron Lett.* **2000**, 41, 6305–6308.
- Palermo, J. A.; Flower, P. B.; Seldes, A. M. *Tetrahedron Lett.* **1992**, 33, 3097–3100.
- Toske, S. G.; Jensen, P. R.; Kauffman, C. A.; Fenical, W. *Tetrahedron* **1998**, 54, 13459–13466.
- Dumdei, E.; Andersen, R. J. *Nat. Prod.* **1993**, 56, 792–794.
- Kagamizono, T.; Sakai, N.; Arai, K.; Kobinata, K.; Osada, H. *Tetrahedron Lett.* **1997**, 38, 1223–1226.
- Azumi, K.; Yokosawa, H.; Ishii, S. *Biochemistry* **1990**, 29, 159–165.
- Kuramochi, K.; Osada, Y.; Kitahara, T. *Tetrahedron* **2003**, 59, 9447–9454.
- Chakrabarty, M.; Basak, R.; Harigaya, Y. *Synthesis* **2003**, 13, 2011–2014.
- Rivas, L.; Quintero, L.; Fourrey, J.; Benhida, R. *Tetrahedron Lett.* **2002**, 43, 7639–7641.
- Su, S.; Kakeya, H.; Osada, H.; Porco, J. A., Jr. *Tetrahedron* **2003**, 59, 8931–8946.
- Beck, B.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2000**, 10, 1701–1705.
- Yang, L.; Deng, G.; Wang, D.; Huang, Z.; Zhu, J.; Wang, M. *Org. Lett.* **2007**, 9, 1387–1390.
- Hogan, I. T.; Sainsbury, M. *Tetrahedron* **1984**, 40, 681–682.
- Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, 2, 3185–3187.
- Burger, A.; Hornbaker, E. D. *J. Am. Chem. Soc.* **1952**, 74, 5514.
- Compound **8**: IR (KBr)  $\nu_{\max}$  3415, 3359, 3286, 1435, 1331, 1049, 894, 803 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  11.02 (br s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.22 (br s, 1H), 7.08 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.00 (br s, 1H), 4.96 (dd, *J* = 7.1, 5.0 Hz, 1H), 2.81 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.76 (dd, *J* = 12.8, 7.1 Hz, 1H), 1.89 (br s, 2H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  138.1, 125.8, 124.0, 122.0, 121.95, 118.9, 114.8, 114.5, 69.8, 49.7; HRFABMS *m/z* calcd for C<sub>10</sub>H<sub>11</sub><sup>79</sup>Br N<sub>2</sub>O M<sup>+</sup>: 254.00548; found: 254.00486.
- Compound **9**: IR (KBr)  $\nu_{\max}$  3375, 3251, 1657, 1601, 1499, 1430 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$  12.22 (br s, 1H), 10.92 (br s, 1H), 8.80 (d, *J* = 3.1 Hz, 1H), 8.57 (t, *J* = 5.8 Hz, 1H), 8.24 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.53 (m, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 2.2 Hz, 1H), 7.26 (m, 2H), 7.08 (td, *J* = 7.1, 1.0 Hz,

- 1H), 6.99 (td,  $J = 7.4$ , 1.0 Hz, 1H), 5.32 (d,  $J = 4.8$  Hz, 1H), 5.08 (m, 1H), 3.71 (m, 1H), 3.53 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  182.7, 164.2, 139.5, 137.3, 137.1, 127.1, 126.7, 124.3, 123.4, 123.1, 122.2, 121.9, 120.1, 119.3, 117.8, 113.4, 113.0, 112.3, 66.4, 46.6; HRFABMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_3$   $M^+$ : 347.1270; found: 347.1280. Compound **10**: IR (KBr)  $\nu_{\text{max}}$  3372, 3251, 1660, 1600, 1492, 1440, 1436, 1064  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  12.22 (br s, 1H), 11.07 (br s, 1H), 8.75 (d,  $J = 3.2$  Hz, 1H), 8.58 (t,  $J = 5.8$  Hz, 1H), 8.21 (m, 1H), 7.65 (d,  $J = 8.5$  Hz, 1H), 7.53 (d,  $J = 1.8$  Hz, 1H), 7.52 (m, 1H), 7.31 (d,  $J = 2.4$  Hz, 1H), 7.25 (m, 2H), 7.11 (dd,  $J = 8.5$ , 1.8 Hz, 1H), 5.37 (d,  $J = 4.9$  Hz, 1H), 5.04 (m, 1H), 3.63 (m, 1H), 3.49 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  182.3, 163.8, 139.1, 137.7, 136.7, 126.7, 125.4, 123.9, 123.8, 123.0, 121.7  $\times$  2, 121.5, 117.7, 114.5, 114.3, 113.0, 112.6, 65.7, 46.2.
18. Coscinamide B **2**: IR (KBr)  $\nu_{\text{max}}$  3436, 3227, 1650, 1597, 1542, 1490, 1442,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  12.30 (br s, 1H), 11.21 (br s, 1H), 10.83 (d,  $J = 10.1$  Hz, 1H), 8.84 (d,  $J = 3.1$  Hz, 1H), 8.28 (m, 1H), 7.69 (br d,  $J = 6.9$  Hz, 1H), 7.55 (m, 1H), 7.49 (d,  $J = 2.5$  Hz, 1H), 7.42 (dd,  $J = 14.8$ , 10.1 Hz, 1H), 7.39 (br d,  $J = 6.8$  Hz, 1H), 7.28 (m, 2H), 7.12 (m, 2H), 6.85 (d,  $J = 14.8$  Hz, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  182.0, 161.2, 139.5, 137.8, 137.2, 127.1, 125.7, 125.2, 124.4, 123.5, 122.5, 122.2, 120.3, 119.9, 119.5, 113.5, 113.2, 112.8, 112.5, 110.9; HRFABMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2$   $M^+$ : 329.1164; found: 329.1158. Compound **11**: IR (KBr)  $\nu_{\text{max}}$  3304, 3051, 1672, 1610, 1535, 1483, 1433, 742  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  12.37 (br s, 1H), 11.45 (br s, 1H), 9.69 (d,  $J = 11.1$  Hz, 1H), 8.93 (br s, 1H), 8.24 (m, 1H), 7.66 (br s, 1H), 7.64 (br d,  $J = 8.1$  Hz, 1H), 7.56 (m, 1H), 7.45 (br d,  $J = 8.0$ , 1H), 7.28 (m, 2H), 7.17 (bt,  $J = 7.5$  Hz, 1H), 7.08 (bt,  $J = 7.4$  Hz, 1H), 6.82 (dd,  $J = 11.1$ , 9.2 Hz, 1H), 6.23 (d,  $J = 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  180.6, 160.7, 140.1, 137.2, 136.7, 127.3, 127.1, 124.6  $\times$  2, 123.7, 122.8, 122.2, 120.3, 119.3, 118.2, 113.6, 112.8, 112.6, 110.5, 106.8; HRFABMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2$   $M^+$ : 329.1164; found: 329.1168.
19. Coscinamide A **1**: IR (KBr)  $\nu_{\text{max}}$  3354, 1664, 1617, 1539, 1488, 1423, 1109  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  12.32 (br s, 1H), 11.35 (br s, 1H), 10.87 (d,  $J = 10.1$  Hz, 1H), 8.84 (s, 1H), 8.29 (m, 1H), 7.63 (d,  $J = 8.6$  Hz, 1H), 7.59 (d,  $J = 1.2$  Hz, 1H), 7.57 (m, 1H), 7.55 (d,  $J = 2.6$  Hz, 1H), 7.41 (dd,  $J = 14.7$ , 10.1 Hz, 1H), 7.29 (m, 2H), 7.25 (dd,  $J = 1.7$ , 8.5 Hz, 1H), 6.83 (d,  $J = 14.7$  Hz, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  181.5, 160.9, 139.1, 138.2, 136.8, 126.7, 125.6, 124.3, 124.0, 123.1, 122.7, 121.8, 121.2, 119.8, 114.9, 114.7, 113.1, 112.7, 112.4, 109.7; HRFABMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{14}^{79}\text{BrN}_3\text{O}_2$   $M^+$ : 407.0269; found: 407.0258. Compound **12**: IR (KBr)  $\nu_{\text{max}}$  3311, 1668, 1621, 1600, 1531, 1483, 1436  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  12.39 (br s, 1H), 11.58 (br s, 1H), 9.70 (d,  $J = 10.8$  Hz, 1H), 8.92 (s, 1H), 8.25 (m, 1H), 7.70 (d,  $J = 2.5$  Hz, 1H), 7.65 (d,  $J = 1.8$  Hz, 1H), 7.62 (d,  $J = 8.5$  Hz, 1H), 7.57 (m, 1H), 7.30 (m, 2H), 7.21 (dd,  $J = 8.5$ , 1.7 Hz, 1H), 6.84 (dd,  $J = 10.8$ , 9.2 Hz, 1H), 6.21 (d,  $J = 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  180.3, 160.5, 139.7, 137.1, 136.8, 126.7, 125.9, 125.2, 124.2, 123.3, 122.7, 121.8, 120.8, 118.5, 115.2, 114.8, 113.2, 112.4, 110.4, 105.8; HRFABMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{14}^{79}\text{BrN}_3\text{O}_2$   $M^+$ : 407.0269; found: 407.0273.
20. Compound **13**: IR (KBr)  $\nu_{\text{max}}$  3415, 3311, 1741, 1686, 1212  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (acetone- $d_6$ , 300 MHz)  $\delta$  10.32 (br s, 1H), 8.10 (br s, 1H), 7.70 (d,  $J = 8.5$  Hz, 1H), 7.62 (dd,  $J = 1.8$  Hz, 0.5 Hz, 1H), 7.38 (dd,  $J = 2.5$ , 0.8 Hz, 1H), 7.18 (dd,  $J = 8.5$ , 1.8 Hz, 1H), 5.20 (m, 1H), 4.55 (d,  $J = 4.4$  Hz, 1H), 3.82 (s, 3H), 3.79 (m, 1H), 3.60 (m, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ , 300 MHz)  $\delta$  161.2, 156.6, 137.8, 125.1, 123.1, 121.8, 121.0, 117.4, 114.5, 114.2, 66.2, 52.4, 46.3; HRFABMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}^{79}\text{BrN}_2\text{O}_4$   $M^+$ : 340.0059; found: 340.0044.
21. Compound **14**: IR (KBr)  $\nu_{\text{max}}$  3303, 1751, 1697, 1533, 1285  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (acetone- $d_6$ , 300 MHz)  $\delta$  10.74 (br s, 1H), 9.20 (d,  $J = 11.9$  Hz, 1H), 7.70 (d,  $J = 1.7$  Hz, 1H), 7.63 (m, 2H), 7.27 (dd,  $J = 8.5$ ,  $J = 1.8$  Hz, 1H), 6.85 (dd,  $J = 11.1$ , 9.2 Hz, 1H), 6.22 (d,  $J = 9.2$  Hz, 1H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (acetone- $d_6$ , 300 MHz)  $\delta$  160.8, 153.4, 137.1, 125.7, 124.1, 122.8, 120.3, 118.4, 115.4, 114.5, 110.5, 105.3, 52.9; HRFABMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{11}^{79}\text{BrN}_2\text{O}_3$   $M^+$ : 321.9953; found: 321.9960.
22. Igzamide **3**: IR (KBr)  $\nu_{\text{max}}$  3391, 3372, 3329, 3233, 1662, 1528, 1040,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  11.56 (br s, 1H), 9.48 (d,  $J = 11.5$  Hz, 1H), 8.39 (br s, 1H), 8.09 (br s, 1H), 7.63 (d,  $J = 1.7$  Hz, 1H), 7.57 (d,  $J = 8.9$ , 1H), 7.56 (br s, 1H), 7.20 (dd,  $J = 8.6$ ,  $J = 1.7$  Hz, 1H), 6.70 (dd,  $J = 11.3$ , 9.4 Hz, 1H), 6.17 (d,  $J = 9.1$  Hz, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  161.9, 157.7, 137.1, 125.8, 124.9, 122.8, 120.8, 118.5, 115.2, 114.8, 110.3, 105.8; HRFABMS  $m/z$  calcd for  $\text{C}_{12}\text{H}_{10}^{79}\text{BrN}_3\text{O}_2$   $M^+$ : 306.9956; found: 306.9944.