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## FACILE SYNTHESIS OF BENZIMIDAZO[2,1-*a*]ISOINDOLES FROM PHENOLIC ADDUCTS OF NINHYDRIN

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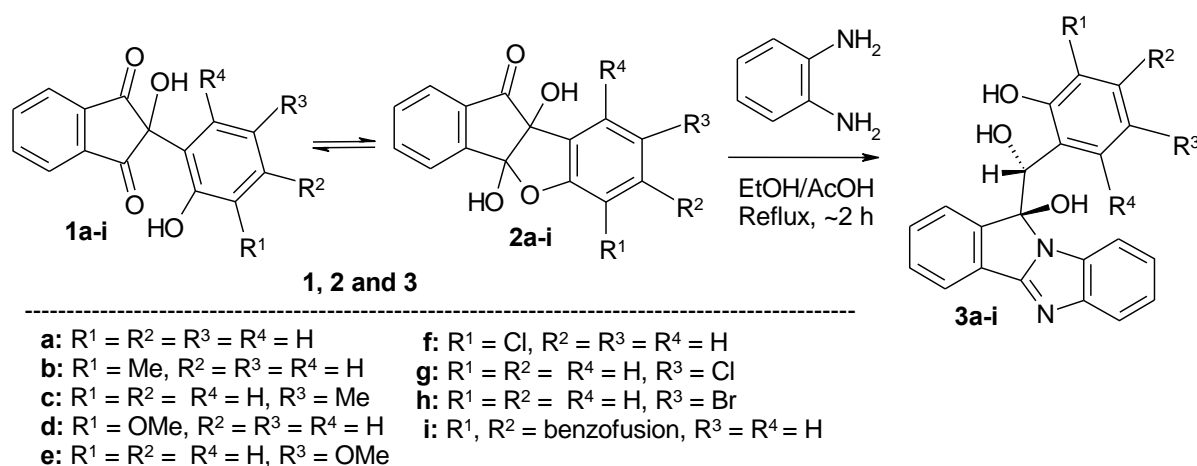
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**Abstract** – An efficient synthesis of substituted benzimidazo[2,1-*a*]isoindoles via the reaction of phenolic adducts of ninhydrin with *o*-phenylenediamine in EtOH/AcOH under reflux conditions is achieved in single step. The process involves acid-catalyzed rearrangement followed by reaction with *o*-phenylenediamine.

Benzimidazole based heterocycles have attracted growing interest over the years due to their wide range of biological activities. Some of their derivatives have been reported to possess anticancer,<sup>1</sup> anxiolytic,<sup>2</sup> antimicrobial,<sup>3</sup> analgesic,<sup>4</sup> anti-HIV,<sup>5</sup> and antiparasytic<sup>6</sup> properties and some are marketed as important drugs.<sup>7</sup> Owing to their diverse pharmacological properties, great attention has been paid to the synthesis of benzimidazole skeletons.<sup>8</sup> Similarly isoindoles are also important heterocyclic scaffolds, found in numerous natural products<sup>9</sup> and exhibit a broad spectrum of biological properties.<sup>10</sup> Indeed, the isoindole fused benzimidazole constitutes a privileged structure in medicinal chemistry.<sup>11</sup> Moreover, compounds containing benzimidazoisoindole nucleus have found industrial applications<sup>12</sup> such as dyes, fluorescent, and additive for polymers etc. Therefore, development of new and efficient methodology towards the synthesis of benzimidazole fused isoindole skeleton is well deserved. Most familiar straightforward approach to access benzimidazoisoindole derivatives is the condensation of phthalic anhydrides with *o*-phenylenediamines.<sup>11a-b,12a</sup> Another well known method involves the reaction between *o*-diacylbenzenes or *o*-acylbenzoic acids and *o*-phenylenediamines.<sup>13</sup> Alternative ways have also been developed which employ transannular cyclization,<sup>14</sup> intramolecular aryl radical cyclization<sup>15</sup> or palladium-catalyzed annulation.<sup>16</sup> However, most of the protocols involve drastic conditions, multi-step, metal-catalysis, longer reaction time and tedious work-up procedures. In the present paper, we have developed a new method to prepare benzimidazo[2,1-*a*]isoindole derivatives from ninhydrin adducts of phenols viz. 2-hydroxy-2-(2'-hydroxy-aryl)-1,3-indanediones under milder and metal-free conditions.

It is worthwhile to mention that several reports available where the reaction of ninhydrin with *o*-phenylenediamines leads to the formation of indenoquinoxaline system.<sup>17</sup> Our results revealed that replacing ninhydrin with its phenolic adducts can lead to the formation of completely different heterocyclic core, namely benzimidazoisindoles. Unlike ninhydrin, the reaction of its phenolic adduct with *o*-phenylenediamine in acidic medium is relatively complicated as the reaction goes through an acid-catalyzed rearrangement. To the best of our knowledge, benzimidazoisindole system has not been obtained before exploiting ninhydrin adducts.

Initially we have prepared ninhydrin adducts of phenols **1**<sup>18</sup> (preferentially remain in the cyclic hemiketal form **2**<sup>18a-c</sup>). Then they are subjected to react with *o*-phenylenediamine. First, the reaction of 2-hydroxy-2-(2'-hydroxyphenyl)-1,3-indanedione **1a** was examined under condition illustrated in Scheme 1. The product was not obtained when ethanol or acetic acid used separately, and ethanol-acetic acid (9:1) mixture proved to be the best solvent under reflux condition. During reflux, formation of red colour solution indicates completion of the reaction (TLC). Thus, upon refluxing **1a** with *o*-phenylenediamine in EtOH/AcOH, benzimidazo[2,1-*a*]isindoles **3a** is formed in good yields. Determination of the structure of **3a** was achieved on the basis of its spectral data. Mass spectrometry and elemental analysis established the molecular formula of the product to be C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>. The <sup>13</sup>C NMR spectrum exhibited twenty one distinct signals including a signal at 69.7 ppm for characteristic -CH(OH) carbon. The <sup>1</sup>H NMR spectral data are in good agreement with the structure of **3a**. Encouraged by this result, *o*-phenylenediamine was then allowed to react with various substituted phenolic adducts of ninhydrin **2b-i** to obtain benzimidazo[2,1-*a*]isindoles **3b-i** in moderate to good yields (Scheme 1, Table 1). To our satisfaction, the reaction holds good for ninhydrin adducts of phenols bearing halogen substituents. The current one-pot protocol possesses a simple work-up and purification procedure, requiring only filtration of the precipitated product followed by crystallization from acetone. It is interesting to note that the reaction is highly stereoselective. In each case a single diastereomer is obtained with the stereochemistry as shown in Scheme 1 and there is no detectable amount of other stereoisomeric products. The exclusive formation of the shown diastereomer is proposed from the spectral data.



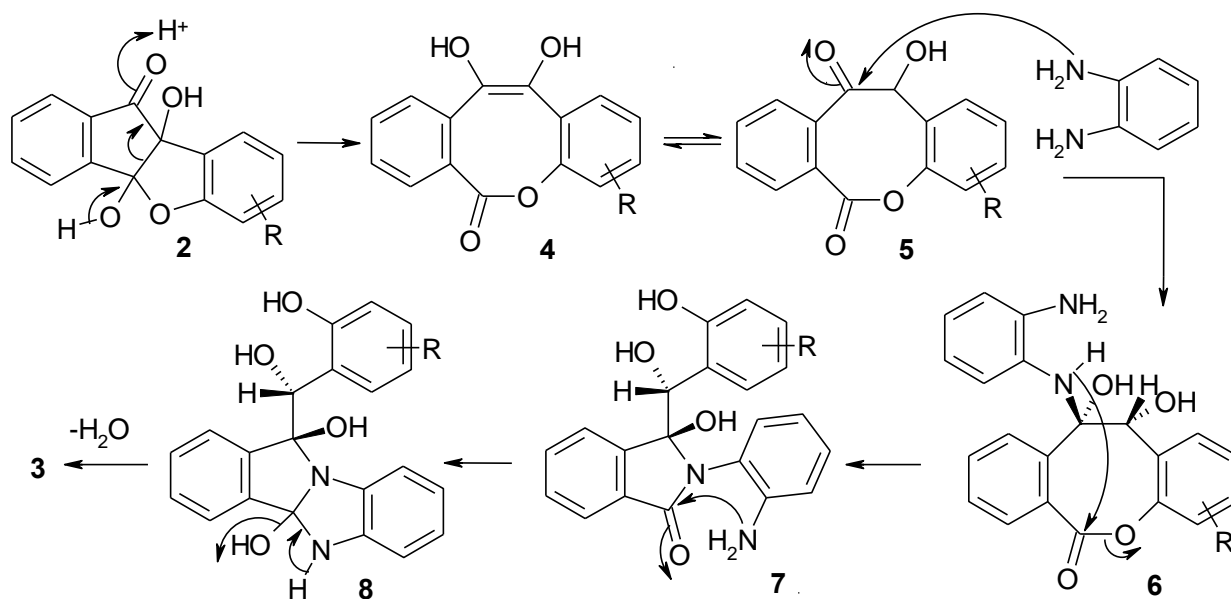
**Scheme 1**

**Table 1.** Synthesis of benzimidazo[2,1-*a*]isoindole derivatives **3**

Entry	Substrates	Product	Time (h)	Yield/% <sup>a</sup>	Mp/°C <sup>b</sup>
1	<b>1a</b>	<b>3a</b>	2.5	75	229-230
2	<b>1b</b>	<b>3b</b>	2.5	72	210-211
3	<b>1c</b>	<b>3c</b>	2.0	68	224-225
4	<b>1d</b>	<b>3d</b>	1.5	72	237-238
5	<b>1e</b>	<b>3e</b>	2.0	75	209-210
6	<b>1f</b>	<b>3f</b>	2.5	60	232-233
7	<b>1g</b>	<b>3g</b>	2.5	54	215-216
8	<b>1h</b>	<b>3h</b>	2.0	68	222-223
9	<b>1i</b>	<b>3i</b>	1.5	58	215-216

<sup>a</sup>Yields are for isolated products.<sup>b</sup>Mps are uncorrected.

A plausible mechanism of the present reaction is depicted in Scheme 2 which is on the basis of earlier results.<sup>19</sup> In acidic condition, the protonation of carbonyl oxygen of bicyclo[3.3.0]octano system **2** triggers the cleavage of the central C-C bond to form an eight-membered lactone intermediate **4**. Then intermediate **4** tautomerizes to keto form **5**. Subsequently amino group of *o*-phenylenediamine approaches the C=O group preferably from less hindered side to produce intermediate **6**. After that, intramolecular nucleophilic attack of the nitrogen on the lactone carbonyl affords isoindolone skeleton **7**. Finally, intermediate **7** undergoes intramolecular cyclization followed by dehydration to furnish desired products **3**. It is noteworthy that none of the intermediates **4-8** was possible to isolate under the reaction conditions.

**Scheme 2**

In conclusion, we have successfully developed a new route for the one-step synthesis of benzimidazo fused isoindole derivatives from phenolic adducts of ninhydrin. An efficient acid-catalyzed method is employed for the construction of the skeleton containing C=N and C-N. Simple available substrates, mild reaction conditions, easy work up and purification procedure showed the superiority of the reaction. To the best of our knowledge this is the first ever synthesis of benzimidazoisoindole framework utilizing C-2 arylated 1,3-indanediones.

## EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded with a Bruker spectrophotometer. The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker DRX-500 (500 MHz) or Bruker Avance III 400 (400 MHz) spectrophotometer in  $\text{DMSO-}d_6$  as the solvent. TLC analyses were run on a Merck Kieselgel 60 PF<sub>254</sub>. Elemental analyses were performed on a Perkin-Elmer 240C analyser.

**General procedure for the preparation of benzimidazo[2,1-*a*]isoindoles (3a-i):** The appropriate substrate **1a-i** (1.4 mmol) was added to a mixture of EtOH (9 mL) and gl AcOH (1 mL) followed by the addition of *o*-phenylenediamine (2.0 mmol, 0.216 g). The reaction mixture was refluxed for about 2 h. and kept undisturbed overnight. The solid product separated was filtered and washed with water. Crystallization from acetone gives pure products **3a-i**.

**11-(Hydroxy(2-hydroxyphenyl)methyl)-11*H*-benzo[4,5]imidazo[2,1-*a*]isoindol-11-ol (3a):** white solid, mp 229-230 °C. IR (KBr): 3340, 3098, 1581, 1488, 1463, 1449  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 9.55 (bs, 1H), 8.17 (d,  $J = 7.2$  Hz, 1H), 7.64-7.59 (m, 2H), 7.52-7.44 (m, 2H), 7.30-7.24 (m, 2H), 7.10 (t,  $J = 7.6$  Hz, 1H), 6.91-6.86 (m, 3H), 6.80 (d,  $J = 8.0$  Hz, 1H), 6.43 (d,  $J = 8.2$  Hz, 1H), 5.87 (bs, 1H), 5.67 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 154.7, 148.0, 143.7, 137.9, 134.4, 130.1, 130.0, 128.7, 127.7, 126.8, 125.7, 124.7, 124.5, 121.9, 121.6, 118.8, 118.7, 116.3, 112.3, 86.8, 69.7. MS (ESI):  $m/z = 345.1$ . Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_3$ : C, 73.24; H, 4.68; N, 8.13. Found: C, 73.16; H, 4.71; N, 8.19.

**11-(Hydroxy(2-hydroxy-3-methylphenyl)methyl)-11*H*-benzo[4,5]imidazo[2,1-*a*]isoindol-11-ol (3b):** white solid, mp 210-211 °C. IR (KBr): 3357, 3032, 1587, 1496, 1461, 1450  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 9.02 (bs, 1H), 8.22 (d,  $J = 5.4$  Hz, 1H), 7.74-7.68 (m, 2H), 7.52-7.48 (m, 2H), 7.24-7.15 (m, 2H), 7.02-6.93 (m, 4H), 6.26 (d,  $J = 7.6$  Hz, 1H), 5.61 (d,  $J = 7.7$  Hz, 1H), 5.43 (s, 1H), 2.14 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 151.8, 148.3, 143.7, 143.5, 136.9, 135.1, 131.8, 130.2, 127.8, 127.1, 125.8, 125.3, 124.7, 124.1, 123.0, 121.5, 119.6, 118.1, 112.8, 84.7, 71.4, 16.2. Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 73.73; H, 5.06; N, 7.82. Found: C, 73.63; H, 5.09; N, 7.73.

**11-(Hydroxy(2-hydroxy-5-methylphenyl)methyl)-11*H*-benzo[4,5]imidazo[2,1-*a*]isoindol-11-ol (3c):** white solid, mp 224-225 °C. IR (KBr): 3357, 3031, 1586, 1495, 1461, 1449  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,

DMSO- $d_6$ )  $\delta$ : 9.39 (s, 1H), 8.21 (d,  $J = 7.4$  Hz, 1H), 7.68-7.64 (m, 2H), 7.56-7.47 (m, 2H), 7.33 (s, 1H), 7.14-7.10 (m, 2H), 6.94-6.88 (m, 2H), 6.74 (d,  $J = 8.1$  Hz, 1H), 6.42 (d,  $J = 8.2$  Hz, 1H), 5.89 (d,  $J = 8.4$  Hz, 1H), 5.73 (d,  $J = 8.1$  Hz, 1H), 2.28 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 152.4, 148.0, 143.6, 138.0, 134.4, 130.4, 130.1, 129.2, 127.6, 127.0, 126.6, 125.4, 124.7, 124.5, 121.9, 121.6, 118.8, 116.2, 112.3, 86.5, 69.7, 20.5. MS (ESI):  $m/z = 359.1$ . Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 73.73; H, 5.06; N, 7.82. Found: C, 73.61; H, 5.11; N, 7.71.

**11-(Hydroxy(2-hydroxy-3-methoxyphenyl)methyl)-11H-benzo[4,5]imidazo[2,1-a]isoindol-11-ol(3d):**

white solid, mp 237-238 °C. IR (KBr): 3227, 2992, 1494, 1467, 1447  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.80 (bs, 1H), 8.18 (d,  $J = 7.0$  Hz, 1H), 7.70-7.59 (m, 2H), 7.52-7.45 (m, 2H), 7.11 (t,  $J = 7.6$  Hz, 1H), 7.04 (d,  $J = 7.6$  Hz, 1H), 6.91-6.81 (m, 4H), 6.50 (d,  $J = 8.0$  Hz, 1H), 5.90 (bs, 1H), 5.70 (s, 1H), 3.77 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$ : 148.0, 147.7, 144.0, 143.7, 137.8, 134.5, 130.1, 127.8, 126.9, 126.0, 124.8, 124.6, 122.0, 121.7, 120.3, 118.9, 118.3, 112.4, 112.3, 87.0, 69.7, 55.9. Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 70.58; H, 4.85; N, 7.48. Found: C, 70.51; H, 4.89; N, 7.39.

**11-(Hydroxy(2-hydroxy-5-methoxyphenyl)methyl)-11H-benzo[4,5]imidazo[2,1-a]isoindol-11-ol (3e):**

white solid, mp 209-210 °C. IR (KBr): 3226, 2991, 1493, 1467, 1447  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 9.09 (s, 1H), 8.17 (d,  $J = 7.3$  Hz, 1H), 7.64-7.61 (m, 2H), 7.53-7.45 (m, 2H), 7.10 (t,  $J = 7.5$  Hz, 1H), 7.97 (d,  $J = 2.5$  Hz, 1H), 6.94-6.86 (m, 3H), 6.73 (d,  $J = 8.7$  Hz, 1H), 6.44 (d,  $J = 8.2$  Hz, 1H), 5.86 (d,  $J = 8.4$  Hz, 1H), 5.68 (d,  $J = 8.3$  Hz, 1H), 3.69 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$ : 152.0, 148.5, 148.1, 143.7, 138.0, 134.5, 130.2, 127.8, 126.8, 126.6, 124.8, 124.7, 122.1, 121.8, 119.0, 116.9, 114.9, 114.7, 112.4, 86.6, 69.7, 55.4. Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 70.58; H, 4.85; N, 7.48. Found: C, 70.52; H, 4.88; N, 7.37.

**11-((3-Chloro-2-hydroxyphenyl)hydroxymethyl)-11H-benzo[4,5]imidazo[2,1-a]isoindol-11-ol (3f):**

white solid, mp 232-233 °C. IR (KBr): 3414, 3057, 1589, 1536, 1496, 1461  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$ : 9.63 (bs, 1H), 8.21 (d,  $J = 7.0$  Hz, 1H), 7.74 (d,  $J = 8.0$  Hz, 1H), 7.68-7.60 (m, 2H), 7.52-7.44 (m, 2H), 7.23 (d,  $J = 7.5$  Hz, 1H), 7.15 (t,  $J = 7.5$  Hz, 1H), 7.04 (bs, 1H), 6.98 (t,  $J = 7.5$  Hz, 1H), 6.87 (t,  $J = 7.5$  Hz, 1H), 6.61 (d,  $J = 7.5$  Hz, 1H), 6.18 (bs, 1H), 5.76 (d,  $J = 8.0$  Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$ : 152.3, 148.1, 143.8, 137.2, 134.2, 130.4, 128.3, 127.2, 125.8, 125.2, 124.7, 123.1, 122.6, 122.4, 121.3, 119.9, 119.1, 113.6, 112.4, 87.7, 70.5. Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{ClN}_2\text{O}_3$ : C, 66.58; H, 3.99; N, 7.39. Found: C, 66.51; H, 3.91; N, 7.28.

**11-((5-Chloro-2-hydroxyphenyl)hydroxymethyl)-11H-benzo[4,5]imidazo[2,1-a]isoindol-11-ol (3g):**

white solid, mp 215-216 °C. IR (KBr): 3415, 3058, 1612, 1589, 1537, 1496, 1462, 1448  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 9.89 (bs, 1H), 8.18 (d,  $J = 7.2$  Hz, 1H), 7.66-7.61 (m, 3H), 7.54 (t,  $J = 7.3$  Hz, 1H), 7.48 (t,  $J = 7.3$  Hz, 1H), 7.36 (dd,  $J = 8.6, 2.6$  Hz, 1H), 7.11 (t,  $J = 7.5$  Hz, 1H), 7.00 (bs, 1H), 6.94 (t,  $J = 7.5$  Hz, 1H), 6.82 (d,  $J = 8.6$  Hz, 1H), 6.32 (d,  $J = 8.2$  Hz, 1H), 5.90 (bs, 1H), 5.68 (s, 1H).  $^{13}\text{C}$  NMR

(125 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 153.6, 147.9, 143.6, 137.8, 134.2, 130.2, 129.7, 128.9, 128.0, 127.6, 126.4, 124.6 (2C), 122.5, 122.1, 121.7, 119.0, 117.9, 111.7, 85.8, 69.3. Anal. Calcd for C<sub>21</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 66.58; H, 3.99; N, 7.39. Found: C, 66.49; H, 3.89; N, 7.31.

**11-((5-Bromo-2-hydroxyphenyl)hydroxymethyl)-11H-benzo[4,5]imidazo[2,1-a]isoindol-11-ol (3h):** white solid, mp 222-223 °C. IR (KBr): 3414, 3057, 1611, 1589, 1536, 1496, 1461, 1447 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 9.93 (s, 1H), 8.18 (d, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.72-7.64 (m, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.50-7.46 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.01 (bs, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 1H), 5.92 (d, *J* = 8.5 Hz, 1H), 5.68 (d, *J* = 8.1 Hz, 1H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 154.1, 148.0, 143.7, 137.9, 134.2, 132.8, 131.8, 130.3, 128.5, 127.7, 126.4, 124.7, 124.6, 122.2, 121.9, 119.1, 118.5, 111.8, 110.3, 85.8, 69.4. Anal. Calcd for C<sub>21</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 59.59; H, 3.57; N, 6.62. Found: C, 59.69; H, 3.54; N, 6.51.

**11-(Hydroxy(1-hydroxynaphthalen-2-yl)methyl)-11H-benzo[4,5]imidazo[2,1-a]isoindol-11-ol (3i):** white solid, mp 215-216 °C. IR (KBr): 3339, 3053, 1571, 1462, 1446 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 8.96 (bs, 1H), 8.26 (s, 1H), 7.79-7.70 (m, 2H), 7.63-7.58 (m, 1H), 7.52-7.46 (m, 4H), 7.28-7.20 (m, 2H), 7.17-7.08 (m, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.32 (bs, 1H), 5.94 (d, *J* = 8.7 Hz, 1H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 152.5, 148.4, 144.0, 136.8, 134.0, 133.7, 130.6, 128.3, 127.6, 127.4, 126.8, 125.8, 125.3, 124.9, 123.8, 122.9, 122.5, 122.2, 119.3, 118.8, 117.8, 113.7, 113.1, 89.4, 72.3. Anal. Calcd for C<sub>25</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 76.13; H, 4.60; N, 7.10. Found: C, 76.08; H, 4.56; N, 7.02.

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