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One-Pot Synthesis of Quinoline-Based Tetracycles by a Tandem Three-Component Reaction

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A practical one-pot synthetic strategy for the efficient synthesis of a range of structurally interesting and bioactive quinoline-based tetracycles has been developed. A key step in the synthesis is a tandem three-component reaction of heteroaromatic amine, methyl 2-formylbenzoate and *t*butyl isonitrile, followed by TFA-mediated lactamization via intramolecular aminolysis of an adjacent ester. Results related to a kinase-panel screening for several selected compounds are also discussed in this article.

Introduction

Cancer drug discovery is one of the most active areas of pharmaceutical research. Regulations of cyclin-dependent kinases (CDKs) in cancers[1] provided the main impetus to search for the inhibitors of kinases. Among the CDK superfamily, CDK2 in complex with cyclin E or cyclin A is a key cell regulator and continues to be an attractive target for the discovery of new antitumor agents.[2] Many novel selective small-molecule inhibitors of CDK2 in complex with cyclin E or cyclin A have been identified; Figure 1 shows four well-known CDK inhibitors.[3] Despite striking chemical diversity,[4] those CDK inhibitors share several common features: (1) they act by competing with ATP for binding in the ATP-binding site; (2) they are flat, hydrophobic heterocycles; (3) they bind mostly by hydrophobic interactions and hydrogen bonds with kinases (Figure 1).

However, synthesis of those compounds usually requires lengthy synthetic routes with overall low yields, which prevents the syntheses of their structurally diverse analogs efficiently, limiting the feasibility to achieve the small molecules with discriminative binding to CDKs.

In connection with our development of a chemical genetic approach to analyzing biological systems by using interfacing libraries of small molecules with creative biological assays,[5] we would like to create some scaffolds with druglike features for the biologically important targets. To this end, we sought to identify the compounds as inhibitors of CDKs, but their syntheses had to be efficient so that structurally diverse analogs could be easily generated. We report herein our recent efforts for development of a one-pot synthesis[6] of heterocycles via a multicomponent reaction as a key step.[7]

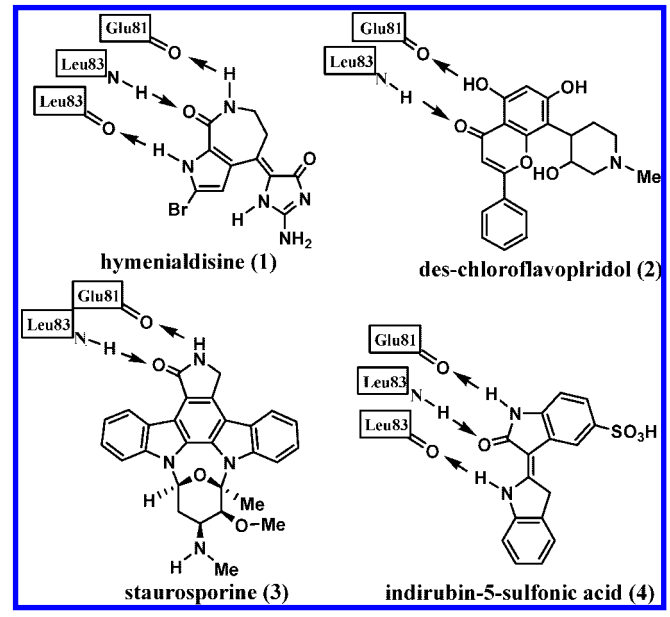

Figure 1. CDK inhibitors and their binding modes.

Results and Discussion

Our study began with the pre-evaluation of a series of derivatives of scaffold **A** (Figure 2) with the crystal structure of CDK2[8] (PDB code 1OI9) based on the aforementioned common properties of the CDK2 inhibitors.

The ATP-binding site located in the deep cleft formed by the N-lobe, C-lobe, and the hinge region (residue 81–84) of CDK2.[9] Predicted by docking software AutoDock3.0,[10] these compounds can bind with CDK2 with high affinity (estimated binding free energy $\Delta G \sim 9$ kcal/mol). The plane of quinoline-based polyheterocycles forms two hydrogen bonds

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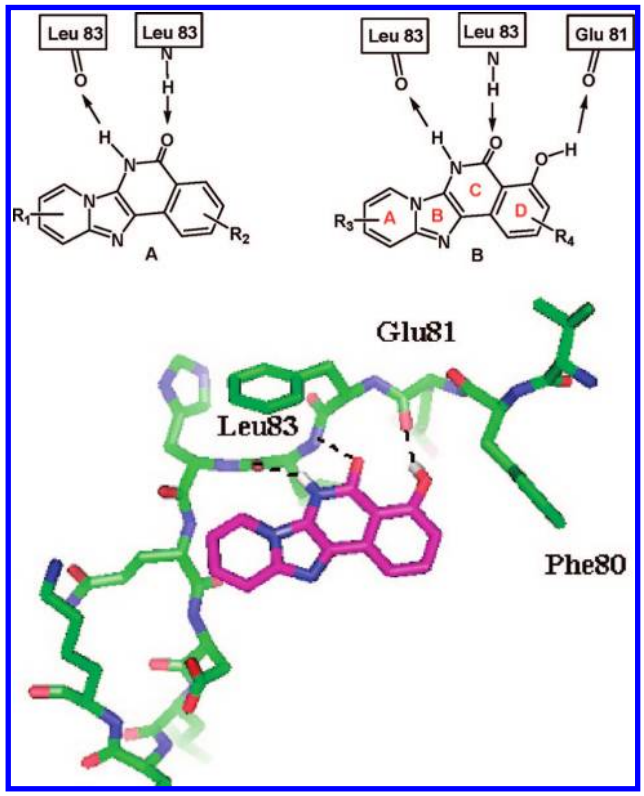
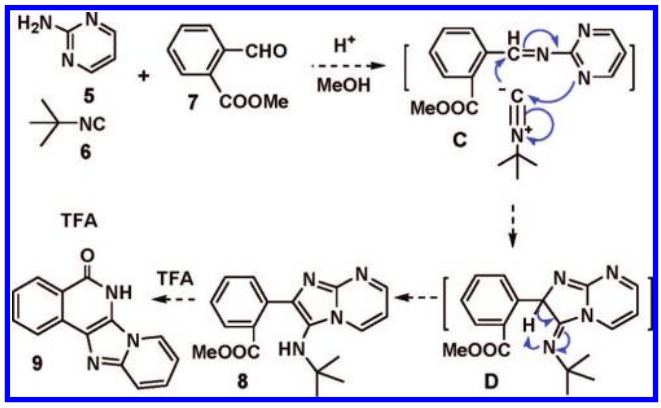


Figure 2. Binding interaction between quinoline derivatives **A** and **B** with CDK2.

Scheme 1. Proposed One-Pot Synthesis of Compound **9**

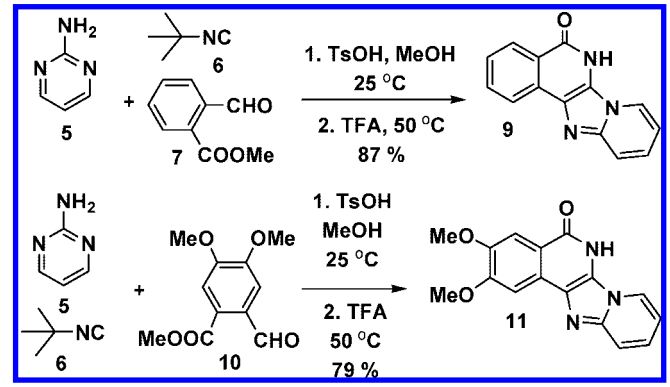


between the lactam motif and the hinge region of CDK2. In addition, several van der Waals and hydrophobic contacts are made between the polyheterocycles and the wall of the ATP-binding cleft, and the edge-face aromatic–aromatic contact is formed between the benzene ring and Phe80. The extending pocket close to Phe80 can tolerate a small hydrophobic group.

To further improve the binding affinity, **B** (Figure 2) was designed with an intention to provide an extra hydrogen-binding between phenolic group of the **D** ring with the carbonyl group of Glu81.[11]

With regard to the formation of the scaffolds of **A** and **B**, we intended to apply Bienaymé's chemistry[12] of a three-component reaction of 2-aminopyridine **5**, isonitrile **6**, and aldehyde **7** to generate compound **8** through intermediates **C** and **D** (Scheme 1), which without purification could undergo TFA-mediated intramolecular amide formation to afford quinoline-based tetracycle **9**, realizing a post-

Scheme 2. Syntheses of Compounds **9** and **11**



transformation strategy to quickly access the core structures of **A** and **B** via a one-pot procedure.

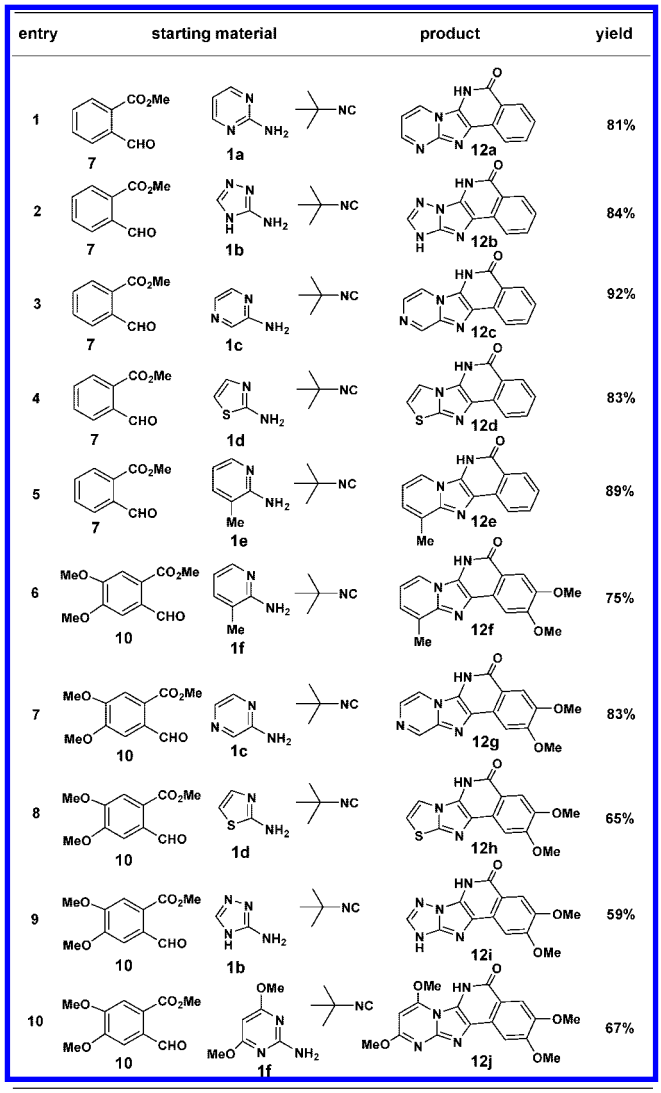
To this end, we used the commercially available starting materials **5** and **6** to react with 2-formyl-benoic acid **7** and 2-formyl-4,5-dimethoxy-benoic acid ester **10** to test our proposed synthetic transformation. Compounds **7** and **10** were prepared by using the published procedures (see the Supporting Information for detail). After screening a variety of conditions for the formation of desired products, we found that TsOH and TFA were the proper acids to promote the desired reactions, and products **9** and **11** were obtained in 87%, and 79% yields, respectively, under the conditions listed in Scheme 2.

To demonstrate the synthetic utility of this newly developed one-pot procedure, the synthesis of structurally diversified tetracyclic heterocycles that share the scaffold of **A** was investigated. We first focused our attention on the evaluation of substrate flexibility of aryl amines in the reaction. Thus, six commercially available aryl amines (**1a**–**1f**) were selected and reacted with 2-isocyano-2-methyl-propane (**6**) and compounds **7** or **10**, respectively. To our delight, the desired products **12a**–**12j** were obtained in good to excellent yields. Table 1 shows the results of these reactions.

The scope of reaction was further studied by exploring the substitutional effect on the aromatic ring of methyl 2-formylbenzoates. To this end, three additional substituted methyl 2-formylbenzoates **13**, **14**, and **15** were made according to literature procedures (see the Supporting Information for details). In the event, when **13**, **14**, and **15** were reacted with the commercially available aryl amines and isonitrile (**6**) under the conditions listed in Scheme 2, it was found that when **13** and **14** were used as substrates, the expected products **16a**–**16j** were obtained in good yields (entries 1–7 in Table 2); however, when the substrate was **15**, relatively low yields were obtained (entries 8–10 in Table 2), presumably due to its negative steric and electronic effect of the methoxy group on the TFA-mediated intramolecular lactamization.

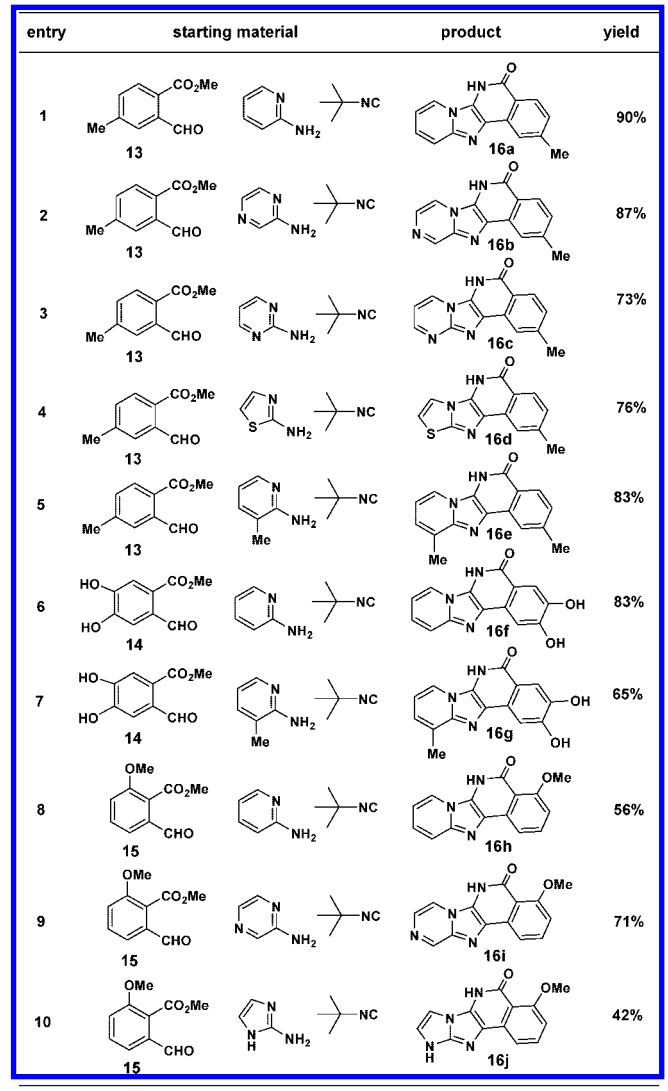
Finally, we directed our efforts for making the molecules with structural features such as compound **B** (Figure 1). Accordingly, compounds **16h** and **16i** were first treated with BBr_3 in CH_2Cl_2 at −78 °C and then warmed up to room temperature, followed by workup. This process gave the expected products **17a** and **17b** in 42% and 67% yields, respectively (Scheme 3).

Table 1. Synthesis of Compounds **12a–12j**[a,b]



[a] Reagents and conditions: To a solution of aryl amine (0.5 mmol) and methyl-2-formylbenzoate (0.5 mL) in methanol (1 mL) was added *tert*-butylisonitrile (0.6 mmol) for 2 h, and then, *p*-toluenesulfonic acid (4.75 mg, 0.025 mmol) was added. The mixture was stirred at room temperature for 12 h. [b] Isolated yield.

Table 2. Synthesis of Compounds **16a–16j**[a,b]



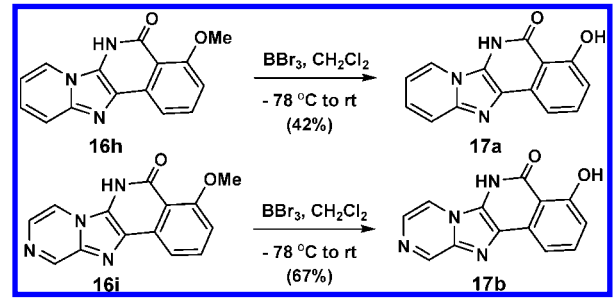
[a] Reagents and conditions: To a solution of aryl amine (0.5 mmol) and methyl-2-formylbenzoate (0.5 mL) in methanol (1 mL) was added *tert*-butylisonitrile (0.6 mmol) for 2 h, and then, *p*-toluenesulfonic acid (4.75 mg, 0.025 mmol) was added. The mixture was stirred at room temperature for 12 h. [b] Isolated yield.

In an initial effort to investigate kinase inhibition of the synthesized compounds, we choose to profile representative ones against a panel of kinases covering the entire human kinome (Figure 3).

We have chosen **9**, **16h**, **17a**, and **17b** which represent the key scaffolds **A** and **B** illustrated in Figure 2. As shown in Figure 3, the four compounds have distinct inhibition profiles against the panel when tested at 10 mM, with compound **9** being the weakest and compound **17** being the most potent yet least selective. Compound **16h** predominantly hits one kinase, and compound **17a** inhibits one kinase strongly (at ~90% inhibition) and three other kinases at medium level. At a high inhibition range (>70%), compounds **16h**, **17a**, and **17b** each inhibit different kinases. The heatmap shown in Figure 3 clearly shows distinct inhibition profiles for the compounds tested.

In summary, we developed a concise approach that enables efficient and flexible synthesis of a range of structurally interesting and bioactive quinoline-based polyheterocycles in one-pot reaction via a tandem three-component reaction as a key step. The substrates are readily available and reactions conditions are mild. This method is of considerable value in combinatorial chemistry, diversity-oriented synthesis and drug discovery.

Scheme 3. BBr_3-Mediated Demethylation of **16h** and **16i**



Experimental Section

General Procedure for One-Pot Synthesis of Quinoline-Based Polyheterocycles. To the solution of the arylamine component (0.5 mmol) and methyl 2-formylbenzoate

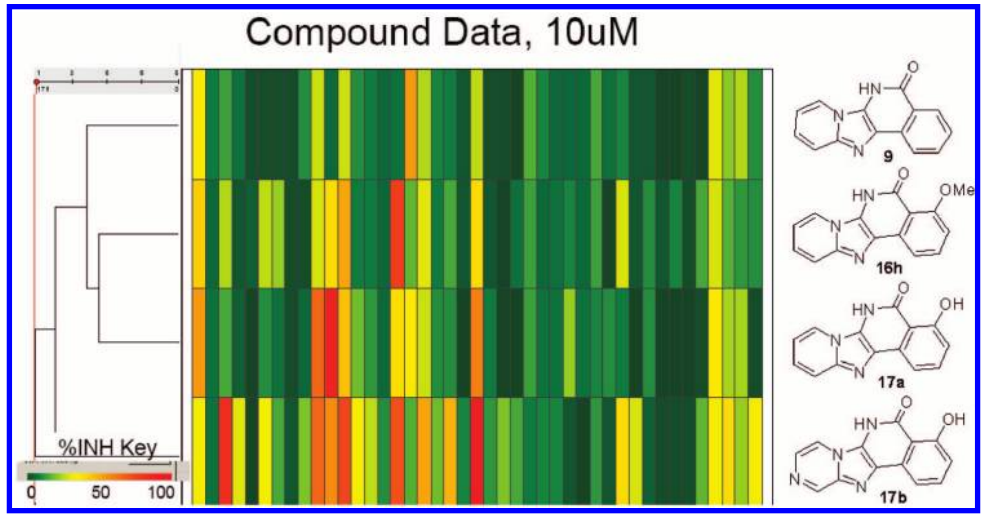


Figure 3. Profile of the representative compounds against a panel of kinases.

(0.5 mmol) in methanol (1 mL) was added *tert*-butylisonitrile (63 μL, 0.6 mmol) through a microsyringe at room temperature, and then, *p*-toluenesulfonic acid (4.75 mg, 0.025 mmol) was added. After stirring at room temperature for 12 h, the solvent was removed, the residue was mixed with trifluroacetic acid (1 mL), and the mixture was then stirred at 40–50 °C for 2 h.

Synthesis 6*H*-Pyrido[2′,1′:1,2]imidazo[5,4-*c*]isoquinolin-5-one (9). After the multicomponent reaction (MCR) described in the general procedure, the trifluroacetic acid was removed under vacuum, the residue was dissolved in a solution of EtOH (0.2 mL) and water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 2/1) to give product **9** (102 mg) in 87% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.85 (s, br, 1H), 8.68 (d, J = 6.8 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.30 (1H), 7.89 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.31(1H), 7.04 (t, J = 6.8 Hz, 1H). ^{13}C NMR (125MHz, DMSO) δ 160.7, 142.2, 133.2, 132.9, 128.6, 126.7, 125.0, 124.5, 123.7, 121.9, 117.9, 112.4. HRMS (*m/z*) calc. for $C_{14}H_9ON_3$ 235.0745, found 235.0747. IR ν 3080, 2752, 1652, 1619, 1587, 1483, 1388, 1334, 1280, 875, 772, 739 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2,3-Dimethoxy-6*H*-pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-one (11). After the multicomponent reaction (MCR) described in the general procedure, the trifluroacetic acid was removed under vacuum, the residue was dissolved in a solution of EtOH (0.2 mL) and water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **11** (116 mg) in 79% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.61 (s, br, 1H), 8.62 (1H), 7.63–7.71 (3H), 7.28 (1H), 7.00 (1H), 4.01 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 160.0, 154.0, 148.8, 141.9, 127.9, 124.7, 123.4, 117.6, 112.1, 109.0, 102.8, 56.3, 56.0. HRMS (*m/z*) calc. for $C_{16}H_{13}O_3N_3$ 295.0957, found 295.0957. IR ν 3390, 3083, 2945, 2841, 1649, 1620, 1597, 1564, 1508, 1477, 1433, 1392, 1261, 1219, 1091, 870, 771 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 6*H*-6,6b,10,11-Tetraaza-benzo[*a*]fluoren-5-one (12a). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was dissolved in a solution of EtOH (0.2 mL) and water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12a** (95 mg) in 81% yield. ^{1}H NMR (500 MHz, DMSO) δ 13.05 (s, br, 1H), 9.10 (1H), 8.56 (1H), 8.36 (2H), 7.89 (1H), 7.61 (1H), 7.31(1H), 7.14 (1H). ^{13}C NMR (125 MHz, DMSO) δ 161.4, 150.2, 144.7, 133.0, 132.7, 131.9, 128.7, 127.0, 125.1, 125.2, 123.8, 122.2, 108.6. HRMS (*m/z*) calc. for $C_{13}H_8ON_4$ 236.0698, found 236.0703. IR ν 3556, 3236, 3085, 1682,1669, 1647, 1614, 1570, 1490,1380, 1204, 1178, 1130775, 720 cm^{-1}. mp 282 °C (sublimation).

Synthesis of 6,9-Dihydro-6,6b,7,9,10-pentaaza-pentaleno[2,1-*a*]naphthalene-5-one (12b). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was dissolved in a solution of EtOH (0.2 mL) and water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 2/1) to give product **12b** (94 mg) in 84% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.55 (s, br, 1H), 8.30 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.07(s, 1H), 7.85 (t, J = 7.3Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ159.0, 155.0, 152.4, 132.3, 128.7, 127.5, 125.6, 120.7, 118.9, 114.6. HRMS (*m/z*) calc. for $C_{11}H_7ON_5$ 225.0650, found 225.0659. IR ν 3420, 3088, 2957, 1680, 1642, 1613, 1600, 1570, 1501, 1436, 1393, 1329, 1198, 1144, 804, 763 cm^{-1}. mp 234 °C.

Synthesis 6*H*-6,6b,9,11-Tetraaza-benzo[a]fluoren-5-one (12c). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12c** (108 mg) in 92% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.95 (s, br, 1H), 9.11 (s, 1H), 8.57 (d, J = 3.9

Hz, 1H), 8.32(d, J = 7.9 Hz 1H), 8.27 (d, J = 7.5Hz, 1H), 7.93 (d, J = 4.4 Hz, 1H), 7.89 (t, J = 7.4 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 161.1, 144.1, 136.9, 133.7, 132.4, 128.9, 128.6, 127.9, 122.3, 116.5. HRMS (*m/z*) calc. for $C_{13}H_8ON_4$ 236.0698, found 236.0697. IR ν 3445, 3088, 1655, 1610, 1574, 1551, 1413, 1380, 1322, 1283, 1142, 1015, 878, 771 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 6*H*-9-Thia-6,6b,10-triaza-pentaleno[2,1-a]-naphthalen-5-one (12d). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with a solution of EtOH (0.2 mL) and water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated, and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 3/1) to give product **12d** (100 mg) in 83% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.72 (s, br, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 7.7 Hz 1H), 8.00 (d, J = 4.5Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.36 (d, J =4.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 160.1, 133.3, 133.1, 128.5, 125.6, 121.1, 117.6, 114.0. HRMS (*m/z*) calc. for $C_{12}H_7ON_3S$ 241.0310, found 241.0314. IR ν 3377, 3105, 1668, 1626, 1577, 1462, 1407, 1334, 1294, 1141, 847, 764 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 11-Methyl-6 *H*-pyrido[2′,2′,2,3]imidazo-[4,5-*c*]isoquinolin-5(6*H*)-one (12e). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 2/1) to give product **12e** (111 mg) in 89% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.76 (s, br, 1H), 8.52 (d, J = 6.8 Hz, 1H), 8.34 (d, J = 8.0 Hz 1H), 8.31 (d, J = 7.9Hz, 1H), 7.87 (t, J = 7.9 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 6.7 Hz, 1H), 6.93 (t, J = 6.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 160.7, 142.8, 133.2, 133.0, 128.6, 127.3, 126.6, 123.7, 122.0, 121.4, 112.4, 17.1. HRMS (*m/z*) calc. for $C_{15}H_{11}ON_3$ 249.0902, found 249.0908. IR ν 3360, 3079, 2956, 2876, 1652, 1621, 1590, 1566, 1388, 1334, 1123, 1015, 872, 769 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2,3-Dimethoxy-11-methyl-6*H*-pyrido-[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-one (12f). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12f** (115 mg) in 75% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.60 (s, br, 1H), 8.49 (1H), 7.71(1H), 7.66 (1H), 7.09 (1H), 6.91 (1H), 4.03 (s, 3H), 3.92 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 159.9, 154.0, 148.8, 127.1, 123.4, 121.2, 112.2, 109.0, 102.7, 56.4, 56.0, 17.2. HRMS (*m/z*) calc. for $C_{17}H_{15}O_3N_3$ 309.1113, found 309.1111. IR ν 3387, 3087, 2950, 2837, 1657, 1620, 1513, 1477, 1433, 1389, 1263, 1090, 859, 762 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2,3-Dimethoxy-6*H*-6,6b,9,11-tetraaza-benzo[*a*]fluoren-5-one (12g). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12 g** (123 mg) in 83% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.64 (s, br, 1H), 9.05 (s, 1H), 8.53(1H), 7.90 (1H), 7.69 (s, 1H), 7.66 (s, 1H), 4.02 (s, 3H), 3.92 (s, 3H). HRMS (*m/z*) calc. for $C_{15}H_{12}O_3N_4$ 296.0909, found 296.0914. IR ν 3400, 3095, 2942, 2847, 1646, 1609, 1518, 1489, 1384, 1298, 1064, 874, 787 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2,3-Dimethoxy-6*H*-9-thia-6,6b,10-triaza-pentaleno[2,1-*a*]naphthalen-5-one (12h). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12h** (98 mg) in 65% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.48 (s, br, 1H), 7.99 (d, J = 4.4 Hz, 1H), 7.64 (s, 1H), 7.52 (s, 1H), 7.33 (d, J = 4.4 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 159.0, 154.1, 148.1, 128.5, 117.7, 113.6, 108.7, 101.9, 56.3, 56.1. HRMS (*m/z*) calc. for $C_{14}H_{11}O_3N_3S$ 301.0521, found 301.0525. IR ν 3136, 3048, 2827, 1668, 1406, 1203, 862, 721 cm^{-1}. mp 222 °C (sublimation).

Synthesis of Dimethoxy-6,9-dihydro-6,6b,7,9,10-penta-aza-pentaleno[2,1-*a*]naphthalene-5-one (12i). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12i** (84 mg) in 59% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.64 (s, br, 1H), 12.19 (s, br, 1H), 8.05 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 3.98 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 157.0, 154.8, 154.0, 151.9, 148.6, 124.1, 115.6, 112.3, 106.4, 101.0, 56.4, 56.1. HRMS (*m/z*) calc. for $C_{13}H_{11}O_3N_5$ 285.0862, found 285.0863. IR ν 3394, 3078, 2965, 2841, 1652, 1615, 1514, 1488, 1421, 1268, 1193, 1053, 802, 763 cm^{-1}. mp 261 °C.

Synthesis of 2,3,7,9-Tetramethoxy-6*H*-6,6b,10,11-tetraaza-benzo[*a*]fluoren-5-one (12j). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **12j** (119 mg) in 67% yield. ^{1}H NMR (500 MHz, DMSO) δ 11.58 (s, br, 1H), 7.63 (s, 1H), 7.51(s, 1H), 6.04 (s, 1H), 4.14 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H). HRMS (*m/z*) calc. for $C_{17}H_{16}O_5N_4$ 356.1120, found 356.1117. IR ν 3510, 3268, 3009, 2951, 2839, 1655, 1626, 1583, 1572, 1500, 1387, 1280, 1220, 1038, 880, 785 cm^{-1}. mp 258 °C (sublimation).

Synthesis of 2-Methyl-6*H*-pyrido[2′,1′:2,3]imidazo-[4,5-*c*]isoquinolin-5-one (16a). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 1/1) to give product **16a** (112 mg) in 90% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.89 (s, br, 1H), 8.72 (1H), 8.21 (1H), 8.04 (1H), 7.79 (1H), 7.55 (1H), 7.44 (1H), 7.22 (1H). ^{13}C NMR (125 MHz, DMSO) δ 160.6, 143.8, 140.8, 129.0, 128.5, 128.4, 125.9, 124.4, 121.7, 119.9, 115.9, 114.3, 22.0. HRMS (mz) calcd for $C_{15}H_{11}ON_3$ 249.0902, found 249.0903. IR ν 3092, 2950, 2850, 1654, 1628, 1566, 1382, 1318, 1190, 1127, 827, 753 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2-Methyl-6*H*-6,6b,9,11-tetraaza-benzo-[*a*]fluoren-5-one (16b). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **16b** (109 mg) in 87% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.78 (s, br, 1H), 9.08 (s, 1H), 8.55 (1H), 8.20 (1H), 8.07 (1H), 7.91 (1H), 7.44 (1H). ^{13}C NMR (125 MHz, DMSO) δ 161.1, 144.2, 136.9, 132.4, 129.3, 128.4, 128.7, 122.1, 116.5, 22.0. HRMS (m/z) calcd for $C_{14}H_{10}ON_4$ 250.0855, found 250.0857. IR ν 3093, 3017, 1918, 1856, 1656, 1612, 1572, 1456, 1380, 856, 783 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2-Methyl-6*H*-6,6b,10,11-tetraaza-benzo-[*a*]fluren-5-one (16c). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **16c** (91 mg) in 73% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.78 (s, br, 1H), 9.00 (1H), 8.57 (1H), 8.25 (1H), 8.13 (1H), 7.42 (1H), 7.16 (1H). ^{13}C NMR (125 MHz, DMSO) δ 160.8, 156.1, 150.3, 143.8, 132.7, 131.7, 128.7, 123.9, 122.1, 108.7, 22.0. HRMS (*m/z*) calcd for $C_{14}H_{10}ON_4$ 250.0855, found 250.0859. IR ν 3376, 3065, 2956, 2833, 1654, 1632, 1611, 1567, 1491, 1371, 1299, 860, 783 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2-Methyl-6*H*-9-thia-6,6b,10-triaza-pentaleno[2,1-*a*]naphthalene-5-one (16d). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 1/1) to give product **16d** (96 mg) in 76% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.54 (s, br, 1H), 8.16 (1H), 7.98 (1H), 7.91 (1H), 7.34 (1H). ^{13}C NMR (125 MHz, DMSO) δ 160.1, 143.4, 133.2, 128.4, 127.0, 120.7, 117.6, 113.9, 22.0. HRMS (m/z) calcd for $C_{13}H_9OSN_3$ 255.0466, found 255.0466. IR ν 3288, 3081, 2917, 2855, 1671, 1629, 1581, 1468, 1412, 1374, 1295, 841, 770 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2,11-Dimethyl-6H-pyrido[2′,1′,2,3]imidazo[4,5-c]isoquinolin-5-one (16e). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 1/1) to give product **16e** (109 mg) in 83% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.68 (s, br, 1H), 8.50 (d, J = 6.8 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.11 (s, 1H), 7.38 (d, J = 8.1 Hz,1H), 7.10 (d, J = 6.5 Hz, 1H), 6.91 (t, J = 6.8 Hz, 1H), 2.57 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 160.7, 143.6, 142.7, 133.1, 128.6, 128.0, 127.3, 123.5, 121.8, 121.3, 112.3, 21.9, 17.1. HRMS (*m/z*) calcd for $C_{16}H_{13}ON_3$ 263.1058, found 263.1059. IR ν 3383, 3097, 2956, 2848, 1656, 1620, 1564, 1393, 848, 737 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 2,3-Dihydroxy-6*H*-pyrido[2′,1′,2,3]imidazo[4,5-*c*]isoquinolin-5-one (16f). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 1/1) to give product **16f** (111 mg) in 83% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.41 (s, br, 1H), 10.26 (s, 1H), 9.69 (s, 1H), 8.61 (d, J = 6.0 Hz, 1H), 7.66 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.56 (s, 1H), 7.24 (1H), 6.98 (1H). ^{13}C NMR (125 MHz, DMSO) δ 160.1, 151.9, 146.2, 141.7, 127.1, 124.3, 123.9, 123.7, 123.3, 117.6, 117.4, 113.5, 112.1, 106.8. HRMS (*m/z*) calcd for $C_{14}H_9O_3N_3$ 267.0644, found 257.0649. IR ν 3382, 3073, 1655, 1621, 1603, 1557, 1504, 1464, 1277, 878, 748 cm^{-1}. mp 263 °C (sublimation).

Synthesis of Dihydroxy-11-methyl-6*H*-pyrido-[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-one (16g). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 1/1) to give product **16 g** (91 mg) in 65% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.39 (s, br, 1H), 9.90 (br, 2H), 8.48 (1H), 7.64 (s, 1H), 7.58 (s, 1H), 7.06 (1H), 6.89 (1H). ^{13}C NMR (125 MHz, DMSO) δ 165.2, 151.9, 146.1, 142.2, 127.3, 127.0, 123.7, 122.8, 121.1, 113.8, 112.0, 106.8, 17.1. HRMS (m/z) calcd for $C_{15}H_{11}O_3N_3$ 281.0800, found 281.0803. IR ν 3177, 3103, 2954, 2920, 1652, 1620, 1592, 1557, 1484, 1360, 1273, 1192, 861, 741 cm^{-1}. mp 275 °C (sublimation).

Synthesis of 4-Methoxy-6*H*-pyrido[2′,1′:2,3]imidazo-[4,5-*c*]isoquinolin-5-one (16h). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 2/1) to give product **16h** (74

mg) in 56% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.25 (s, br, 1H), 8.64 (d, J = 6.6 Hz, 1H), 7.93 (1H), 7.79 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.33 (1H), 7.15 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 6.5 Hz, 1H), 4.01 (s, 1H). ^{13}C NMR (125 MHz, DMSO) δ 158.9, 148.3, 138.0, 135.5, 135.0, 133.8, 125.9, 125.8, 123.8, 117.8, 114.3, 113.4, 112.2, 109.1, 56.6. HRMS (m/z) calcd for $C_{15}H_{11}O_2N_3$ 265.0851, found 265.0846. IR ν 3415, 3077, 2943, 2841, 1665, 1623, 1595, 1575, 1550, 1485, 1388, 1284, 1043, 811, 754 cm^{-1}. mp 239–241 °C.

Synthesis of 4-Methoxy-6*H*-6,6b,9,11-tetraaza-benzo-[a]fluoren-5-one (16i). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization from EtOH to give product **16i** (94 mg) in 71% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.31 (s, br, 1H), 9.08 (1H), 8.54 (1H), 7.80–7.90 (3H), 7.19 (1H), 3.95 (s, 3H). HRMS (*m/z*) calcd for $C_{16}H_{12}O_3N$ 266.0817, found 266.0811. IR ν 3413, 3069, 2959, 2838, 1680, 1609, 1589, 1480, 1381, 1257, 1047, 810 cm^{-1}. mp 249 °C.

Synthesis of 4-Methoxy-6,9-dihydro-6,6b,7,9,10-pentaaza-pentaleno[2,1-a]naphthalene-5-one (16j). After the MCR, the trifluroacetic acid was removed under vacuum, the residue was mixed with water (1 mL) and EtOH (0.2 mL), and the mixture was treated with an ammonia solution (10%) to pH = 8. The formed solid was filtrated and washed with water (2 mL) and EtOAc (1 mL), and the solid then underwent a recrystallization (EtOAc/EtOH, 2/1) to give product **16j** (54 mg) in 42% yield. ^{1}H NMR (500 MHz, DMSO) δ 12.84 (s, br, 1H), 11.49 (s, br, 1H), 8.09 (1H), 7.78 (2H), 7.09 (1H), 4.01 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 159.0, 157.6, 155.3, 152.8, 133.1, 130.3, 128.4, 115.6, 112.9, 107.8, 106.8, 56.8. HRMS (*m/z*) calcd for $C_{12}H_9O_2N_5$ 255.0756, found 255.0755. IR ν 3369, 3062, 2935, 2819, 1658, 1603, 1557, 1541, 1493, 1460, 1397, 1265, 1192, 1044, 834, 773 cm^{-1}. mp 225–227 °C.

Synthesis of 4-Hydroxy-6*H*-pyrido[2′,1′:2,3]imidazo-[4,5-*c*]isoquinolin-5-one (17a). To a solution of **16h** (100 mg, 0.37 mmol) in dry CH_2Cl_2 (20 mL) was added BBr_3 (69 μL, 0.74 mmol) under nitrogen through a microsyringe at −78 °C, and the reaction mixture was warmed gradually to room temperature and stirred overnight. The reaction was quenched by ethyl acetate (100 mL), and the organic phase was washed with brine (3 × 15 mL) and water (2 × 10 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography (*n*-hexane/ethyl acetate/methanol, 2/2/1) to give product **17a** (39 mg) in 42% yield. ^{1}H NMR (500 MHz, DMSO) δ 13.48 (s, br, 1H), 13.34 (s, 1H), 8.68 (d, J = 6.9 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 7.66–7.69 (2H), 7.33 (t, J = 7.1 Hz, 1H), 7.05 (t, J = 6.7 Hz, 1H), 6.90 (d, J = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 162.7, 135.9, 125.8, 123.9, 117.9, 113.3, 112.7, 111.8, 110.1. HRMS (*m/z*) calcd for $C_{14}H_9O_2N_3$ 251.0695, found 251.0692. IR ν 3444, 3085, 1649, 1629, 1560, 1458, 1356, 1265, 822, 752 cm^{-1}. mp >300 °C (sublimation).

Synthesis of 4-Hydroxy-6*H*-6,6b,9,11-tetraaza-benzo-[*a*]fluoren-5-one (17b). To the solution of **16i** (100 mg, 0.37 mmol) in dry CH_2Cl_2 (20 mL) was added BBr_3 (69 μL, 0.74 mmol) under nitrogen through a microsyringe at −78 °C, and the reaction mixture was warmed gradually to room temperature and stirred overnight. The reaction was quenched by ethyl acetate (100 mL), and the organic phase was washed with brine (3 × 15 mL) and water (2 × 10 mL) and then dried over Na_2SO_4. After evaporation of the solvent under vacuum, the residue was purified through recrystallization with EtOH to give the product **17b** (62mg, 67%). ^{1}H NMR (500 MHz, DMSO) δ 13.64 (s, br, 1H), 13.05 (s, br, 1H), 9.30 (s, 1H), 8.68 (d, J = 4.7 Hz, 1H), 8.03 (d, J = 4.7 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 166.1, 162.6, 143.2, 136.8, 136.3, 133.0, 127.4, 127.1, 124.6, 117.2, 115.2, 112.5, 110.5. HRMS (*m/z*) calcd for $C_{13}H_8O_2N_4$ 252.0647, found 252.0649. IR (cm^{-1}) 3369, 3062, 2935, 2819, 1658, 1603, 1557, 1541, 1493, 1460, 1397, 1265, 1192, 1044, 834, 773. mp 225–227 °C. IR ν 3444, 3085, 1649, 1629, 1560, 1458, 1356, 1265, 822, 752 cm^{-1}. mp >300 °C (sublimation).

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Supporting Information Available. Experimental procedure and NMR, ^{13}C NMR, and IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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