A Facile and Efficient Synthesis of *N*-Substituted Furo[3,4-*b*] indeno[2,1-*e*]pyridine Analogues of Azapodophyllotoxin *via* Microwave-Assisted Multicomponent Reactions

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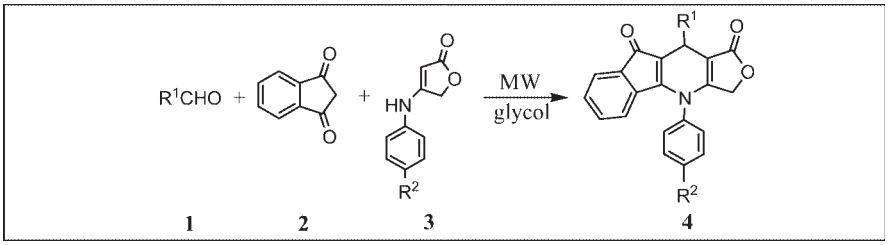

The efficient and facile synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin was achieved *via* microwave-assisted multicomponent reactions of aldehyde, 2*H*-indene-1,3-dione and 4-(arylamino)furan-2(5*H*)-one in glycol without catalyst. This method has the obvious advantages over traditional heating ones on short reaction time, high yield, operational simplicity as well as being environmental friendly.

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INTRODUCTION

Tetronic acid derivatives and their metabolites are interesting and intriguing compounds because of their antibiotic [1], anticoagulant [2], antiepileptic [3], antifungal [4], anti-inflammatory [5], and anti-HIV [6] activities. Among them, azapodophyllotoxin (Fig. 1) derivatives are also well-known anticancer agents [7] besides their cardiotonic [8], inotropic [9], pesticidal [10], potassium channel opening [11], and calcium channel agonistic [12] activities. Moreover, more potent and less toxic azapodophyllotoxin derivatives with antitumor activities have also been obtained by extensive structural modifications [13]. However, most modifications were performed on ring B and C (Fig. 1), and the modifications both on ring A and on nitrogen atom were not well documented.

Indenopyridine skeletons, existed in many natural products, such as, onychine and oracin (Fig. 2) as well as lots of synthesized heterocyclic compounds, possess numerous significant bioactivities, namely, anticancer [14], antiinfective [15], anti-inflammatory [16], calcium antagonistic [17], DNA-damaging [18], antimicrobial [19] and anticandidal activities [20]. In addition, not only they are inhibitors against phosphodiesterase [21], cyclic nucleotide synthesis [22], bovine liver glutathione S-transferase (GT) [23], and proliferation of vascular smooth muscle cells [24] but also antagonists of adenosine A2a receptor [25] and human fatty acid synthase thioesterase [26]. It is promising that the modifications on ring A of azapodophyllotoxin, changed into indenole ring, may bring about novel or improved significant bioactivities.

However, survey of the literature reveals only two typical methods on synthesizing *N*-unsubstituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin. One method is a multistep reaction composed by cyclocondensation of arylideneindandione with 3-aminocrotonic acid ester, both of which should be prepared beforehand, and subsequently intramolecular cyclization treated with NBS to give the target compounds (Scheme 1) [27]. Evidently, this method suffers from the drawbacks of long route, low yields, as well as complicated operation.

Another method is Hantzsch condensation of 1,3-indandione, ammonium acetate, and 3-benzylidenefuran-2,4(3*H*,5*H*)-dione (Scheme 2), which was prepared in advance by condensation of tetronic acid with aromatic aldehyde [21]. However, this method still has some disadvantages such as long reaction time and moderate yields.

In addition, these two methods did not offer the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine

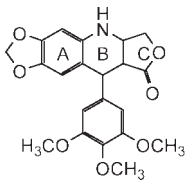


Figure 1. Structure of azapodophyllotoxin.

analogues of azapodophyllotoxin, which may bring about great changes in the bioactivities by the modifications both on nitrogen atom and on ring A of azapodophyllotoxin.

As a result, developing a facile and efficient method on the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin is of great significance.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear-type syntheses [28]. On the other hand, microwave-assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation, and shorter reaction time as compared with the traditional heating method [29]. Thus, it goes without saying that the use of atom-economical MCRs, together with the employment of energy-efficient microwave irradiation (MW), must be considered to be facile and efficient synthetic strategy of heterocyclic compounds with important bioactivities in the sense that the combination in itself offers greater potential than the two parts in isolation.

As a continuation of our efforts on structural modifications of azapodophyllotoxin with facile and efficient method [30], herein, we wish to report the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin through three-component reactions of aldehyde **1**, 2*H*-indene-1,3-dione **2** and 4-(arylamino)furan-2(5*H*)-one **3** in glycol under microwave irradiation without catalyst (Scheme 3).

RESULTS AND DISCUSSION

Initially, the three-component reaction of 4-bromobenaldehyde **1c**, 2*H*-indene-1,3-dione **2** and 4-(phenylamino)

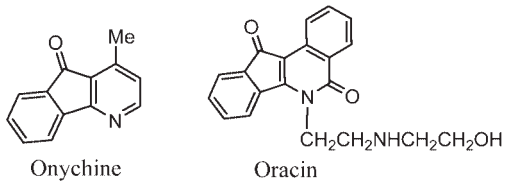
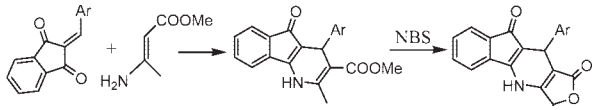


Figure 2. Structures of onychine and oracin.

Scheme 1



furan-2(5*H*)-one **3c** was used to optimize the reaction conditions. To find the best suitable solvent, we compared the synthesis of **4c** in different solvents, such as, water, glycol, DMF, glacial acetic acid, and ethanol. The mixture of 4-bromobenaldehyde **1c** (1 mmol), 2*H*-indene-1,3-dione **2** (1 mmol), 4-(phenylamino)furan-2(5*H*)-one **3c** (1 mmol), and corresponding solvent (2 mL) was irradiated under MW at 90°C and 200 W for a given time, then the crude product was purified by recrystallization from EtOH.

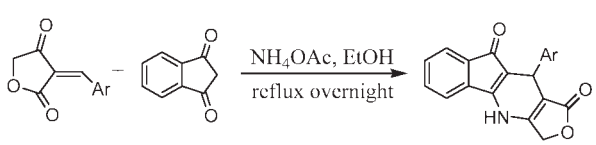
The results (Table 1) reveal that glycol as solvent not only improve the yield but also shorten the time of this reaction. Therefore, glycol was preferred as solvent for all further microwave-assisted reactions.

To optimize the reaction temperature, the reaction of **1c** (1 mmol), **2** (1 mmol), and **3c** (1 mmol) was carried out using glycol (2 mL) as solvent under MW (200 W) at temperatures ranging from 70 to 110°C, with an increment of 10°C each time. Similarly, the crude product was purified by recrystallization from EtOH. The results are shown in Table 2. The yield of product **4c** was increased and the reaction time was shortened when the temperature was increased from 70 to 100°C (Entries 1−4, Table 2), whereas the yield leveled off when the temperature was further increased to 110°C (Entry 5, Table 2). Thus, 100°C is assigned as the most suitable reaction temperature. Furthermore, we found that the yield of this reaction was affected by the volume of glycol. The synthesis of **4c** was tested in different volumes of glycol at 100°C. The outcomes show that 2.0 mL of glycol is optimal as solvent because it generates the highest yield of **4c**.

Under these optimized reaction conditions (2.0 mL of glycol, 100°C), a series of novel *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin **4** were synthesized under MW, and the results were summarized in Table 3. As shown in Table 3, this method can be applied to various aromatic aldehydes and enamines of tetronic acid with high yields under the same conditions. Therefore, this synthetic approach has wide scope of applicability.

Moreover, we also performed the synthesis of **4** in glycol at 100°C under standard heating conditions (SC).

Scheme 2



Scheme 3

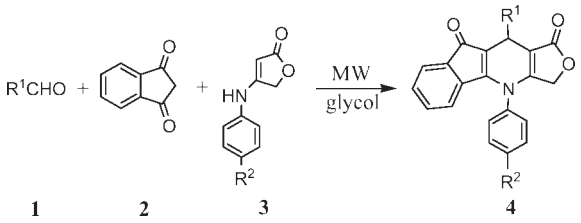


Table 2

Temperature optimization for the synthesis of **4c**.

Entry	*T* (°C)	Time (min)	Yield (%)
1	70	15	77
2	80	12	83
3	90	10	88
4	100	8	92
5	110	8	92

The results (Table 3) reveal that microwave irradiation efficiently promoted the reactions, resulting in dramatic reduction of reaction time, from hours to minutes, and remarkable increase in yields as well.

Although the detailed mechanism of the earlier reaction remains to be fully clarified, the formation of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin **4** could be explained by a reaction sequence of condensation, addition, cyclization, and dehydration (Scheme 4). First, the condensation of aldehyde **1** and 2*H*-indene-1,3-dione **2** gave the intermediate product **5**. The addition of **3**–**5** then furnished the intermediate product **6**, which upon intramolecular cyclization and dehydration gave rise to **4**.

All the products were characterized by IR, ^{1}H NMR, and HRMS (ESI). Moreover, the structure of **4g** was also established by X-ray crystallography (Fig. 3) [31].

In conclusion, we have developed an efficient and facile approach to the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin via microwave-assisted MCRs without catalyst. This method has the obvious advantages over traditional heating ones on short reaction time, high yield, operational simplicity as well as being environmental friendly. Besides, this method may provide a shortcut for further investigations on the pharmacological activities of this type of compounds as important and novel azapodophyllotoxin analogues.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys^{TM} Creator from Personal Chemistry, Uppsala, Sweden.

Table 1

Solvent optimization for the synthesis of **4c**.

Entry	Solvent	Time (min)	Yield (%)
1	DMF	10	80
2	EtOH	12	69
3	HOAc	12	76
4	Water	12	45
5	Glycol	10	88

Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FTIR-Tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. HRMS (ESI) was determined by using micrOTOF-QII HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the synthesis of compounds 4 with microwave irradiation. Typically, a mixture of aromatic aldehyde **1** (1.0 mmol), 2*H*-indene-1,3-dione **2** (1.0 mmol), 4-(arylamino)furan-2(5*H*)-one **3** (1.0 mmol), and glycol (2.0 mL) was added to the reaction vessel of the monomodal Emrys^{TM} Creator microwave synthesizer and allowed to react under MW at 200 W power (initial power 100 W) and 100°C for several minutes. Upon completion, monitored by TLC, the reaction vessel was cooled to room temperature. The solid compound was collected by filtration and recrystallized from EtOH (95%) to give pure azapodophyllotoxin derivatives **4**.

General procedure for the synthesis of compounds 4 with conventional heating. A mixture containing aromatic aldehyde **1** (1.0 mmol), 2*H*-indene-1,3-dione **2** (1.0 mmol), 4-(arylamino)furan-2(5*H*)-one **3** (1.0 mmol), and glycol (2.0 mL) was introduced into a 10 mL Emrys^{TM} reaction vial, capped, and then stirred at 100°C (oil bath temperature) for a given time. The subsequent work-up procedure was the same as in the microwave irradiation reactions.

10-(4-Fluorophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4a). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.86–7.85 (m, 1H, ArH), 7.76–7.67 (m, 4H, ArH), 7.52–7.48 (m, 2H, ArH), 7.31–7.25 (m, 2H, ArH), 7.17–7.09 (m, 3H, ArH), 5.53 (d, 1H, J = 7.2 Hz, ArH) 4.79 (s, 1H, CH), 4.76–4.75 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3487, 3068, 2864, 1757, 1689, 1669, 1596, 1553, 1505, 1455, 1407, 1396, 1349, 1319, 1283, 1224, 1185, 1156, 1140, 1113, 1074, 1025, 1013, 899, 861, 836, 803, 787, 775, 764, 730, 707, 620. HRMS (ESI) *m*/*z*: calc. for $C_{26}H_{16}FNO_3$: 432.1007 $[M + Na]^+$, found: 432.0998 $[M + Na]^+$.

10-(4-Chlorophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4b). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.87–7.85 (m, 1H, ArH), 7.78–7.67 (m, 4H, ArH), 7.50 (d, 2H, J = 8.4 Hz, ArH), 7.39 (d, 2H, J = 8.4 Hz, ArH), 7.32–7.21 (m, 2H, ArH), 7.13–7.09 (m, 1H, ArH), 5.54 (d, 1H, J = 7.6 Hz, ArH), 4.80(s, 1H, CH), 4.76–4.71(m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3474, 3061, 1754, 1694, 1669, 1595, 1560, 1490, 1454, 1391, 1351, 1283, 1182, 1143, 1114, 1086, 1039, 1025, 1010, 900, 846, 777, 763, 736, 724, 697, 678, 617. HRMS (ESI) *m*/*z*: calc. for $C_{26}H_{16}ClNO_3$: 448.0711 $[M + Na]^+$, found: 448.0703 $[M + Na]^+$.

Table 3

Synthesis of **4** in glycol at 100°C under MW and SC.

Entry	4	R^1	R^2	Time (min)		Yield (%)		Mp (°C)
				MW[a]	SC[b]	MW[a]	SC[b]	
1	**4a**	4-FC_6H_4	H	7	180	89	71	290–291
2	**4b**	4-ClC_6H_4	H	10	240	93	74	280–281
3	**4c**	4-BrC_6H_4	H	8	180	92	73	>300
4	**4d**	C_6H_5	H	10	270	74	61	297–298
5	**4e**	2,4-$Cl_2C_6H_3$	H	7	180	90	76	>300
6	**4f**	4-FC_6H_4	CH_3	8	180	82	68	>300
7	**4g**	4-ClC_6H_4	CH_3	10	210	88	71	>300
8	**4h**	4-BrC_6H_4	CH_3	10	240	85	69	>300
9	**4i**	C_6H_5	CH_3	13	360	71	58	285–286
10	**4j**	2,4-$Cl_2C_6H_3$	CH_3	8	210	91	75	>300
11	**4k**	4-BrC_6H_4	Cl	9	240	86	70	>300
12	**4l**	2,4-$Cl_2C_6H_3$	Cl	8	240	89	73	>300
13	**4m**	4-ClC_6H_4	Cl	10	300	84	72	>300

[a] The time and yields under microwave irradiation conditions.
[b] The time and yields under standard heating conditions.

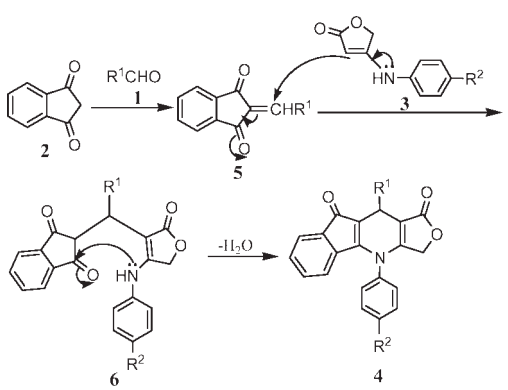
10-(4-Bromophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4c). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.86–7.84 (m, 1H, ArH), 7.76–7.66 (m, 4H, ArH), 7.52 (d, 2H, J = 8.4 Hz, ArH), 7.43 (d, 2H, J = 8.4 Hz, ArH), 7.31–7.25 (m, 2H, ArH), 7.13–7.09 (m, 1H, ArH), 5.53 (d, 1H, J = 7.6 Hz, ArH), 4.79 (s, 1H, CH), 4.76–4.71 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3446, 3077, 3036, 2926, 2872, 1749, 1690, 1596, 1484, 1454, 1351, 1282, 1182, 1067, 1008, 838, 729, 695. HRMS (ESI) *m/z*: calc. for $C_{26}H_{16}BrNO_3$: 492.0206 $[M + Na]^+$, found: 492.0195 $[M + Na]^+$.

4,10-Diphenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]-fluorene-1,9-dione (4d). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.85–7.84 (m, 1H, ArH), 7.76–7.67 (m, 4H, ArH), 7.45 (d, 2H, J^-= 7.6 Hz, ArH), 7.35–7.21(m, 5H, ArH), 7.10 (t, 1H, J = 7.6 Hz, ArH), 5.53(d, 1H, J = 7.6 Hz, ArH), 4.77 (s, 1H, CH), 4.76–4.72 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3494, 3063, 3030, 2931, 2862, 1754, 1685, 1595, 1551, 1490, 1451, 1413, 1396, 1349, 1319, 1283, 1182, 1139, 1112, 1074, 1023, 1012, 946, 897, 835, 802, 790, 765, 727, 717, 696, 624. HRMS (ESI) *m/z*: calc. for $C_{26}H_{17}NO_3$: 414.1101 $[M + Na]^+$, found: 414.1108 $[M + Na]^+$.

10-(2,4-Dichlorophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4e). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.85 (d, J = 7.2 Hz, 1H, ArH), 7.76 (d, J = 7.6 Hz, 1H, ArH), 7.73–7.68 (m, 3H, ArH), 7.65 (d, J = 8.4 Hz, 1H, ArH), 7.58 (d, J = 2.0 Hz, 1H, ArH), 7.40 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.29–7.26 (m, 2H, ArH), 7.14–7.08 (m, 1H, ArH), 5.54 (d, J = 7.6 Hz, 1H, ArH), 5.23 (s, 1H, CH), 4.80–4.70 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3060, 1758, 1691, 1668, 1595, 1557, 1497, 1469, 1454, 1407, 1392, 1354, 1283, 1185, 1144, 1038, 1025, 1011, 900, 869, 845, 763, 724, 708, 697. HRMS (ESI) *m/z*: calc. for $C_{26}H_{15}Cl_2NO_3$: 482.0322 $[M + Na]^+$, found: 482.0320 $[M + Na]^+$.

10-(4-Fluorophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4f). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, J = 8.0 Hz, ArH), 7.61 (d, 1H, J = 7.6 Hz, ArH), 7.50–7.45 (m, 4H, ArH), 7.31–7.24 (m, 2H, ArH), 7.17–7.11 (m, 3H, ArH), 5.61 (d, 1H, J = 7.6 Hz, ArH), 4.78 (s, 1H, CH), 4.74–4.73 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3483, 3067, 2923, 2871, 1756, 1684, 1604, 1552, 1510, 1455, 1412, 1348, 1319, 1283, 1224, 1185, 1153, 1143, 1112, 1093, 1074, 1038, 1027, 1011, 951, 901, 867, 848, 833, 806, 790, 761, 732, 709, 695, 682,

Scheme 4



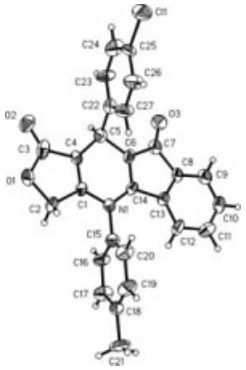


Figure 3. ORTEP diagram of **4g**.

649, 606, 588. HRMS (ESI) *m/z*: calc. for $C_{27}H_{18}FNO_3$: 446.1163 $[M + Na]^+$, found: 446.1160 $[M + Na]^+$.

10-(4-Chlorophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4g). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, J = 8.0 Hz, ArH), 7.61 (d, 1H, J = 8.0 Hz, ArH), 7.50–7.37 (m, 6H, ArH), 7.31–7.25 (m, 2H, ArH), 7.13 (t, 1H, J = 6.8 Hz, ArH), 5.61 (d, 1H, J = 7.6 Hz, ArH), 4.78 (s, 1H, CH), 4.74–4.73 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3446, 2869, 1751, 1682, 1552, 1486, 1349, 1283, 1141, 1086, 1011, 864, 761, 694, 682. HRMS (ESI) *m/z*: calc. for $C_{27}H_{18}ClNO_3$: 462.0868 $[M + Na]^+$, found: 462.0860 $[M + Na]^+$.

10-(4-Bromophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4h). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, J = 8.0 Hz, ArH), 7.61 (d, 1H, J = 8.0 Hz, ArH), 7.53–7.41 (m, 6H, ArH), 7.31–7.25 (m, 2H, ArH), 7.15–7.11 (m, 1H, ArH), 5.61 (d, 1H, J = 8.0 Hz, ArH), 4.78 (s, 1H, CH), 4.77–4.69 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3488, 3065, 2926, 2868, 1752, 1682, 1553, 1483, 1348, 1183, 1071, 835, 761, 695, 679, 647, 583. HRMS (ESI) *m/z*: calc. for $C_{27}H_{18}BrNO_3$: 506.0363 $[M + Na]^+$, found: 506.0345 $[M + Na]^+$.

10-Phenyl-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4i). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72–7.70 (m, 1H, ArH), 7.63–7.61 (m, 1H, ArH), 7.49–7.44 (m, 4H, ArH), 7.35–7.21 (m, 5H, ArH), 7.15–7.11 (m, 1H, ArH), 5.62 (d, 1H, J = 7.2 Hz, ArH), 4.79 (s, 1H, CH), 4.78–4.72 (m, 2H, CH_2), 2.45 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3378, 3054, 2922, 2858, 1747, 1686, 1543, 1319, 1180, 1045, 826, 798, 682, 669, 634, 576. HRMS (ESI) *m/z*: calc. for $C_{27}H_{19}NO_3$: 428.1258 $[M + Na]^+$, found: 428.1260 $[M + Na]^+$.

10-(2,4-Dichlorophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4j). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.73–7.71 (m, 1H, ArH), 7.64–7.61 (m, 2H, ArH), 7.58–7.57 (m, 1H, ArH), 7.48 (t, 2H, J = 8.0 Hz, ArH), 7.40 (dd, 1H, J = 8.0, 2.0 Hz, ArH), 7.28–7.27 (m, 2H, ArH), 7.16–7.12 (m, 1H, ArH), 5.63 (d, 1H, J = 8.0 Hz, ArH), 5.22 (s, 1H, CH), 4.78–4.69 (m, 2H, CH_2), 2.46 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3071, 1756, 1691, 1666, 1596, 1584, 1557, 1510, 1469, 1394, 1347, 1321, 1282, 1234, 1185, 1144, 1098, 1074, 1038, 1024, 1012, 901, 868, 844, 823, 792, 762, 730, 706, 692. HRMS (ESI) *m/z*: calc. for $C_{27}H_{17}Cl_2NO_3$: 496.0478 $[M + Na]^+$, found: 496.0470 $[M + Na]^+$.

10-(4-Bromophenyl)-4-(4-chlorophenyl)-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4k). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.73 (d, 1H, J = 8.0 Hz, ArH), 7.64 (d, 1H, J = 8.0 Hz, ArH), 7.58–7.49 (m, 6H, ArH), 7.39–7.28 (m, 2H, ArH), 7.22–7.17 (m, 1H, ArH), 5.69 (d, 1H, J = 8.0 Hz, ArH), 4.80 (s, 1H, CH), 4.78–4.69 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3078, 1762, 1689, 1557, 1473, 1320, 1234, 1177, 1079, 1027, 1016, 838, 765, 698, 679, 643, 586. HRMS (ESI) *m/z*: calc. for $C_{26}H_{15}BrClNO_3$: 525.9817 $[M + Na]^+$, found: 525.9783 $[M + Na]^+$.

10-(2,4-Dichlorophenyl)-4-(4-chlorophenyl)-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4l). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.77–7.72 (m, 1H, ArH), 7.68–7.63 (m, 2H, ArH), 7.60–7.57 (m, 1H, ArH), 7.50 (t, 2H, J = 8.0 Hz, ArH), 7.43 (d, 1H, J = 8.0 Hz, ArH), 7.30–7.27 (m, 2H, ArH), 7.20–7.13 (m, 1H, ArH), 5.67 (d, 1H, J = 8.0 Hz, ArH), 5.28 (s, 1H, CH), 4.79–4.71 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3085, 1768, 1680, 1579, 1490, 1322, 1236, 1180, 1056, 1026, 1018, 840, 769, 698, 675, 646, 588. HRMS (ESI) *m/z*: calc. for $C_{26}H_{14}Cl_3NO_3$: 515.9932 $[M + Na]^+$, found: 515.9918 $[M + Na]^+$.

4,10-Di-(4-chlorophenyl)-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4m). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, J = 8.0 Hz, ArH), 7.66 (d, 1H, J = 8.0 Hz, ArH), 7.59–7.48 (m, 6H, ArH), 7.40–7.32 (m, 2H, ArH), 7.26–7.19 (m, 1H, ArH), 5.72 (d, 1H, J = 8.0 Hz, ArH), 4.81 (s, 1H, CH), 4.79–4.69 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3085, 1776, 1687, 1565, 1468, 1328, 1239, 1172, 1085, 1032, 1018, 839, 764, 688, 673, 645, 587. HRMS (ESI) *m/z*: calc. for $C_{26}H_{15}Cl_2NO_3$: 482.0322 $[M + Na]^+$, found: 482.0307 $[M + Na]^+$.

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[31] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer. Crystal data for **4g**: $C_{27}H_{18}ClNO_3$, red brown, crystal dimension 0.09 mm × 0.06 mm × 0.04 mm, monoclinic, space group P2(1)/c, $a = 10.822(5)$ Å, $b = 10.783(6)$ Å, $c = 18.355(9)$ Å, $\alpha = \gamma = 90°$, ß = 94.289(11)°, $V = 2135.8(18)$ Å^3, $M_r = 439.87$, $Z = 4$, Dc = 1.368 mg/m^3, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 0.209$ mm^{-1}, $F(000) = 912$, $R_1 = 0.0892$, $wR_2 = 0.1061$.