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PAPER

A domino synthetic strategy leading to two-carbon-tethered fused acridine/indole pairs and fused acridine derivatives†

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A series of new poly-functionalized two-carbon-tethered fused acridine/indole pairs were synthesized *via* Brønsted acid-promoted domino reactions between indoline-2,3-dione and C_2-tethered indol-3-yl enaminones. The reactions were further expanded to prepare C-tethered fused acridine/pyridine pairs, *N*-substituted amino acids, *N*-cyclopropyl and *N*-aryl substituted fused acridine derivatives, as well as bis-furan-3-yl-substituted indoles. During these reaction processes, the domino construction of a fused acridine skeleton with concomitant formation of two new rings was readily achieved in a one-pot operation. The procedures are facile, avoiding time-consuming and costly syntheses, tedious work-up and purification of precursors.

Introduction

Heterocyclic compounds embedded with nitrogen are prevalent in numerous natural products and pharmaceutical leads. Among the nitrogen heterocycles, the partially fused acridine derivatives are important motifs, displaying remarkable pharmaceutical or biochemical activities,[1] such as antitumor[2] and antifungal.[3] On the other hand, the indole moiety has been found in various pharmacologically and biologically active compounds.[4] Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties,[5] such as anticancer, anti-tumour,[6] anti-inflammatory, hypoglycemic, analgesic and anti-pyretic activities.[7] Thus, an assembly of these two motifs could potentially lead to a series of structurally and biologically interesting compounds. Although the synthesis and application of fused acridines[1] and indole[8,9] derivatives have been reported, respectively, in the literature, to the best of our knowledge the direct synthesis of two-carbon-tethered fused acridine/indole pairs has been not achieved so far.

Creation of complex polycyclic skeletons of chemical and biomedical importance from simple and readily available precursors, while combining economic and environmental aspects, stands as one of the crowning achievements in organic chemistry.[10,11] The state of the art synthetic strategy reflects the sum of enormous efforts aimed at understanding the rules for controlling the efficiency and selectivity of the starting materials cascade responsible for multi-ring construction. The domino reactions for use in the total synthesis of natural products or natural-like structures were one of the key tools that enabled the multi-ring-junction frameworks to be predicted by controlling the reaction process.[12,13] They also form an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, *e.g.* ligands for catalysis or bioactive compounds. Very recently, we have developed a series of new domino reactions that provided easy access to multiply functionalized ring structures of chemical and pharmaceutical interest.[14,15] In the course of our continuous efforts on the development of useful domino reactions herein, we would like to report another new synthetic strategy for the efficient preparation of polyfunctionalized heterocycles containing fused acridine and indole skeletons through intermolecular domino reactions. This reaction was achieved from the available starting materials such as indoline-2,3-dione and C_2-tethered indol-3-yl enaminones in HOAc under microwave heating conditions (Scheme 1). The great aspect of the present domino reaction is shown by the fact that the synthesis of new polyfunctionalized heterocycles containing fused acridines/indole units connected through a sp^3–C_2 bridge was readily achieved via a Brønsted acid-promoted domino reaction in a single step, and two new

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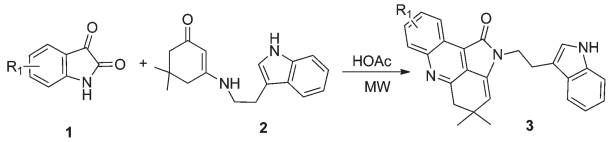


Scheme 1 The synthesis of fused acridine/indole pairs **3**.

rings including pyrrole and pyridine frameworks were readily constructed in an intermolecular domino manner and in a one-pot operation.

Results and discussion

The chemistry of enaminones possessing 1,3-bisnucleophilic centers has numerous attractive features that have made them important building blocks in current organic trends. They have gained considerable prominence due to their use in the treatment of epilepsy and because they possess a variety of other medicinal properties.[16] Over the decades, enaminones have been used for the synthesis of a wide variety of heterocyclic compounds.[15a,b,17] We have planned to link two biologically important nuclei, fused acridines and indoles, to generate a new set of compounds: two-carbon-tethered fused acridine/indole pairs, using domino heterocyclization of structurally diverse indoline-2,3-dione and C_2-tethered indol-3-yl enaminones, based on the fact that two carbonyl groups of indoline-2,3-diones would undergo double nucleophilic addition with enaminones, leading to ring-opening of the indoline-2,3-diones through ring cleavage; and the new formation of the amino group can further attack the carbonyl group of the enaminones to form a pyrrole ring (Scheme 3).[18] Based on the above analysis, we started this study by subjecting a preformed 2-(indol-3-yl)ethyl substituted enaminone **2a** to the reaction with 5-chloroindoline-2,3-dione **1a** in HOAc at 90 °C under microwave irradiation. The reaction smoothly gave the desired product **3a** in 78% chemical yield. This good result prompts us to further optimize the reaction conditions. The same reactions were performed in different solvents, such as DMF, EtOH, and toluene. All the cases scarcely proceeded in these solvents. We reasoned that the acidic solvent can be used as a Brønsted acid promotor and improve the yields of the desired product **3**. Next, this chemistry was carried out in EtCOOH, HCOOH and CF_3COOH. An incomplete reaction was observed using EtCOOH or CF_3COOH as an acidic solvent, while the HCOOH gave a 64% yield of **3a**. Therefore, HOAc was proven to be the best base (Table 1, entry 5). Subsequently, the reaction was performed in HOAc and repeated many times in different temperatures in a sealed vessel under microwave irradiation for 20 min. The best yield of product **3a** (84%) was obtained as the reaction temperature was increased to 110 °C.

With these optimized conditions in hand, we examined the scope of this new domino process by using various easily available starting materials. As revealed in Table 2, a range of invaluable fused acridine derivatives with different substituted patterns can be synthesized in good to excellent yields. The reaction is easy to perform simply by subjecting a mixture of indoline-2,3-dione and various enaminones **2** in acetic acid to microwave heating. Firstly, in the one-pot domino reaction for the synthesis of two-carbon-tethered fused acridine/indole **3**, the indoline-2,3-dione scope of this interesting transformation was investigated. Using various indoline-2,3-diones **1b–1f**, such as 5-bromo (**1b**), 6-bromo (**1c**), 5-fluoro (**1d**), indoline-2,3-dione (**1e**), and 5-methyl (**1f**), together with enaminone **2a**, resulted in smooth cyclization to the corresponding substituted fused acridine **3b–3f**. The pyridin-2-ylmethyl substituted enaminones **2b** were converted into the corresponding C-tethered fused acridine–pyridine

Table 1 Optimization of the catalyst in the synthesis of **4a** under MW

Entry	Solvent	T (°C)	Time (min)	Yield[a] (%)
1	DMF	90	20	Trace
2	EtOH	90	20	Trace
3	Toluene	90	20	Trace
4	HOAc	90	20	78
5	HOAc	110	20	84
6	EtCOOH	90	20	38
7	HCOOH	90	20	64
8	CF_3COOH	90	20	45

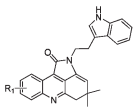
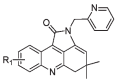
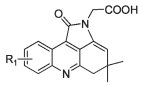
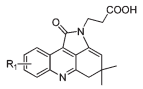
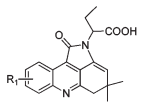
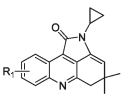
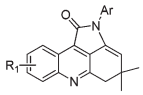
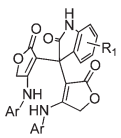
[a] Isolated yield.

pairs **3g–3j** in 70%–82% yields (Scheme 2; Table 2, entries 7–10). Alternatively, a number of *N*-substituted amino acids have been recognized as pharmacologically potent compounds. For this reason, the preformed *N*-carboxyl enaminones **2c–2e** were subjected to the reaction with indoline-2,3-dione **1**, providing the corresponding polycyclic substituted amino acid derivatives **3k–3p** in good to excellent yields. In addition, *N*-cyclopropyl enaminone also gave the *N*-cyclopropyl fused acridine **3q** in 74% yield. To further expand the scope of *N*-substituted enaminone substrates, different indoline-2,3-diones were used as model substrates and various *N*-aryl enaminones including 4-chlorophenyl **2g**, 4-bromophenyl **2h**, 4-tolyl **2i**, phenyl **2j**, 3-chlorophenyl **2k**, and 4-methoxyphenyl **2l** were examined. In all these cases, the reactions proceeded smoothly to give the corresponding polyfunctionalized fused acridine substituted at multiple sites in good yields with very high regioselectivities (Table 2, entries 18–32). The results exhibit the scope and generality of the intermolecular domino reaction with respect to a range of enaminone and isatin substrates. Additionally, functional groups like bromide and chloride were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example by modern cross-coupling reactions.

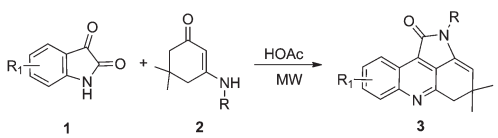
In view of these results, we then investigated several differently substituted enaminones. When *N*-substituted 3-aminocyclohex-2-enones employed in the above system were replaced by *N*-substituted 4-aminofuran-2(5*H*)-ones, the similar quinoline derivatives were not generated. Instead, the reaction occurred in another direction to form symmetrical multifunctionalized indoles **4** that belong to another family of important scaffolds for organic synthesis and drug design in pharmaceutical science (Scheme 3).[4] Two molecules of *N*-substituted 4-aminofuran-2(5*H*)-ones were introduced into the final polysubstituted indoles. Next, the reactions of *N*-substituted 4-aminofuran-2(5*H*)-ones **2m–2o** with **1** in a 2 : 1.1 ratio were carried out under the above conditions for a short period (15–20 min), providing structurally diverse bis-furan-3-yl-substituted multifunctionalized indoles **4a–4d** in 80–89% chemical yields.

In all cases, the complexity of the resulting products from this new reaction illustrates the remarkable regioselectivity of the sequence, starting from very common and easily accessible starting materials. Furthermore, the reaction occurred at a fast speed; in fact, all cases can be finished within 16–32 min. Water is nearly a sole by-product, which makes work-up convenient. In most cases, the products can precipitate out after cold water was poured into the reaction mixture. The structural elucidation was

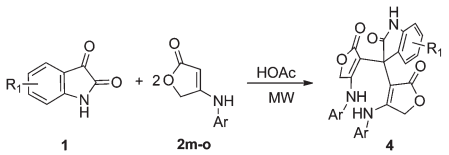
Table 2 Domino synthesis of fused acridine **3a–3ff** and indoles **4a–4d** under MW

Entry	Product		R_1	Enaminones **2** (R)	Time/min	Yield[a]/%
1		**3a**	5-Chloro (**1a**)	2-(Indol-3-yl)ethyl (**2a**)	20	84
2		**3b**	5-Bromo (**1b**)	2-(Indol-3-yl)ethyl (**2a**)	24	82
3		**3c**	6-Bromo (**1c**)	2-(Indol-3-yl)ethyl (**2a**)	24	78
4		**3d**	5-Fluoro (**1d**)	2-(Indol-3-yl)ethyl (**2a**)	25	80
5	**3a-3f**	**3e**	H (**1e**)	2-(Indol-3-yl)ethyl (**2a**)	26	76
6		**3f**	5-Methyl (**1f**)	2-(Indol-3-yl)ethyl (**2a**)	30	75
7		**3g**	5-Chloro (**1a**)	Pyridin-2-ylmethyl (**2b**)	30	82
8		**3h**	5-Bromo (**1b**)	Pyridin-2-ylmethyl (**2b**)	30	75
9		**3i**	6-Bromo (**1c**)	Pyridin-2-ylmethyl (**2b**)	28	70
10	**3g-3j**	**3j**	H (**1e**)	Pyridin-2-ylmethyl (**2b**)	30	72
11		**3k**	5-Chloro (**1a**)	Carboxymethyl (**2c**)	26	89
12		**3l**	5-Methyl **1f**)	Carboxymethyl (**2c**)	24	85
	3k-3l					
13		**3m**	5-Chloro (**1a**)	2-Carboxyethyl (**2d**)	28	74
14		**3n**	H (**1e**)	2-Carboxyethyl (**2d**)	28	71
	3m-3n					
15		**3o**	H (**1e**)	1-Carboxypropyl (**2e**)	32	69
16		**3p**	5 Methyl **1f**)	1-Carboxypropyl (**2e**)	30	65
	3o-3p					
17		**3q**	5-Chloro (**1a**)	Cyclopropyl (**2f**)	32	74
	3q					
18		**3r**	5-Chloro (**1a**)	4-Chlorophenyl (**2g**)	18	84
19		**3s**	5-Chloro (**1a**)	4-Bromophenyl (**2h**)	16	88
20		**3t**	5-Chloro (**1a**)	4-Tolyl (**2i**)	18	89
21		**3u**	5-Bromo (**1b**)	4-Tolyl (**2i**)	20	82
22		**3v**	5-Bromo (**1b**)	Phenyl (**2j**)	22	85
23		**3w**	H (**1e**)	4-Chlorophenyl (**2g**)	25	78
24		**3x**	H (**1e**)	4-Bromophenyl (**2h**)	26	81
25		**3y**	H (**1e**)	4-Tolyl (**2i**)	26	83
26		**3z**	H (**1e**)	Phenyl (**2j**)	28	75
27		**3aa**	H (**1e**)	3-Chlorophenyl (**2k**)	30	71
28		**3bb**	5-Methyl (**1f**)	4-Chlorophenyl (**2g**)	32	79
29		**3cc**	5-Methyl (**1f**)	4-Tolyl (**2i**)	30	84
30		**3dd**	5-Methyl (**1f**)	Phenyl (**2j**)	30	80
31		**3ee**	5-Methyl (**1f**)	3-Chlorophenyl (**2k**)	28	73
32		**3ff**	5-Methyl (**1f**)	4-Methoxyphenyl (**2l**)	28	82
33		**4a**	5-Bromo (**1b**)	4-Tolyl (**2m**)	18	80
34		**4b**	5-Methyl (**1f**)	4-Chlorophenyl (**2n**)	15	85
35		**4c**	H (**1e**)	4-Bromophenyl (**2o**)	20	89
36		**4d**	H (**1e**)	4-Tolyl (**2m**)	18	84
	4a-4d					

[a] Isolated yield.



Scheme 2 The synthesis of pyrrolo[2,3,4-*kl*]acridine **3**.



Scheme 3 The synthesis of multifunctionalized indoles **4**.

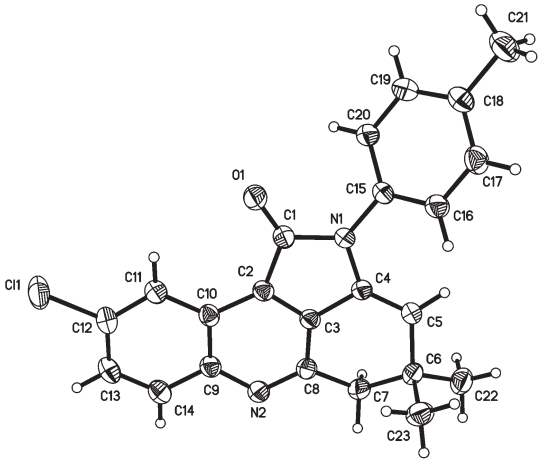


Fig. 1 X-ray structure of **3t**.

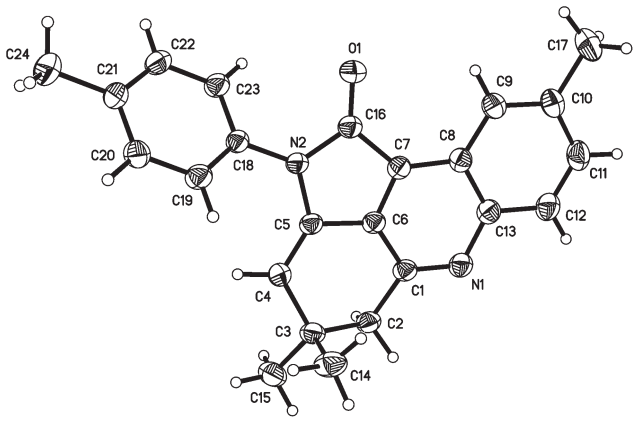


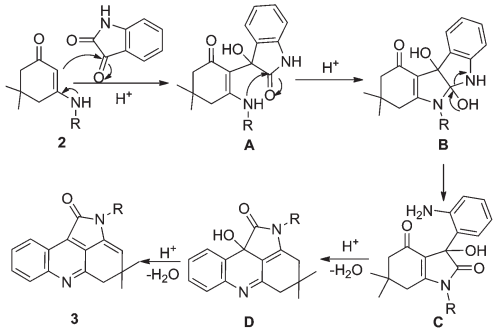
Fig. 2 X-ray structure of **3cc**.

unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of single crystals that were obtained by slow evaporation of the solvent, as in the cases of products **3t** and **3cc** (Fig. 1 and 2). During these domino processes, the new formation of pyrrole and pyridine rings was readily achieved in a one-pot operation. Up to three sigma-bonds including two C–N bonds were formed, accompanied by the cleavage of C═O and C–N bonds of the indoline-2,3-diones **1** (Scheme 3).

On the basis of all the above results, the mechanism hypothesis for the domino reaction has been proposed and is shown in Scheme 4. The reaction involves the ring closure cascade reactions, which consist of initial nucleophilic addition (**2** to **A**), intramolecular cyclization (**A** to **B**) and ring-opening of indoline-2,3-dione **1** (**B** to **C**), re-cyclization and dehydration (**C** to **3**).

Conclusions

In summary, we have described Brønsted acid-promoted domino heterocyclization as an alternative method for the synthesis of a set of C_2-tethered fused acridine/indole pairs and C-tethered fused acridine/pyridine pairs with concomitant formation of three sigma-bonds in a one-pot reaction. This reaction provides a facile and efficient strategy for the construction of a structurally diverse fused acridine skeleton. The ready accessibility of the starting materials, the broad compatibility of N-substituted enaminone substrates, and the generality of this process make the reaction highly valuable in view of the synthetic and medicinal importance of a multi-heterocyclic framework of this type. Features of this strategy include short reaction times, convenient one-pot operation, and high regioselectivity. Further investigations are in progress in our laboratory to evaluate the process with a broader range of substrates, and to synthesize more complex products and test their biological activity.



Scheme 4 The possible mechanism of formation of products **3**.

Experimental section

General

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured by an infrared detector during microwave heating.

General procedure for the synthesis of compounds 3

Microwave heating: in a 10 mL reaction vial, indoline-2,3-dione (1.1 mmol), enaminones (1 mmol) and AcOH (1.5 mL) were mixed and stirred at room temperature for 3 min. Then the system was heated for a given time at 110 °C under microwave irradiation. Automatic stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into the cold water. The solid product was collected by Büchner filtration and washed with water and EtOH (95%), and subsequently dried and recrystallized from EtOH (95%) to give the pure product.

General procedure for the synthesis of compounds 4

Microwave heating: in a 10 mL reaction vial, indoline-2,3-dione (1.1 mmol), *N*-substituted 4-aminofuran-2(5*H*)-ones (2 mmol) and AcOH (1.5 mL) were mixed and stirred at room temperature for 3 min. Then the system was heated for a given time at 110 °C under microwave irradiation. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into the cold water. The solid product was

collected by Büchner filtration and washed with water and EtOH (95%), and subsequently dried and recrystallized from EtOH (95%) to give the pure product **4**.

2-(2-(1*H*-Indol-3-yl)ethyl)-4,4-dimethyl-4,5-dihydropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (3e). Yellow solid; mp: 230.1–230.9 °C.

IR (KBr, *ν*, cm^{-1}): 3693, 3172, 1688, 1651, 1584, 1338, 1031, 733.

^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 10.80 (s, 1H, NH), 8.53 (d, J = 8.0 Hz, 1H, ArH), 8.09 (d, J = 8.4 Hz, 1H, ArH), 7.78 (t, J = 7.6 Hz, 1H, ArH), 7.70 (t, J = 7.6 Hz, 1H, ArH), 7.53 (d, J = 7.6 Hz, 1H, ArH), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.04 (t, J = 7.6 Hz, 1H, ArH), 6.91 (t, J = 7.6 Hz, 1H, CH), 5.45 (s, 1H, CH), 4.04 (t, J = 6.4 Hz, 2H, CH_2), 3.09 (t, J = 6.4 Hz, 2H, CH_2), 2.98 (s, 2H, CH_2), 1.08 (s, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6) (δ ppm): 166.4, 154.5, 148.8, 136.2, 132.1, 129.3, 129.2, 127.6, 127.3, 126.0, 124.3, 123.2, 123.2, 121.8, 120.9, 118.2, 118.1, 118.0, 112.7, 111.4, 110.9, 43.2, 40.7, 36.4, 30.1, 24.3.

HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{24}N_3O$: 394.1919; found: 394.1942.

2-(4,4-Dimethyl-1-oxo-4,5-dihydropyrrolo[2,3,4-*kl*]acridin-2(1*H*)-yl)butanoic acid (3o). Yellow solid; mp: 222.3–222.4 °C.

IR (KBr, *ν*, cm^{-1}): 3694, 2961, 1694, 1655, 1524, 1463, 1414, 1339, 1299, 1254, 1223, 1152, 1045, 913, 871.

^1H NMR (400 MHz, $CDCl_3$) (δ ppm): 8.66 (d, J = 8.0 Hz, 1H, ArH), 8.18 (d, J = 8.4 Hz, 1H, ArH), 7.72 (t, J = 7.6 Hz, 1H, ArH), 7.64 (t, J = 7.4 Hz, 1H, ArH), 5.63 (s, 1H, CH), 5.32–4.93 (m, 1H, CH), 3.20 (s, 2H, CH_2), 2.46–2.27 (m, 1H, CH), 2.26–2.11 (m, 1H, CH), 1.32 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.96 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 173.1, 167.5, 154.4, 131.5, 129.8, 128.5, 128.0, 126.8, 125.2, 124.2, 122.5, 119.2, 55.4, 43.2, 37.2, 30.9, 30.8, 22.9, 10.8.

HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{21}N_2O_3$: 337.1552 $[M + H]^+$; found: 337.1522.

2-(4-Bromophenyl)-9-chloro-4,4-dimethyl-4,5-dihydropyrrolo-[2,3,4-*kl*]acridin-1(2*H*)-one (3s). Yellow solid, mp: 177–178 °C.

IR (KBr, *ν*, cm^{-1}): 2957, 1703, 1646, 1602, 1508, 1492, 1441, 1365, 1341, 1209, 1152, 1139, 1086, 1077, 889.

^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.46 (s, 1H, ArH), 8.15 (d, J = 8.8 Hz, 1H, ArH), 7.85–7.78 (m, 3H, ArH), 7.51 (d, J = 8.0 Hz, 2H, ArH), 5.87 (s, 1H, CH), 3.17 (s, 2H, CH_2), 1.28 (s, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 167.6, 165.3, 155.5, 147.4, 133.6, 132.3, 131.8, 131.4, 130.9, 129.9, 128.4, 122.4, 121.9, 120.4, 120.3, 117.1, 43.2, 37.0, 30.7, 30.2.

HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{17}BrClN_2O$, 439.0213 $[M + H]^+$; found: 439.0190.

3,3′-(5-Bromo-2-oxoindoline-3,3-diyl)bis(4-(*p*-tolylamino)furan-2(5*H*)-one) (4a). White solid; mp: 267.7–279.4 °C.

IR (KBr, *ν*, cm^{-1}): 3337, 3036, 2861, 1750, 1716, 1604, 1475, 1056, 818, 759.

^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 10.52 (s, 1H, NH), 8.97 (s, 2H, NH), 7.42 (d, J = 2.0 Hz, 1H, ArH), 7.33 (s, 1H, ArH), 7.14 (d, J = 8.0 Hz, 4H, ArH), 7.00 (d, J = 8.0 Hz, 4H, ArH), 6.71 (d, J = 8.0 Hz, 1H, ArH), 4.67 (s, 4H, CH_2), 2.28 (s, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 177.8, 171.5, 163.3, 141.6, 136.1, 134.8, 134.1, 130.1, 129.6, 127.8, 123.8, 112.6, 110.7, 65.5, 48.9, 20.4.

HRMS (ESI) *m*/*z*: calcd for $C_{30}H_{25}BrN_3O_5$: 586.09778 $[M + H]^+$; found: 586.09789.

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