Monatsh Chem
DOI 10.1007/s00706-013-1118-0

ORIGINAL PAPER

Pseudo five-component synthesis of 5-phenyldihydrospiro[diindenopyridine-indenoquinoxaline]dione derivatives via a one-pot condensation reaction

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Received: 10 June 2013 / Accepted: 31 October 2013

Abstract Simple and efficient synthesis of novel 5-phenyl-5,5a-dihydro-4b*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,11′-indeno[2,1-*b*]quinoxaline]-10,12(10a*H*,11a*H*)-diones via a one-pot pseudo five-component cyclocondensation reaction of 1*H*-indene-1,2,3-trione, benzene-1,2-diamine, 1*H*-indene-1,3(2*H*)-dione, and anilines in refluxing acetonitrile is reported.

Keywords Multicomponent reaction · Quinoxaline · Indenoquinoxaline · Spiro compound

Introduction

Multicomponent reactions (MCRs) have attracted much attention because of their convergence, efficiency, ease of execution, and generally high yields of products [1, 2]. This methodology affords molecular diversity and complexity, and leads to interesting heterocyclic scaffolds useful for combinatorial chemistry [3–7] because of its valuable features such as atom economy, environmental friendliness, straightforward reaction design, and the opportunity to create target compounds by the introduction of several diversity elements in a single chemical operation [8–11]. Over the past decade, great efforts have been made to develop novel MCRs, which have led to tremendous advances in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of potent drug candidates [4, 12].

Heterocyclic compounds occur commonly in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals critical for enhancing the quality of life [13, 14]. Improvement of new efficient methods to synthesize N-heterocycles with structural diversity is an important goal of modern synthetic organic chemistry [15–17].

Quinoxalines are a main class of nitrogen-containing benzoheterocycles which have received much attention in recent years owing to both their biological properties and pharmaceutical applications. These derivatives are particularly interesting because some of them show antimicrobial [18–20], anticancer [21–26], antimalarial [27–34], anti-inflammatory [35–38], antinociceptive [39, 40], antitubercular [41, 42], anthelmintic [43–45], antidiabetic [46, 47], antiepileptic [48], antimetabolism and antiviral properties [49]. Also, quinoxaline moieties are present in the structure of various antibiotics such as echinomycin, levomycin, and actinoleutin, which are known to inhibit the growth of gram positive bacteria and they are active against various transplantable tumors [50–52].

Indenoquinoxaline derivatives are another important class of nitrogen-containing heterocycles which are useful intermediates in organic synthesis (e.g., of organic semiconductors) [53, 54] and they also have applications in dyes.

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Published online: 26 November 2013

Scheme 1

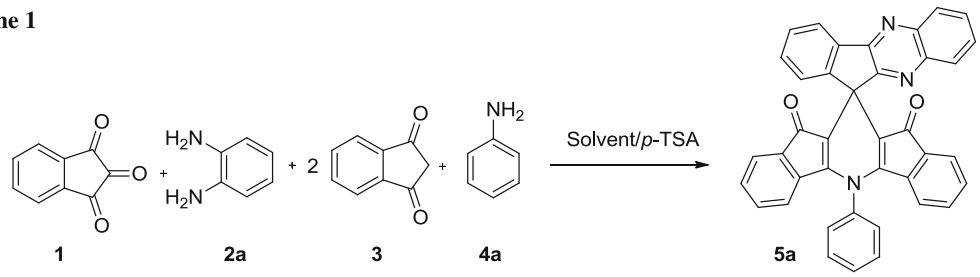


Table 1 Screening of solvents for the synthesis of **5a**

Entry	Solvent	Time/h	Yield/%[a]
1	MeOH	24	51
2	EtOH	24	56
3	DMF	24	55
4	CH_3CN	16	96
5	Water	24	48
6	THF	30	<50
7	HOAc	20	45
8	Toluene	24	–

The reaction was carried out using 1*H*-indene-1,2,3-trione (**1**), benzene-1,2-diamine (**2**), 1*H*-indene-1,3(2*H*)-dione (**3**), and aniline (**4**) in the presence of *p*-TSA (10 mol%) and 5 cm^3 solvent

[a] Isolated yield of pure compound

Table 2 Screening of ionic liquids for the synthesis of **5a**

Ionic liquid	Time/h	Yield/%[a]
[bmim]Br	24	51
[bmim]PF_6	24	58
[bmim]BF_4	24	53
[HNMP]HSO_4	24	61

The reaction was carried out using 1*H*-indene-1,2,3-trione (**1**), benzene-1,2-diamine (**2**), 1*H*-indene-1,3(2*H*)-dione (**3**), and aniline (**4**) in the presence of *p*-TSA (10 mol%) and 1 cm^3 ionic liquid

[a] Isolated yield of pure compound

Table 3 Screening of catalyst for the synthesis of **5a**

Catalyst	Yield/%[a]
Nano ZnO	<50
Nano MgO	<50
Nano Fe_3O_4	52
Nano $CuFe_2O_4$	53
Nano $MnFe_2O_4$	55

The reaction was carried out using 1*H*-indene-1,2,3-trione (**1**), benzene-1,2-diamine (**2**), 1*H*-indene-1,3(2*H*)-dione (**3**), and aniline (**4**) in the presence of *p*-TSA (10 mol%) and 5 cm^3 acetonitrile

[a] Isolated yield of pure compound

In continuation of our previous works on the synthesis of heterocyclic spiro compounds [55–61], herein, we report a simple and efficient one-pot, pseudo five-component method for the preparation of novel 5-phenyldihydrospiro[diindenopyridine-indenoquinoxaline]dione derivatives in refluxing conditions by using *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and nontoxic catalyst.

Results and discussion

We first tested the condensation reaction of 1*H*-indene-1,2,3-trione (**1**), benzene-1,2-diamine (**2**), 1*H*-indene-1,3(2*H*)-dione (**3**), and aniline (**4**) as a simple model substrate in various polar and nonpolar solvents in the presence of *p*-TSA as an inexpensive and available catalyst (Scheme 1). The results are summarized in Table 1. Of the various solvents screened, acetonitrile resulted in the best yield and shortest reaction time. The model reaction was also carried out in different ionic liquids at 80 °C and different catalysis. The results are summarized in Tables 2 and 3.

As can be seen in Table 2, the model reaction was done in various ionic liquids in the presence of *p*-TSA as catalyst in 80 °C, but the yields were not very high. Also, as can be seen in Table 3, the model reaction was carried out with various nano-catalysts in acetonitrile in refluxing conditions, but the yields were only moderate. Therefore, acetonitrile was chosen as the most appropriate solvent (Table 1, entry 4), and *p*-TSA was chosen as the most appropriate catalyst for this reaction. TLC showed that a new compound, which turned out to be the desired product, was formed and general workup afforded the product **5a** in excellent yield (96 %) and high purity. It contrast, without *p*-TSA the yield of product was very low (<40 %) even after 24 h.

In order to optimize the reaction conditions, we also evaluated the amount of catalyst required for this transformation. The model reaction was performed in the presence of different amounts of catalyst. It was found that using 30 mol% *p*-TSA in acetonitrile was sufficient to drive the reaction to completion. Increasing the amount of *p*-TSA to more than 30 mol% showed no substantial

improvement in the yield, whereas the yield was decreased by using less than 30 mol% of the catalyst. Thus, 30 mol% of catalyst was chosen as the optimal quantity.

A catalyst plays a crucial role in the success of a reaction in terms of the reaction rate and yield. The recovery and reuse of catalyst are highly preferable for synthesis. As shown in Fig. 1, the possibility of recycling the *p*-TSA was studied in model substrates. It is important to highlight that the catalyst was recovered in excellent yield (94–96 %) after each reaction. The recovered catalyst was simply washed with acetone several times. The procedure was repeated and the results indicated that in four consecutive runs, the isolated yields remained similar with no detectable loss.

Encouraged by this success, we extended the scope of this reaction to 1*H*-indene-1,2,3-trione (**1**), benzene-1,2-diamines **2a**, **2b**, and 1*H*-indene-1,3(2*H*)-dione (**3**) with a range of aromatic amines **4a–4e** with both electron-withdrawing and electron-releasing substituents under similar conditions (MeCN, *p*-TSA), and corresponding 5-phenyl-5,5a-dihydro-4b*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,11′-indeno[2,1-*b*]quinoxaline]-10,12(10a*H*,11a*H*)-diones **5a–5j** were synthesized in high yields (Scheme 2). We have shown that the use of a wide diversity of substituents in benzene-1,2-diamines **2** and aromatic amines **4** in this pseudo five-component reaction makes possible the synthesis of libraries under similar circumstances (Table 4). All indenoquinoxalines synthesized by this pseudo five-component reaction were novel.

When this reaction was carried out with aliphatic amines such as *n*-propylamine, TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; and the yield of the expected product was very poor.

Although the detailed mechanism of the reaction has not been clarified yet, we propose a pathway wherein the spiro product **5** is formed via domino reactions. As shown in Scheme 3, compound **5** could be synthesized via sequential iminization–aromatization, condensation, addition, enamination, and cyclization. The reaction may proceed in a stepwise manner, in which the 1*H*-indene-1,2,3-trione (**1**) first reacts with benzene-1,2-diamine (**2**) to afford 11*H*-indeno[2,1-*b*]quinoxalin-11-one (**6**) in the presence of *p*-TSA in acetonitrile. This step was regarded as a fast iminization–aromatization reaction. Then, compound **6** is condensed with 1*H*-indene-1,3(2*H*)-dione (**3**) to afford 2-(11*H*-indeno[2,1-*b*]quinoxalin-11-ylidene)-1*H*-indene-1,3(2*H*)-dione (**7**). This step was regarded as a fast Knoevenagel condensation reaction. Then, compound **7** is attacked by Michael-type addition with another 1*H*-indene-1,3(2*H*)-dione (**3**) to produce the intermediate **8**. Finally, compound **8** reacted with aniline **4** to produce 2-[11-[1-oxo-3-(phenylamino)-1*H*-inden-2-yl]-11*H*-indeno[2,1-*b*]quinoxalin-11-yl]-1*H*-indene-1,3(2*H*)-dione (**9**), followed by

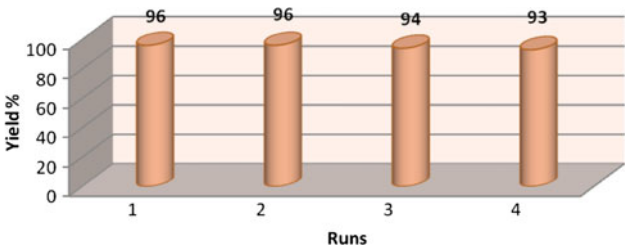


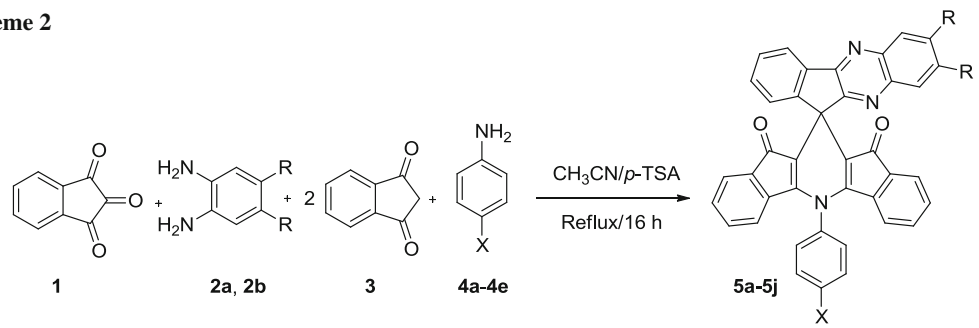
Fig. 1 Recyclability study of catalyst in the synthesis of **5a**

Table 4 Synthesis of novel 5-phenyldihydrospiro[diindenopyridine-indenoquinoxaline]dione derivatives **5a–5j**

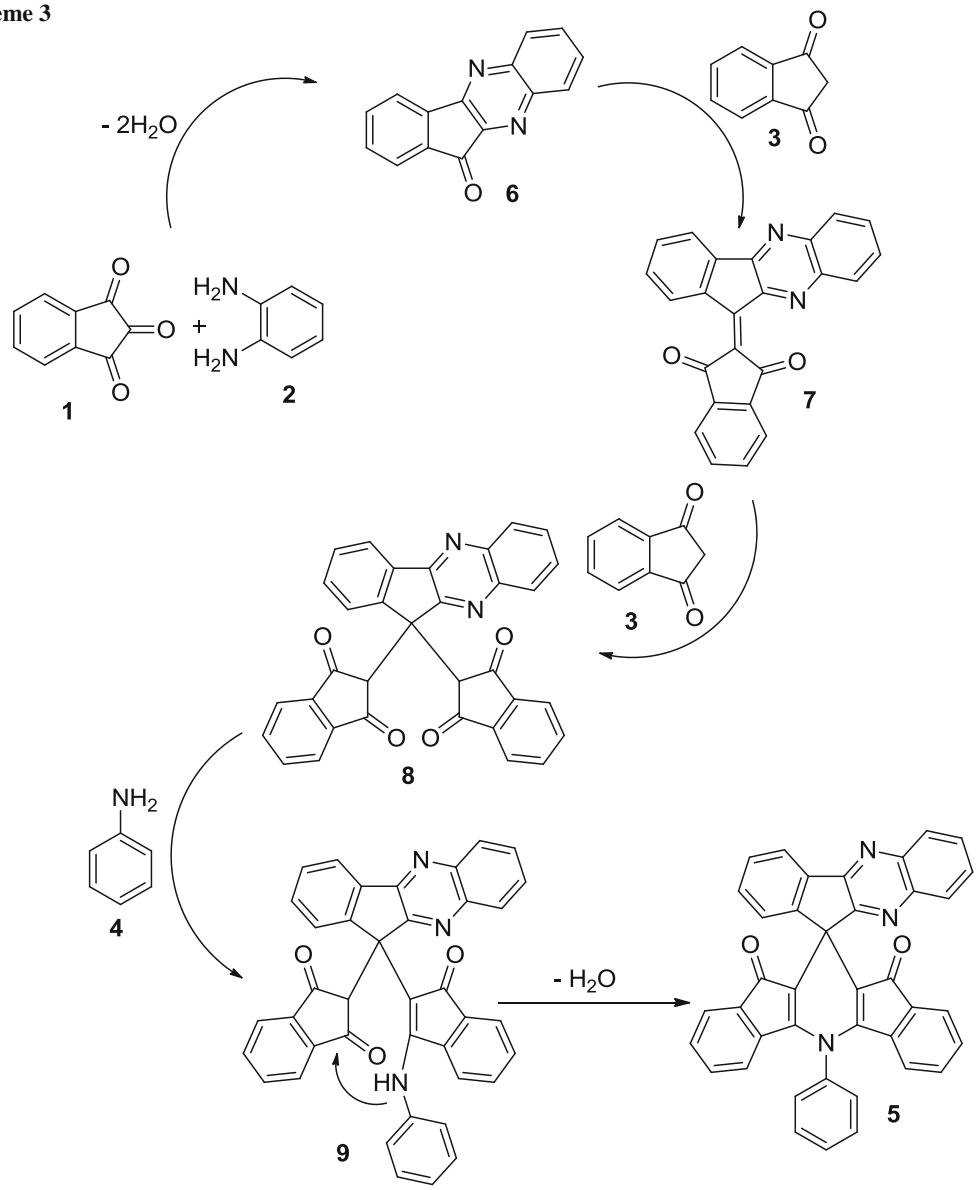
Product	R	X	Yield/%[a]
5a	H	H	96
5b	H	Me	95
5c	H	OMe	71
5d	H	Br	68
5e	H	NO_2	62
5f	Me	H	67
5g	Me	Me	91
5h	Me	OMe	83
5i	Me	Br	72
5j	Me	NO_2	51

[a] Isolated yields

Scheme 2



Scheme 3



intramolecular cyclization and tautomerization to afford the product **5**.

In conclusion, we have described a successful strategy for the efficient and convenient synthesis of novel 5-phenyldihydrospiro[diindenopyridine-indenoquinoxaline]diones in a one-pot, pseudo five-component cyclocondensation reaction of 1*H*-indene-1,2,3-trione, benzene-1,2-diamine, 1*H*-indene-1,3(2*H*)-dione, and anilines using an inexpensive, nontoxic, and easily available catalyst.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. ^{1}H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6 using TMS as internal standard. IR spectra were recorded using an FTIR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

Typical procedure: 5-phenyl-5H-spiro[diindeno-[1,2-b:2′,1′-e]pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5a**, $C_{39}H_{21}N_3O_2$)

A mixture of 0.16 g 1*H*-indene-1,2,3-trione (1 mmol), 0.11 g benzene-1,2-diamines (1 mmol), and *p*-TSA (30 mol%) in 5 cm^3 refluxing acetonitrile was stirred for

5 min then 0.30 g 1,3-indandione (2 mmol) and 0.09 g aniline (1 mmol) were added to the mixture and stirred for 16 h. After completion of the reaction confirmed by TLC (EtOAc/*n*-hexane, 1:3), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with 10 cm^3 water and 5 cm^3 hot ethanol to afford the pure product **5a** as a dark red powder. Yield 96 %; m.p.: >280 °C; IR (KBr): $\bar{\nu}$ = 1,697, 1,623 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.50 (2H, bs, ArH), 7.09–8.21 (19H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 113.3, 121.9, 126.5, 129.4, 129.6, 130.8, 132.2, 132.5, 132.9, 136.6, 141.5, 142.3, 155.0, 156.9, 165.3, 190.1 ppm.

5-(p-Tolyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5b**, $C_{40}H_{23}N_3O_2$)
Dark-red powder; yield 95 %; m.p.: 193–205 °C (dec); IR (KBr): $\bar{\nu}$ = 1,693, 1,649 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.08 (3H, s, CH_3), 5.61 (2H, d, J = 8 Hz, ArH), 7.08–8.32 (18H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 79.6, 113.3, 121.92, 125.9, 126.5, 128.7, 129.4, 130.3, 130.8, 131.2, 132.6, 133.0, 135.7, 136.7, 138.7, 141.5, 142.0, 142.4, 145.3, 152.0, 157.1, 165.4, 190.1 ppm.

5-(4-Methoxyphenyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]-pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5c**, $C_{40}H_{23}N_3O_3$)
Dark-red powder; yield 71 %; m.p.: 233–240 °C (dec); IR (KBr): $\bar{\nu}$ = 1,694, 1,621 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.98 (3H, s, OCH_3), 5.68 (2H, d, J = 8 Hz, ArH), 7.08–8.25 (18H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.3, 56.3, 113.2, 115.6, 115.9, 121.9, 122.1, 126.5, 129.4, 129.5, 130.3, 130.7, 130.8, 131.4, 131.7, 132.6, 132.7, 133.1, 136.5, 136.8, 141.5, 142.4, 152.0, 155.0, 157.4, 161.5, 165.4, 190.2 ppm.

5-(4-Bromophenyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]-pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5d**, $C_{39}H_{20}BrN_3O_2$)
Dark-red powder; yield 68 %; m.p.: 210–220 °C (dec); IR (KBr): $\bar{\nu}$ = 1,697, 1,623 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.63 (2H, bs, ArH), 7.11–8.25 (18H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.3, 113.4, 121.9, 122.1, 125.6, 126.6, 129.3, 129.5, 130.3, 130.9, 132.5, 132.7, 133.2, 134.0, 136.6, 17.6, 141.5, 142.4, 151.9, 155.0, 156.7, 165.3, 190.1 ppm.

5-(4-Nitrophenyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]-pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5e**, $C_{39}H_{20}N_4O_4$)
Dark-red powder; yield 62 %; m.p.: 175–180 °C (dec); IR (KBr): $\bar{\nu}$ = 1,695, 1,627 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.63 (2H, d, J = 8 Hz, ArH), 6.58–8.65 (18H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 48.5, 115.7, 123.8, 125.5, 127.6, 128.2, 130.2, 132.8, 133.3, 134.9, 135.6, 135.9, 136.3, 137.0, 138.7, 139.9, 143.5, 145.3, 153.4, 157.2, 158.6, 168.1, 192.4 ppm.

7′,8′-Dimethyl-5-phenyl-5H-spiro[diindeno[1,2-b:2′,1′-e]-pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5f**, $C_{41}H_{25}N_3O_2$)
Dark-red powder; yield 67 %; m.p.: >280 °C; IR (KBr): $\bar{\nu}$ = 1,700, 1,616 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.42 (6H, s, CH_3), 5.52 (2H, d, J = 8 Hz, ArH), 7.08–8.29 (17H, m, ArH) ppm; because of very low solubility of the product **4f**, we cannot report the ^{13}C NMR data for this product.

7′,8′-Dimethyl-5-(p-tolyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]-pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5g**, $C_{42}H_{27}N_3O_2$)
Dark-red powder; yield 91 %; m.p.: 260–270 °C (dec); IR (KBr): $\bar{\nu}$ = 1,697, 1,626 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.27 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.56 (3H, s, CH_3), 5.60 (2H, d, J = 8 Hz, ArH), 7.07–8.12 (16H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.2, 20.3, 21.6, 46.2, 113.4, 121.6, 121.9, 125.9, 128.6, 129.4, 129.9, 130.3, 130.8, 132.2, 132.6, 133.0, 135.8, 136.7, 138.5, 139.5, 140.3, 141.1, 142.1, 145.5, 151.8, 154.0, 156.9, 164.4, 190.1 ppm.

5-(4-Methoxyphenyl)-7′,8′-dimethyl-5H-spiro[diindeno-[1,2-b:2′,1′-e]pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5h**, $C_{42}H_{27}N_3O_3$)
Dark-red powder; yield 83 %; m.p.: 260–270 °C (dec); IR (KBr): $\bar{\nu}$ = 1,696, 1,626 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.42 (6H, s, CH_3), 3.98 (3H, s, OCH_3), 5.67 (2H, d, J = 8 Hz, ArH), 7.08–8.17 (16H, m, ArH) ppm; because of very low solubility of the product **4h**, we cannot report the ^{13}C NMR data for this product.

5-(4-Bromophenyl)-7′,8′-dimethyl-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5i**, $C_{41}H_{24}BrN_3O_2$)
Dark-red powder;yield 72 %; m.p.: 260–270 °C (dec); IR (KBr): $\bar{\nu}$ = 1,698, 1,625 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.40 (3H, s, CH_3), 2.47 (3H, s, CH_3), 5.64 (2H, d, J = 8 Hz, ArH), 7.08–8.30 (16H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.2, 20.3, 21.2, 46.2, 79.6, 113.6, 121.6, 121.8, 122.0, 125.5, 125.9, 128.5, 128.7, 130.8, 132.2, 132.5, 133.2, 136.6, 136.6, 137.7, 138.6, 139.6, 140.3, 141.1, 145.4, 151.7, 154.0, 156.6, 164.3, 190.1 ppm.

7′,8′-Dimethyl-5-(4-nitrophenyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,11′-indeno[2,1-b]quinoxaline]-10,12-dione (**5j**, $C_{41}H_{24}N_4O_4$)
Dark-red powder; yield 51 %; m.p.: 260–270 °C (dec); IR (KBr): $\bar{\nu}$ = 1,698, 1,625 cm^{-1}; ^{1}H NMR (300 MHz,

DMSO-d_6): $\delta = 2.42$ (6H, s, CH_3), 5.63 (2H, d, $J = 8$ Hz, ArH), 7.09–8.65 (16H, m, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.3$, 113.7, 122.1, 125.9, 126.1, 128.5, 129.5, 130.8, 132.4, 133.4, 136.4, 136.9, 140.3, 143.6, 149.7, 156.3, 190.0 ppm.

Acknowledgments We gratefully acknowledge financial support from the Avicenna Research Institute.

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