A Facile, Atom-Economical, and One-Pot Pseudo Four-Component Synthesis of Isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones Catalyzed by *p*TSA

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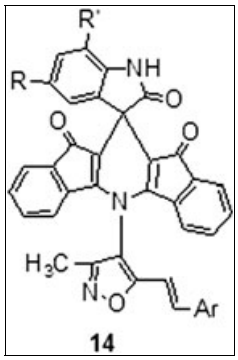

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A facile, atom-economical, and one-pot pseudo four-component method for the synthesis of isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione derivatives (**14**) is described. Prominent advantages of this new method are operational simplicity, excellent yields with high purity, short reaction time, easy workup, and mild conditions.

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INTRODUCTION

Among the strategies utilized, multi-component reactions have emerged as a powerful tool for delivering the molecular diversity needed in combinatorial approaches for the preparation of bioactive compounds [1–3]. In this context, heterocycles containing an indenone moiety show interesting features that makes them attractive for use in multi-component reactions.

The indole moiety is probably the most well-known heterocycle, frequently found in a variety of natural products and medicinal agents [4]. Furthermore, sharing the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances the biological activity [5–7]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [8–18]. Naturally occurring spirooxindole alkaloids, such as spirotryprostatin A (**1**), a natural product isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly [19]. Alstonisine (**2**) is a useful bioactive natural product. Mitraphylline (**3**) isolated from *Uncaria tomentosa* possesses anti-tumor activity against human brain cancer cell lines [20]. Indenone-fused heterocycles possess important biological and medicinal properties. Thus, the indeno pyridine skeleton is present in the 4-azafluorenone group of alkaloids, represented by its simplest member onychnine (**4**) [21]. Indeno pyridine derivatives are found to possess cytotoxic, adenosine A2a receptor antagonistic, anti-inflammatory, anti-allergic, coronary-dilating, and calcium-modulating activities [22–27]. Indeno pyrazoles (**5**) and indeno pyridazines (**6**) are reported to exhibit cyclin-dependent kinase [28] and selective monoamide oxidase B(MAO-B) [29] inhibitors activity (Fig. 1).

From our laboratories, we have earlier reported spirooxindole-fused heterocycles carrying isoxazole moiety with potent anti-microbial, anti-inflammatory, and analgesic activity (Fig. 2) [30].

Encouraged by the previous reports, and as a sequel to our program aimed at developing new methodologies [31], we report, herein, the synthesis of novel new isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones via a facile, atom-economical, and one-pot pseudo four-component procedure.

RESULTS AND DISCUSSION

The reaction was first explored by stirring a mixture of 1,3-indandione **11**, 4-amino-3-methyl-5-styrylisoxazole **12**, and isatin **13** with 10 mol% of *p*-toluene sulfonic acid (*p*TSA), a Lewis acid catalyst, under reflux in CH_3CN for 1 h. The reaction afforded the isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (**14**) in excellent yield (Scheme 1).

To establish the feasibility of the strategy, and optimize reaction conditions, the reaction was initially carried out in

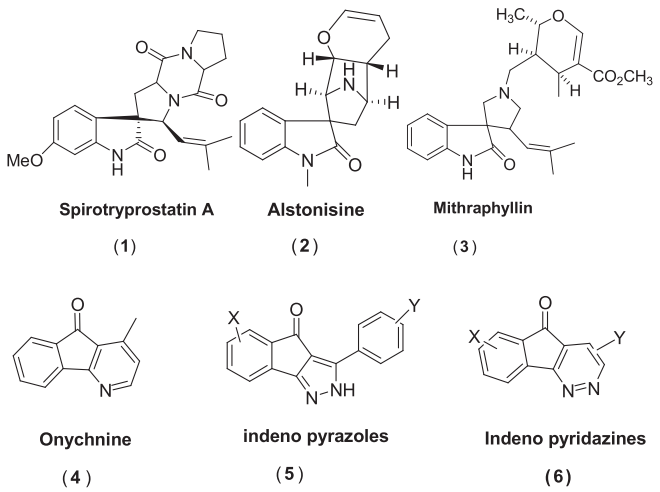


Figure 1. Representatives of important indenone fused heterocycles and spirooxindoles.

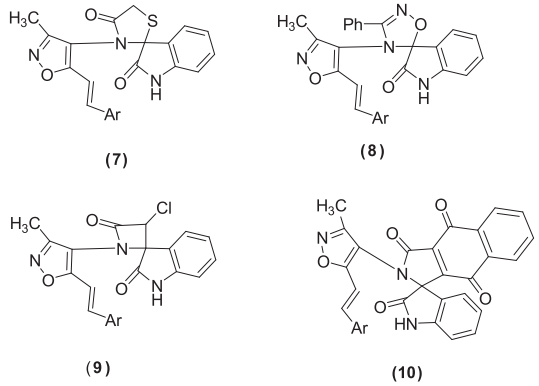
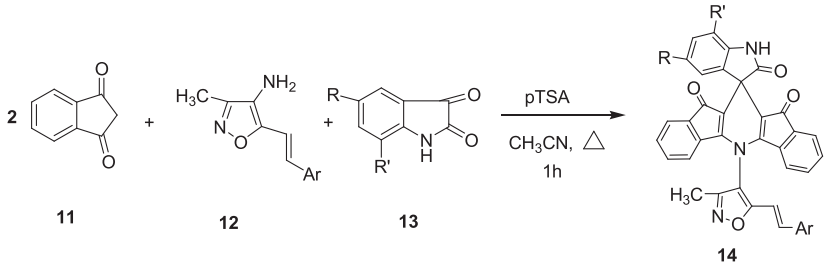


Figure 2. Biologically active isoxazolyl spirooxindole derivatives.

the presence of *p*TSA, as an inexpensive and readily available catalyst. Different Lewis acid catalysts including LiCl, $ZnCl_2$, $AlCl_3$, CAN, silica gel, $InCl_3$, I_2, and $FeCl_3$ were also screened (Table 1). The best overall yield (85%) was obtained with *p*TSA (10 mol%). However, in the absence of catalyst, the reaction did not proceed even after prolonged reaction time (24 h).

A systematic study was carried out for the catalytic evaluation of *p*TSA in the reaction of 1,3-indandione **11** and 4-amino-3-methyl-5-styrylisoxazole **12** with isatin **13** by using a variety of solvents such as CH_3CN, EtOH, MeOH, H_2O, DMF, EtOAc, DMSO, DCM, and 1,4-dioxane with different catalytic loads (Table 2). The best result was

Scheme 1. Synthesis of isoxazolyl spiro(diindeno pyridine-indoline) triodes.



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	Ar	R	R′		Ar	R	R′
a)	C_6H_5	H	H	g)	C_6H_5	Cl	H
b)	4-$CH_3C_6H_4$	H	H	h)	C_6H_5	Br	H
c)	4-$OCH_3C_6H_4$	H	H	i)	C_6H_5	CH_3	H
d)	2-ClC_6H_4	H	H	j)	C_6H_5	OCH_3	H
e)	2-BrC_6H_4	H	H	k)	C_6H_5	H	CH_3
f)	2-$OCH_3C_6H_4$	H	H	l)	C_6H_5	H	Cl

Table 1

Effect of different catalysts on the synthesis of isoxazolylspiro[diindeno [1,2-*b*;2′,1′-*e*] pyridine-11,3′-indoline]-2′,10,12-triones **14**.[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	None	24.4	–
2	*p*TSA	1.0	85
3	LiCl	2.5	25
4	$ZnCl_2$	2.0	42
5	$AlCl_3$	3.5	50
6	CAN	3.0	55
7	Silica gel	2.5	15
8	$InCl_3$	4.0	60
9	I_2	2.5	25
10	$FeCl_3$	3.0	30

[a]Reaction conditions: 1,3-indandione **11** (0.02 mol), 4-amino-3-methyl-5-styrylisoxazole **12** (0.01 mol), isatin **13** (0.01 mol), *p*TSA (10 mol%), solvent (10 mL).
[b]Isolated and unoptimized yields.

Table 2

Optimization of catalytic and solvent conditions on the synthesis of isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones **14**.[a]

Entry	Solvent	Catalyst (*p*TSA) (mol%)	Time (h)	Yield[b] (%)
1	CH_3CN	5	1.5	75
2	CH_3CN	10	1.0	85
3	CH_3CN	20	1.0	85
4	EtOH	10	3.5	55
5	MeOH	10	1.2	45
6	H_2O	10	4.0	30
7	DMF	10	3.4	42
8	EtOAc	10	2.2	25
9	DMSO	10	2.0	35
10	DCM	10	2.2	46
11	1,4-Dioxane	10	2.0	15

[a]Reaction conditions: 1,3-indandione **11** (0.02 mol), 4-amino-3-methyl-5-styrylisoxazole **12** (0.01 mol), isatin **13** (0.01 mol), *p*TSA (10 mol%), solvent (10 mL).
[b]Isolated and unoptimized yields.

obtained with 10 mol% of catalyst in CH_3CN solvent, in terms of reaction time, and yield.

From Tables 1 and 2, it is clear that in the presence of *p*TSA, acetonitrile is the solvent of choice for the reaction, and the desired product is obtained in excellent yield and high purity.

To investigate the scope of *p*TSA-catalyzed synthesis of isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones **14**, several substituted isatins and wide range of functional groups, that is, electron withdrawing as well as electron releasing groups on aromatic ring attached to isoxazole moiety, in CH_3CN were examined, and results are summarized in Table 3. In each case, the reaction proceeded very cleanly under mild conditions and is compatible with a wide range of functional groups (Table 3).

Table 3

Effects of different substituents on the synthesis of isoxazolylspiro [diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones **14**.[a]

Compound	Ar	R	R′	Time (h)	Yield[b] (%)
14a	C_6H_5	H	H	1.0	85
14b	4-$CH_3C_6H_4$	H	H	1.0	85
14c	4-$OCH_3C_6H_4$	H	H	1.0	90
14d	2-ClC_6H_4	H	H	1.2	80
14e	2-BrC_6H_4	H	H	1.0	88
14f	2-$OCH_3C_6H_4$	H	H	1.0	92
14g	C_6H_5	Cl	H	1.3	88
14h	C_6H_5	Br	H	1.0	82
14i	C_6H_5	CH_3	H	1.0	85
14j	C_6H_5	OCH_3	H	1.1	95
14k	C_6H_5	H	CH_3	1.0	95
14l	C_6H_5	H	Cl	1.1	85

[a]Reaction conditions: 1,3-indandione **11** (0.02 mol), 4-amino-3-methyl-5-styrylisoxazole **12** (0.01 mol), isatin **13** (0.01 mol), *p*TSA (10 mol%), solvent (10 mL).
[b]Isolated and unoptimized yields.

The plausible mechanism involves the reaction of two moles of indandione (**11**) with isatin (**13**) under the influence of *p*TSA catalyst to give the intermediate **A**. The C=O group of indanone then undergoes condensation with aminoisoxazole (**12**) to give compound **B**, which then tautomerizes and attacks the carbonyl group of other indanone moiety; thereby, cyclization takes place to afford the product (**14**) involving dehydration (Scheme 2).

The present method should be applicable to synthesis of libraries of isoxazolyl diindenoindoline derivatives with high diversity by using readily available isatins and isoxazole amines. This method finds application in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

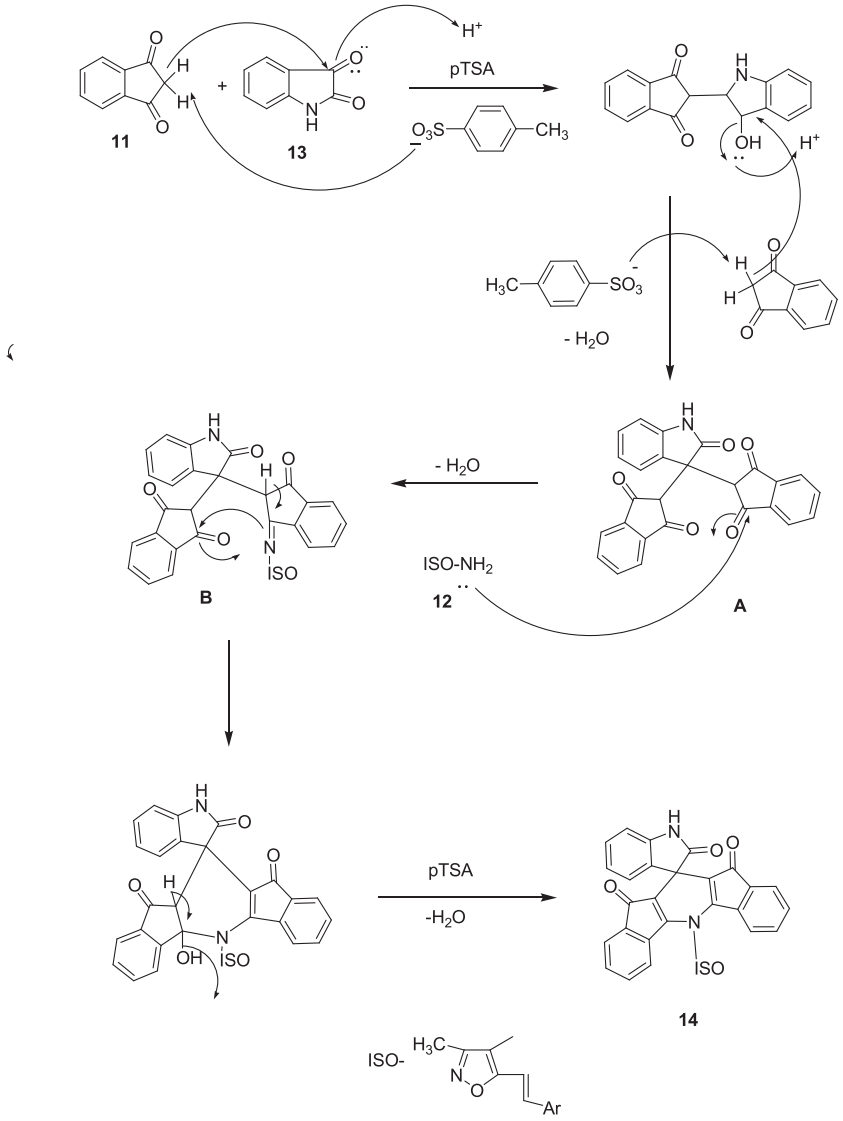
CONCLUSION

In conclusion, an efficient, atom-economical, and simple method for the synthesis of isoxazolylspiro[diindeno[1,2-*b*;2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones using readily available starting materials is reported. Prominent advantages of this new method are operational simplicity, excellent yields, short reaction time, easy workup, and mild conditions. The products are isolated in pure from by recrystallization without intervention of chromatography, making the technology practical, easy to perform, and facile.

EXPERIMENTAL

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical thin-layer

Scheme 2. Plausible mechanism for the formation of isoxazolyl spiro(diindeno pyridine-indoline)triodes



chromatography was performed on Merck precoated 60 F_{254} silica gel plates (Darmstadt, Germany). Visualization was performed by exposing to iodine vapor. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer (Waltham, MA). ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer (Germany). ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as internal standard. Electrospray ionization (ESI) mass spectra were recorded on an Agilent LC-MSD mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of isoxazolylspiro [diindeno[1,2-*b*;2′,1′-*e*] pyridine-11,3′-indoline]-2′,10,12-trione (14a–l). A mixture of 1,3-indandione **11** (0.02 mol), 4-amino-3-methyl-5-styrylisoxazoles **12** (0.01 mol), and substituted isatins **13** (0.01 mol) and *p*TSA (10 mol%) were taken in acetonitrile (10 mL), and the contents were refluxed with stirring for 1 h. After completion of the reaction (monitored by thin-layer chromatography), the reaction mixture was cooled at room temperature. The solid separated was filtered and washed with water (10 mL) and ethanol (10 mL). The crude product was purified by recrystallization from ethyl acetate.

(E)-5-(3-Methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno[1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14a). Pale yellow; mp 248–250°C; *Anal*. Calcd. For $C_{38}H_{23}N_3O_4$: C, 77.94; H, 3.93; N, 7.17. Found. C, 77.91; H, 3.92; N, 7.14; IR (KBr) cm^{-1}: 3435 (NH), 1703 (C=O), 1660 (CONH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole-CH_3), 6.50 (d, 1H, CH=CH, J = 12 Hz), 6.72 (d, 1H, CH=CH, J = 12 Hz), 7.00–8.00 (m, 17H, ArH), 10.65 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.91, 47.30, 107.28, 108.18,

111.22, 117.32, 118.51, 118.90, 120.02, 121.32, 122.50, 123.36, 123.95, 126.12, 127.11, 127.85, 129.30, 132.50, 133.87, 134.45, 137.32, 138.65, 143.23, 144.56, 149.02, 152.25, 154.59, 177.89, 192.62; ESI-MS (*m/z*): 586 $[M+H]^+$.

(E)-5-(3-Methyl-5-(methylstyryl)isoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14b). Pale yellow; mp 239–241°C; *Anal*. Calcd. For $C_{39}H_{25}N_3O_4$: C, 78.13; H, 4.17; N, 7.01. Found. C, 78.15; H, 4.16; N, 7.05; IR (KBr) cm^{-1}: 3437 (NH), 1710 (C=O), 1666 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole-CH_3), 2.50 (s, 3H, ArCH_3), 6.61 (d, 1H, CH=CH, *J* = 12 Hz), 6.70 (d, 1H, CH=CH, *J* = 12 Hz), 7.10–8.50 (m, 16H, ArH), 10.05 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.36, 24.56, 45.41, 105.31, 108.62, 111.15, 118.32, 120.75, 121.81, 122.66, 122.84, 123.75, 124.64, 125.67, 126.21, 126.67, 128.15, 129.08, 130.74, 132.11, 132.36, 136.45, 137.42, 141.56, 142.44, 148.61, 150.17, 158.22, 177.74, 190.19; ESI-MS (*m/z*): 600 $[M+H]^+$.

(E)-5-(5-(4-Methoxystyryl)-3-methylisoxaozl-4-yl)-5H-spiro [diindeno[1,2-b;2′,1′-e] pyridine-11-3′-indoline]-2′,10,12-trione (14c). Pale yellow; mp 260–262°C; *Anal*. Calcd. For $C_{39}H_{25}N_3O_5$: C, 76.09; H, 4.06; N, 6.82. Found. C, 76.06; H, 4.08; N, 6.81; IR (KBr) cm^{-1}: 3431 (NH), 1707 (C=O), 1662 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole-CH_3), 3.62 (s, 3H, OCH_3), 6.55 (d, 1H, CH=CH, *J* = 12 Hz), 6.60 (d, 1H, CH=CH, *J* = 12 Hz), 7.05–8.13 (m, 16H, ArH), 10.22 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.36, 45.44, 56.34, 105.44, 108.66, 111.16, 118.38, 120.58, 121.54, 122.64, 122.81, 123.51, 124.79, 125.63, 126.21, 126.39, 128.19, 129.21, 130.71, 132.14, 132.17, 136.43, 137.28, 141.19, 142.38, 148.76, 150.31, 158.21, 177.76, 190.14; ESI-MS (*m/z*): 616 $[M+H]^+$.

(E)-5-(5-(2-Cholrostyryl)-3-methylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14d). Pale yellow; mp 288–290°C; *Anal*. Calcd. For $C_{38}H_{22}N_3O_4Cl$: C, 73.66; H, 3.55; N, 6.78. Found. C, 73.63; H, 3.59; N, 6.79; IR (KBr) cm^{-1}: 3429 (NH), 1716 (C=O), 1660 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H, isoxazole-CH_3), 6.63 (d, 1H, CH=CH, *J* = 12 Hz), 6.58 (d, 1H, CH=CH, *J* = 12 Hz), 7.11–8.26 (m, 16H, ArH), 10.00 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):11.56, 45.42,105.31, 108.56, 111.31, 118.24, 120.64, 121.72, 122.63, 122.84, 123.74, 124.82, 125.69, 126.12, 126.64, 128.31, 129.24, 130.46, 132.16, 132.31, 136.48, 137.28, 141.31, 142.48, 148.76, 150.21, 158.22, 177.76, 190.19; ESI-MS (*m/z*): 620 $[M+H]^+$.

(E)-5-(5-(2-Bromostyryl)-3-methylisoxaozl-4-yl)-5H-spiro [diindeno[1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14e). Pale yellow; mp 302–304°C; *Anal*. Calcd. For $C_{38}H_{22}N_3O_4Br$: C, 68.77; H, 3.31; N, 6.33. Found. C, 68.76; H, 3.35; N, 6.31; IR (KBr) cm^{-1}: 3425 (NH), 1710 (C=O), 1660 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole-CH_3), 6.58 (d, 1H, CH=CH, *J* = 12 Hz), 6.70 (d, 1H, CH=CH, *J* = 12 Hz), 7.09–8.10 (m, 16H, ArH), 10.15 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):11.82, 45.29, 105.21, 108.36, 111.30, 118.36, 120.73, 121.74, 122.64, 122.84, 123.68, 124.87, 125.63, 126.21, 126.64, 128.31, 129.19, 130.72, 132.11, 132.31, 136.67, 137.28, 141.34, 142.46, 148.71, 150.19, 158.16, 177.64, 190.24; ESI-MS (*m/z*): 664 $[M+H]^+$.

(E)-5-(5-(2-Methoxystyryl)-3-methylisoxaozl-4-yl)-5H-spiro [diindeno[1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14f). Pale yellow; mp 255–257°C; *Anal*. Calcd. For $C_{39}H_{25}N_3O_5$: C, 76.09; H, 4.06; N, 6.82. Found. C, 76.11; H, 4.03; N, 6.81; IR (KBr) cm^{-1}: 3432 (NH), 1718 (C=O), 1659 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H, isoxazole-CH_3), 3.58 (s, 3H, OCH_3), 6.65 (d, 1H, CH=CH, *J* = 12 Hz), 6.70 (d, 1H, CH=CH, *J* = 12 Hz), 7.11–8.68 (m, 16H, ArH), 10.06 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.06, 45.26, 105.19, 108.63, 111.24, 118.29, 120.75, 121.69, 122.67, 122.81, 123.77, 124.82, 125.64, 126.21, 126.43, 128.31, 129.09, 130.74, 132.00, 132.35, 136.47, 137.28, 141.19, 142.46, 148.74, 150.16, 158.36, 177.26, 190.46; ESI-MS (*m/z*): 616 $[M+H]^+$.

(E)-5′-Chloro-5-(3-methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14g). Pale yellow; mp 271–273°C; *Anal*. Calcd. For $C_{38}H_{22}N_3O_4Cl$: C, 73.66; H, 3.55; N, 6.78. Found. C, 73.62; H, 3.54; N, 6.76; IR (KBr) cm^{-1}: 3433 (NH), 1705 (C=O), 1662 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole-CH_3), 6.55 (d, 1H, CH=CH, *J* = 12 Hz), 6.68 (d, 1H, CH=CH, *J* = 12 Hz), 7.00–8.46 (m, 16H, ArH), 10.08 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.56, 45.38, 105.25, 108.66, 111.26, 118.23, 120.76, 121.81, 122.64, 122.83, 123.79, 124.92, 125.80, 126.12, 126.66, 128.19, 129.15, 130.74, 132.12, 132.31, 136.46, 137.36, 141.30, 142.49, 148.72, 150.31, 158.26, 177.74, 190.31; ESI-MS (*m/z*): 620 $[M+H]^+$.

(E)-5′-Bromo-5-(3-methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14h). Pale yellow; mp 306–308°C; *Anal*. Calcd. For $C_{38}H_{22}N_3O_4Br$: C, 68.77; H, 3.31; N, 6.33. Found. C, 68.79; H, 3.34; N, 6.30; IR (KBr) cm^{-1}: 3429 (NH), 1710 (C=O), 1660 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H, isoxazole-CH_3), 6.61 (d, 1H, CH=CH, *J* = 12 Hz), 6.72 (d, 1H, CH=CH, *J* = 12 Hz), 7.11–8.36 (m, 16H, ArH), 10.49 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.84, 45.41,105.31, 108.62, 111.26, 118.39, 120.76, 121.77, 122.56, 122.86, 123.74, 124.84, 125.73, 126.13, 126.46, 128.20, 129.18, 130.74, 132.13, 132.21, 136.45, 137.36, 141.29, 142.62, 148.86, 150.21, 158.26, 177.81, 190.19; ESI-MS (*m/z*): 664 $[M+H]^+$.

(E)-5′-Methyl-5-(3-methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14i). Pale yellow; mp 233–235°C; *Anal*. Calcd. For $C_{39}H_{25}N_3O_4$:

C, 78.13; H, 4.17; N, 7.01. Found. C, 78.16; H, 4.18; N, 7.03; IR (KBr) cm^{-1}: 3430 (NH), 1711 (C=O), 1659 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole-CH_3), 2.54 (s, 3H, ArCH_3), 6.52 (d, 1H, CH=CH, $J = 12$ Hz), 6.62 (d, 1H, CH=CH, $J = 12$ Hz), 7.08–8.22 (m, 16H, ArH), 10.23 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):11.59, 26.45, 45.50, 105.46, 108.54, 111.20, 118.48, 120.64, 121.74, 122.54 122.74, 123.62, 124.56, 125.52, 126.30, 126.58, 128.20, 129.03, 130.64, 132.21, 132.25, 136.39, 137.40, 141.61, 142.50, 148.59, 150.21, 158.23, 177.59, 190.20; ESI-MS (*m/z*): 600 $[M + H]^+$.

(E)-5′-Methoxy-5-(3-methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14j). Pale yellow; mp 265–267°C; *Anal*. Calcd. For $C_{39}H_{25}N_3O_5$: C, 76.09; H, 4.06; N, 6.82. Found. C, 76.06; H, 4.05; N, 6.84; IR (KBr) cm^{-1}: 3435 (NH), 1702 (C=O), 1660 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole-CH_3), 3.70 (s, 3H, OCH_3), 6.52 (d, 1H, CH=CH, $J = 12$ Hz), 6.85 (d, 1H, CH=CH, $J = 12$ Hz), 7.00–8.51 (m, 16H, ArH), 10.20 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.21, 45.56, 56.31, 105.26, 108.51, 111.20, 118.41, 120.53, 121.68, 122.62, 122.85, 123.60, 124.68, 125.62, 126.18, 126.26, 128.17, 129.20, 130.65, 132.20, 132.16, 136.39, 137.32, 141.26, 142.40, 148.68, 150.36, 158.26, 177.64, 190.09; ESI-MS (*m/z*): 616 $[M + H]^+$.

(E)-7′-Methyl-5-(3-methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14k). Pale yellow; mp 245–247°C; *Anal*. Calcd. For $C_{39}H_{25}N_3O_4$: C, 78.13; H, 4.17; N, 7.01. Found. C, 78.11; H, 4.18; N, 7.04; IR (KBr) cm^{-1}: 3430 (NH), 1700 (C=O), 1662 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.23 (s, 3H, isoxazole-CH_3), 2.51 (s, 3H, ArCH_3), 6.61 (d, 1H, CH=CH, $J = 12$ Hz), 6.70 (d, 1H, CH=CH, $J = 12$ Hz), 7.00–8.20 (m, 16H, ArH), 10.31 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):11.56, 25.86, 45.33, 105.29, 108.54, 111.23, 118.39, 120.64, 121.78, 122.56, 122.71, 123.64, 124.55, 125.51, 126.18, 126.53, 128.22, 129.19, 130.61, 132.24, 132.34, 136.42, 137.55, 141.59, 142.40, 148.64, 150.18, 158.26, 177.70, 190.23; ESI-MS (*m/z*): 600 $[M + H]^+$.

(E)-7′-Chloro-5-(3-methyl-5-styrylisoxaozl-4-yl)-5H-spiro[diindeno [1,2-b;2′,1′-e]pyridine-11-3′-indoline]-2′,10,12-trione (14l). Pale yellow; mp 280–282°C; *Anal*. Calcd. For $C_{38}H_{22}N_3O_4Cl$: C, 73.66; H, 3.55; N, 6.78. Found. C, 73.65; H, 3.58; N, 6.80; IR (KBr) cm^{-1}: 3432 (NH), 1710 (C=O), 1661 (CONH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole-CH_3), 6.52 (d, 1H, CH=CH, $J = 12$ Hz), 6.60 (d, 1H, CH=CH, $J = 12$ Hz), 7.01–8.21 (m, 16H, ArH), 10.09 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):11.26, 45.28, 105.31, 108.61, 111.26, 118.22, 120.74, 121.76, 122.64, 122.88, 123.67, 124.76, 125.75, 126.23, 126.61, 128.19, 129.20, 130.75, 132.16, 132.31, 136.47, 137.29, 141.24, 142.58, 148.73, 150.09, 158.15, 177.76, 190.19; ESI-MS (*m/z*): 620 $[M + H]^+$.

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