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ORIGINAL PAPER

An efficient catalyst-free approach for the synthesis of novel isoxazolo[5,4-*b*]pyridine derivatives via one-pot three-component reaction

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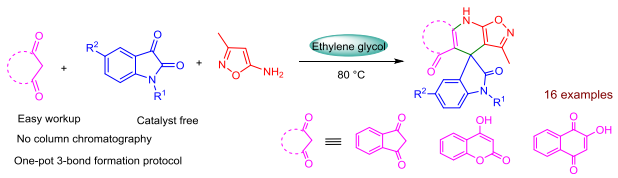
Abstract

A catalyst-free, one-pot, three-component condensation procedure for the synthesis of novel isoxazolo[5,4-*b*]pyridine derivatives has been reported by condensation of isatins, 3-methylisoxazol-5-amine, and cyclic enolizable carbonyl compounds in ethylene glycol at 80 °C. The structures of the synthesized compounds have been confirmed by spectral and X-ray studies. Crystal packing of one compound has also been reported. Less reaction time, easy work-up, and high yields are the important features of the present protocol.

Graphical abstract



Keywords Ethylene glycol · Heterocycles · Isoxazole · MCRs · One-pot synthesis · Spiro compounds

Introduction

Multicomponent reactions (MCRs), reactions [1] can be used to overcome the challenge of synthesizing compounds having structural complexity, diversity and having promising biological properties by designing efficient reaction methodologies. The MCR one-pot procedures are of interest as they are low cost, being environmentally benign and have high atom efficiency [2].

Spiro compounds display a wide array of biological applications such as antidiabetic [3], antimycobacterial [4], antimicrobial [5], anticholinesterase [6], anticancer [7], etc. Spirocyclic compounds also belong to the category of fluorescent chemosensors, as they induce brilliant coloration on irradiation [8–10]. In particular, spirooxindoles are of great interest because of their prevalence in numerous natural products and biologically active synthetic molecules [11–15]. The spiro ring fused at the C3 position of the oxindole core with varied heterocyclic motifs is the key structural characteristic of these compounds. Natural occurring spirooxindole alkaloids, viz., spirotryprostatins have been reported to show anticancer activity [16]. In addition to the naturally occurring spirooxindoles, a synthetic derivative, MI-888 is in preclinical trials for the treatment of human cancers [17]. In view of the excellent biological activity of spirooxindole

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hybrids, development of new methodologies for the synthesis of novel spirooxindole hybrids is imperative for the pharmaceutical industry.

In our endeavor of exploring new synthetic strategies for the synthesis of various kind of heterocycles [18–23], herein we decided to investigate the synthesis of novel spirooxindole derivatives by one-pot multicomponent reaction of indane-1,3-dione, isatin, and 3-methylisoxazol-5-amine.

Results and discussion

We report herein a facile and efficient one-pot synthesis of novel spiroisooxazoles, namely, 3-methylspiro[indeno[2,1-*e*]isoxazolo[5,4-*b*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione derivatives **4a**–**4e** by catalyst-free three-component condensation of isatins **1**, 3-methylisoxazol-5-amine (**2**), and indane-1,3-dione (**3a**); synthesis of novel 8-methylspiro[chromeno[3,4-*e*]isoxazolo[5,4-*b*]pyridine-7,3′-indoline]-2′,6(11*H*)-diones **5a**–**5f** via condensation of isatins **1**, 3-methylisoxazol-5-amine (**2**), and 4-hydroxycoumarin (**3b**), and synthesis of novel 3-methyl-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione derivatives **6a**–**6e** by condensation of isatins **1**, 3-methylisoxazol-5-amine (**2**), and 2-hydroxy-1,4-naphthoquinone (**3c**) in ethylene glycol at 80 °C.

The reactions of isatin (**1**, 1.0 mmol), 3-methylisoxazol-5-amine (**2**, 1.0 mmol), and indane-1,3-dione (**3a**, 1.0 mmol) initially attempted in various protic solvents under catalyst free conditions to identify appropriate reaction conditions. Firstly, the reaction was attempted in water at 80 °C, but there was no reaction even after 24 h (Table 1, entry 1). The same reaction carried out using glycerol as solvent at 80 °C showed formation of a new product though it was incomplete even after 24 h. The new product was separated and identified as desired 3-methylspiro[indeno[2,1-*e*]isoxazolo[5,4-*b*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (**4a**) in 27% yield (Table 1, entry 2; Scheme 1).

Table 1 Optimization of reaction conditions for the synthesis of 3-methylspiro [indeno[1,2-*b*]isoxazolo[4,5-*e*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione **4a**

Entry	Solvent	Temp./°C	Time/h	Yield/%
1	Water	80	24	–[a]
2	Glycerol	80	24	27[b]
3	PEG-400	80	24	42[b]
4	PEG-600	80	24	38[b]
5	MeOH	80	24	37[b]
6	Ethylene glycol	80	0.33	92
7	Ethylene glycol	60	24	62[b]
8	Ethylene glycol	100	0.25	92
9	[bmim]Br	80	24	88
10	[bmim]BF_4	80	24	–[a]

Reaction carried out with isatin (1.0 mmol), 3-methylisoxazole-5-amine (1.0 mmol), and indane-1,3-dione (1.0 mmol)

[a]No reaction

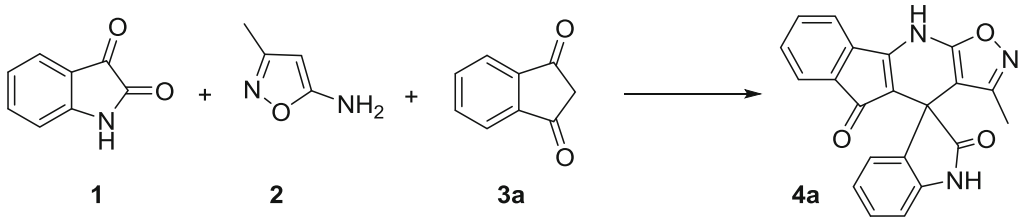
[b]Incomplete reaction

The reactions were then performed in PEG-400, PEG-600, and methanol at 80 °C. The reactions were incomplete even after 24 h but gave 42, 38, and 37% of the product **4a**, respectively (Table 1, entries 3–5). The same reaction when attempted using ethylene glycol at 80 °C was complete in 20 min and yielded 92% of the desired product **4a** (Table 1, entry 6). The reaction in ethylene glycol was also attempted at 60 and 100 °C. While the reaction at 60 °C was incomplete even after 24 h and gave 62% yield of the desired product **4a** (Table 1, entry 7), the reaction attempted at 100 °C did not show any significant difference in reaction time and yield of the product (Table 1, entry 8). Ionic liquids [bmim]Br and [bmim]BF_4 were also used as reaction medium under identical conditions. The reaction was complete in [bmim]Br after 24 h and yielded 88% of **4a** (Table 1, entry 9) while in [bmim]BF_4 there was no reaction even after 24 h (Table 1, entry 10).

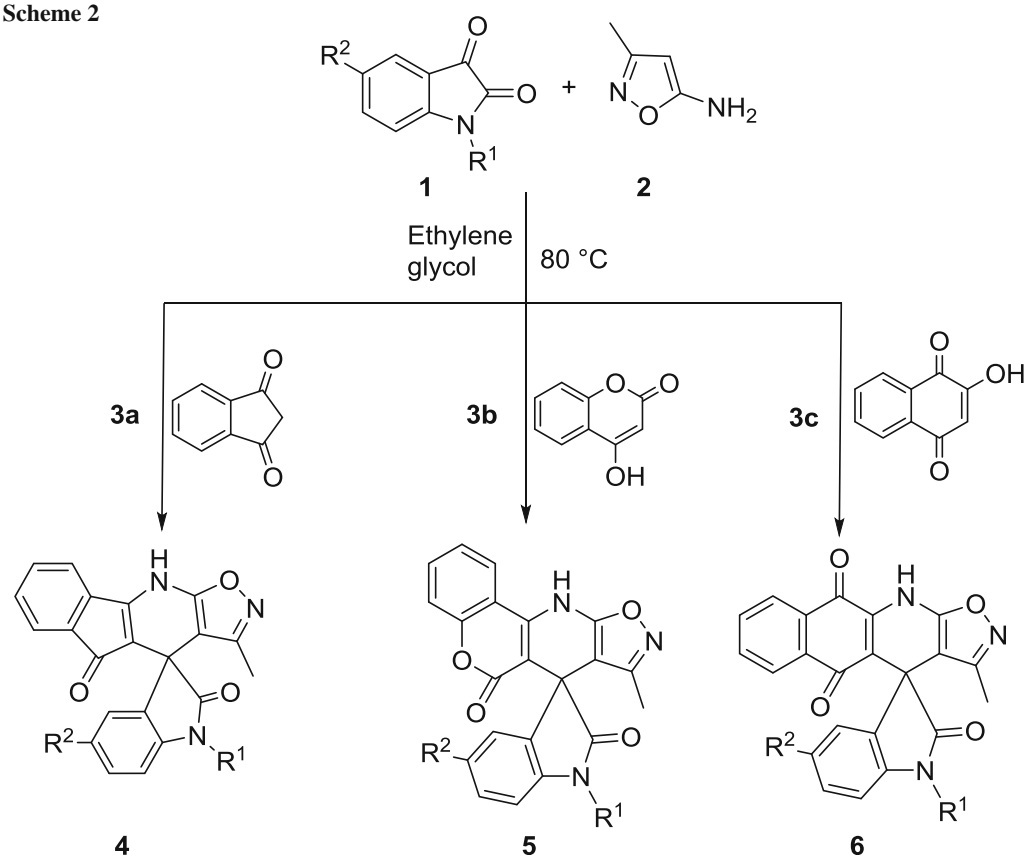
Therefore, it can be inferred from the above results that a catalyst-free one-pot three-component condensation of isatin (1.0 mmol), 3-methylisoxazol-5-amine (1.0 mmol), and indane-1,3-dione (1.0 mmol) in ethylene glycol at 80 °C is the optimum condition for the synthesis of spirooxindoles. Subsequently, reactions of different isatins **1** and 3-methylisoxazol-5-amine (**2**) were attempted with indane-1,3-dione (**3a**), 4-hydroxycoumarin (**3b**), and 2-hydroxy-1,4-naphthoquinone (**3c**) under the optimized conditions. All the reactions proceeded smoothly and were complete in 20–240 min affording the corresponding 3-methylspiro[indeno[2,1-*e*]isoxazolo[5,4-*b*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione derivatives **4a**–**4e**, 8-methylspiro[chromeno[3,4-*e*]isoxazolo[5,4-*b*]pyridine-7,3′-indoline]-2′,6(11*H*)-diones **5a**–**5f**, and 3-methyl-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione derivatives **6a**–**6e** in high yields (Scheme 2). All the results have been compiled in Table 2. Structural assignments have been made on the basis of ^{1}H NMR, ^{13}C NMR, IR, and mass spectra.

^{1}H NMR spectra of compound **4a** showed a singlet at δ = 1.55 ppm for three methyl protons, one N–H proton appeared at 1.89 ppm and eight aromatic protons appeared in the range of 6.90–7.61 ppm and 1 N–H proton appeared as a singlet at 10.70 ppm. The methyl carbon in ^{13}C NMR appeared at δ = 9.02 ppm and one quaternary carbon appeared at 46.68 ppm. The 15 aromatic carbons and 2 olefinic carbons appeared in the range of 96.00–161.63 ppm. Two carbonyl carbons appeared at

Scheme 1



Scheme 2



177.70 and 189.33 ppm. IR spectra showed peaks at 3331 and 3310 cm^{-1} (N–H stretch) and 1692 and 1672 cm^{-1} (carbonyl stretch). Mass spectrum of **4a** showed a molecular ion peak at m/z = 356.1039 ($[M + H]^+$).

The structure of the synthesized novel 3-methylspiro[indeno[2,1-*e*]isoxazolo[5,4-*b*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (**4a**) has been confirmed by the single crystal X-ray diffraction analysis (Fig. 1 left). A single crystal of **4a** suitable for X-ray diffraction was obtained by solution of the compound in DMSO at room temperature. The crystal packing shows two molecules in a unit cell (Fig. 1 right).

A probable mechanism involved in the formation of products is outlined in Scheme 3. The condensation of isatin and 3-methylisoxazol-5-amine gives intermediate **7** via dehydration of **6**. The intermediate **7** reacts with indane-1,3-dione to give intermediate **8** which undergoes intramolecular cyclisation to give **9** followed by loss of water to give the final product **4**.

Conclusion

In conclusion, we have developed an eco-friendly catalyst-free methodology for the synthesis of novel isoxazolo[5,4-*b*]pyridine derivatives via reactions of isatins, 3-methylisoxazol-5-amine, and cyclic enolizable carbonyl compounds in ethylene glycol at 80 °C. The advantages of

Table 2 Synthesis of isoxazolo[5,4-*b*]pyridine derivatives

Product	R^1	R^2	**3**	Time/min	Yield/%
4a	H	H	**3a**	20	92
4b	H	Br	**3a**	60	91
4c	H	NO_2	**3a**	25	92
4d	H	Cl	**3a**	30	91
4e	$–CH_2–CH=CH_2$	H	**3a**	60	89
5a	H	H	**3b**	120	89
5b	H	Br	**3b**	180	90
5c	H	NO_2	**3b**	120	89
5d	H	Cl	**3b**	180	90
5e	$–CH_2–C\equiv CH$	H	**3b**	120	88
5f	$–CH_2–CH=CH_2$	H	**3b**	180	89
6a	H	H	**3c**	240	87
6b	H	NO_2	**3c**	60	87
6c	H	Cl	**3c**	90	84
6d	$–CH_2–C\equiv CH$	H	**3c**	120	84
6e	$–CH_2–CH=CH_2$	H	**3c**	120	86

Reaction of isatin (1.0 mmol), 3-methylisoxazol-5-amine (1.0 mmol), and indane-1,3-dione (**3a**)/4-hydroxycoumarin (**3b**)/2-hydroxy-1,4-naphthoquinone (**3c**) (1.0 mmol) in ethylene glycol at 80 °C

this protocol are environmentally benign conditions and high atom-economy. All the compounds were obtained in high yields.

Experimental

All the chemicals were commercial and purchased from Sigma-Aldrich or Merck and used as received. Thin layer chromatography (GF254) was used to monitor reaction progress. Melting points were measured on Buchi M-560 melting point apparatus. IR (KBr) spectra were recorded on a Perkin-Elmer FTIR spectrophotometer and the values are expressed in cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 and 100 MHz respectively, using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hz. Mass spectral data were recorded on a Bruker Micro TOFQ–II mass spectrometer.

X-ray data collection and refinement

The intensity data for compound **4a** were collected on an Oxford Xcalibur CCD diffractometer equipped with graphite monochromatic MoKα radiation (λ = 0.71073 Å) at 293(2) K. A multiscan absorption correction was applied. The structure was solved by direct methods and refined by full-matrix least squares refinement techniques on F2 using SHELXL-97 [24]. The coordinates of non-hydrogen atoms were refined anisotropically using SHELXL-97. The positions of hydrogen atoms were obtained from difference Fourier maps and were included in the final cycles of refinement. All calculations were done using the WinGX software package [25]. Complete crystallographic data (excluding factors) of **4a** have been deposited at the Cambridge Crystallographic Data Centre under number CCDC 1520597.

General procedure for the synthesis of isoxazolo[5,4-*b*]pyridine derivatives

A mixture of isatin (1.0 mmol), 3-methylisoxazol-5-amine (1.0 mmol), cyclic enolizable carbonyl compound (1.0 mmol), and 3 cm^3 ethylene glycol was placed in a 50 cm^3 round-bottomed flask and the contents were stirred

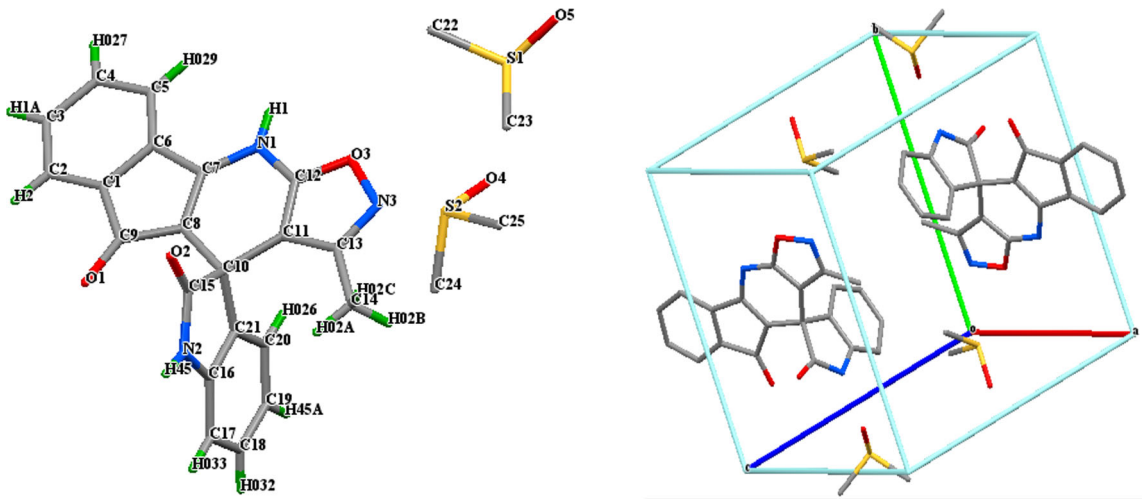
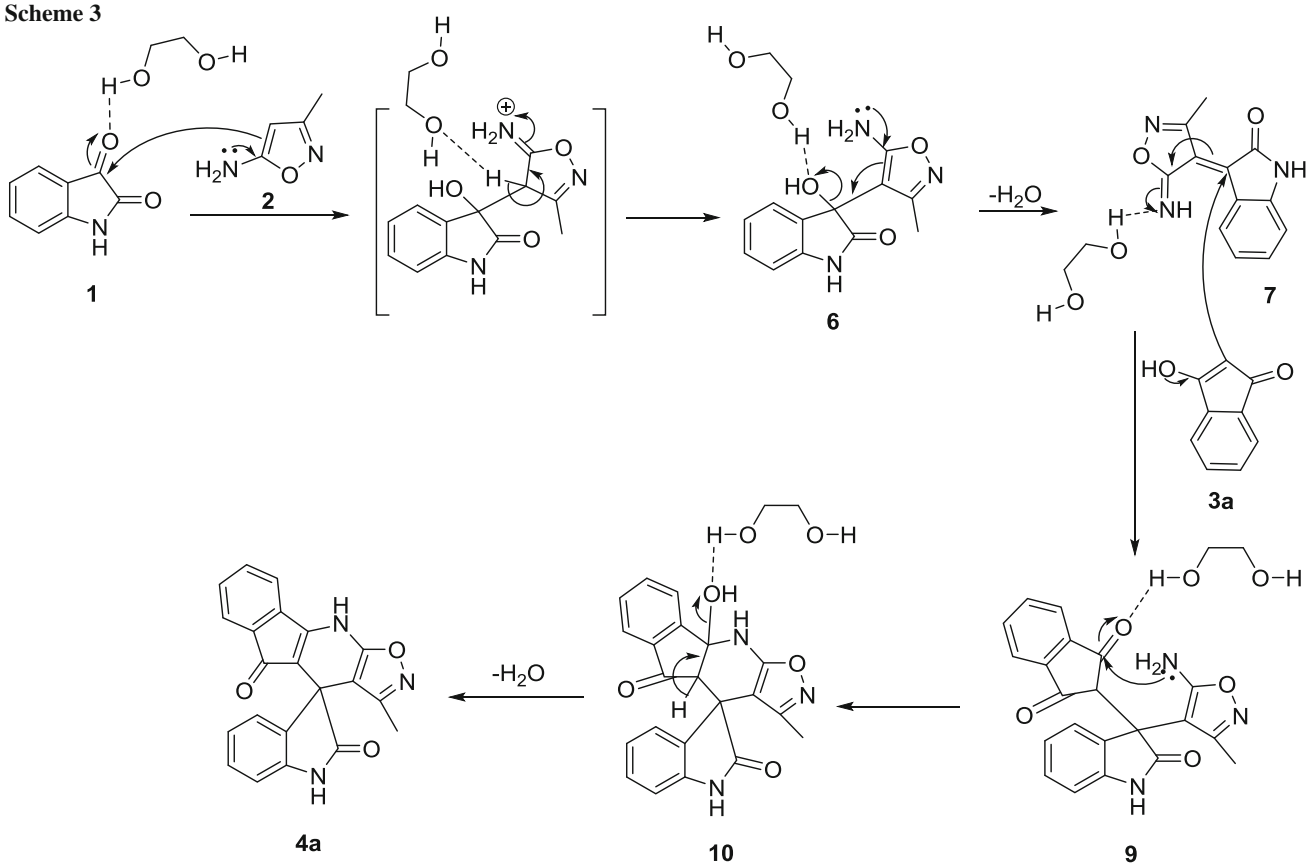


Fig. 1 (Left) X-ray crystal structure of **4a**; (right) view of crystal packing of **4a** shown along *b* axis

Scheme 3



magnetically in an oil-bath maintained at 80 °C for the appropriate time as indicated in Table 2. The progress of the reaction was monitored by TLC using ethyl acetate/petroleum ether (30:70, v/v) as eluent. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and diluted with 5 cm^3 water. The solid separated was collected by filtration at the pump and washed with water. The products were purified by recrystallizing from ethanol. The products were characterized by ^{1}H NMR, ^{13}C NMR, DEPT, IR, mass spectra, and an X-ray crystallographic study.

3-Methylspiro[indeno[1,2-*b*]isoxazolo[4,5-*e*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (4a, $C_{21}H_{13}N_3O_3$) Orange solid; yield: 92%; m.p.: 250 °C (decomp.); R_f = 0.07 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.70 (s, 1H, CONH), 7.61–7.59 (m, 1H, Ar), 7.51 (t, J = 7.6 Hz, 1H, Ar), 7.39 (t, J = 7.6 Hz, 1H, Ar), 7.25–7.20 (m, 2H, Ar), 7.08–7.06 (m, 1H, Ar), 6.93–6.90 (m, 2H, Ar) 1.89 (s, 1H, NH), 1.55 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.33, 177.70, 161.63, 157.84, 156.55, 141.44, 135.86, 133.69, 133.21, 132.44, 130.96, 128.91, 124.64, 122.42, 120.99, 119.81, 109.56, 106.26, 96.00, 46.68, 9.02 ppm; IR (KBr): $\bar{\nu}$ = 3331, 3310, 1692, 1672 cm^{-1}; HRMS (ESI): m/z calc. for $[M + H]^+$ 356.1035, found 356.1039.

5′-Bromo-3-methylspiro[indeno[1,2-*b*]isoxazolo[4,5-*e*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (4b, $C_{21}H_{12}BrN_3O_3$) Orange solid; yield: 91%; m.p.: 267 °C (decomp.); R_f = 0.08 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ =10.85 (s, 1H, CONH), 7.61–7.49 (m, 2H, Ar), 7.41–7.36 (m, 3H, Ar), 7.26–7.24 (m, 1H, Ar), 6.89–6.87 (m, 1H, Ar), 1.89 (s, 1H, NH), 1.59 (s, 3H, CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3293, 1698, 1676 cm^{-1}; HRMS (ESI): m/z calc. for $[M + H]^+$ 434.0140, found 434.0117, 436.0159 ($[M + H + 2]^+$).

3-Methyl-5′-nitrospiro[indeno[1,2-*b*]isoxazolo[4,5-*e*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (4c, $C_{21}H_{12}N_4O_5$) Orange solid; yield: 92%; m.p.: 286–288 °C; R_f = 0.06 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.45 (s, 1H, CONH), 8.23 (dd, J = 2.0, 8.8 Hz, 1H, Ar), 8.096–8.093 (m, 1H, Ar), 7.63 (d, J = 7.2 Hz, 1H, Ar), 7.53 (t, J = 7.6 Hz, 1H, Ar), 7.41 (t, J = 6.8 Hz, 1H, Ar), 7.21–7.24 (m, 1H, Ar), 7.14 (d, J = 9.2 Hz, 1H, Ar), 1.60 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.27, 178.25, 162.13, 157.65, 157.13, 147.83, 143.03, 135.82, 134.38, 133.17, 132.52, 131.12, 126.36,

121.10, 120.70, 120.13, 109.86, 105.06, 94.88, 46.70, 9.17 ppm; IR (KBr): $\bar{\nu}$ = 3282, 1706, 1672 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 401.0886, found 401.0882.

5′-Chloro-3-methylspiro[indeno[1,2-*b*]isoxazolo[4,5-*e*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (4d, $C_{21}H_{12}ClN_3O_3$) Orange solid; yield: 91%; m.p.: 293–295 °C; R_f = 0.08 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.82 (s, 1H, CONH), 7.58–7.56 (m, 1H, Ar), 7.49–7.46 (m, 1H, Ar), 7.38–7.46 (m, 1H, Ar), 7.25–7.21 (m, 3H, Ar), 6.89 (d, *J* = 8 Hz, 1H, Ar), 1.56 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 189.26, 177.44, 161.84, 157.67, 156.84, 140.33, 132.44, 131.02, 128.85, 124.94, 121.02, 119.90, 110.99, 105.61, 95.44, 46.88, 9.06 ppm; IR (KBr): $\bar{\nu}$ = 3316, 3064, 1678, 1650 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 390.0641, found 390.0642.

1′-Allyl-3-methylspiro[indeno[1,2-*b*]isoxazolo[4,5-*e*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (4e, $C_{24}H_{17}N_3O_3$) Orange solid; yield: 89%; m.p.: 264–265 °C; R_f = 0.07 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.59–7.57 (m, 1H, Ar), 7.50 (t, *J* = 7.2 Hz, 1H, Ar), 7.38–7.34 (m, 1H, Ar), 7.28–7.21 (m, 2H, Ar), 7.13–7.12 (m, 1H, Ar), 7.01–6.95 (m, 2H, Ar), 5.91–5.81 (m, 1H, =CH), 5.49–5.44 (m, 1H, =CH_2), 5.19 (d, *J* = 10 Hz, 1H, =CH_2), 4.47–4.42 (m, 1H, –CH_2), 4.31–4.26 (m, 1H, –CH_2), 1.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.19, 175.71, 161.75, 157.72, 156.70, 141.96, 135.80, 133.16, 132.77, 132.47, 131.50, 131.03, 128.93, 124.46, 123.09, 121.03, 119.87, 117.41, 109.12, 105.89, 95.76, 46.29, 42.11, 9.14 ppm; IR (KBr): $\bar{\nu}$ = 3070, 1675, 1663 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 396.1348, found 396.1343.

8-Methylspiro[chromeno[4,3-*b*]isoxazolo[4,5-*e*]pyridine-7,3′-indoline]-2′,6(11*H*)-dione (5a, $C_{21}H_{13}N_3O_4$) White solid; yield: 89%; m.p.: 295–297 °C; R_f = 0.05 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.65 (s, 1H, CONH), 8.21 (d, *J* = 7.6 Hz, 1H, Ar), 7.70 (t, *J* = 7.6 Hz, 1H, Ar), 7.47–7.39 (m, 2H, Ar), 7.19 (t, *J* = 7.6 Hz, 1H, Ar), 7.05–7.03 (m, 1H, Ar), 6.89–6.84 (m, 2H, Ar), 1.86 (s, 1H, NH), 1.56 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.22, 160.04, 159.13, 157.23, 152.14, 145.06, 141.59, 135.13, 133.01, 128.72, 124.57, 124.14, 123.29, 122.26, 116.96, 112.96, 109.27, 98.76, 93.46, 49.41, 8.92 ppm; IR (KBr): $\bar{\nu}$ = 3350, 3154, 1697, 1686 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 372.0984, found 372.0981.

5′-Bromo-8-methylspiro[chromeno[4,3-*b*]isoxazolo[4,5-*e*]pyridine-7,3′-indoline]-2′,6(11*H*)-dione (5b, $C_{21}H_{12}BrN_3O_4$) White solid; yield: 90%; m.p.: 267–269 °C; R_f = 0.10 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.77 (s, 1H, CONH), 8.22 (bs, 1H, Ar), 7.67 (s, 1H, Ar), 7.44–7.33 (m, 4H, Ar), 6.83 (bs, 1H, Ar), 1.60 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.90, 160.26, 159.30, 157.09, 152.18, 145.43, 140.93, 137.27, 133.10, 131.50, 127.20, 124.61, 123.38, 117.02, 113.97, 113.07, 111.24, 98.21, 92.94, 49.61, 8.99 ppm; IR (KBr): $\bar{\nu}$ = 3501, 3226, 1700, 1690 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 450.0089, found 450.0085.

8-Methyl-5′-nitrospiro[chromeno[4,3-*b*]isoxazolo[4,5-*e*]pyridine-7,3′-indoline]-2′,6(11*H*)-dione (5c, $C_{21}H_{12}N_4O_6$) White solid; yield: 89%; m.p.: 287–289 °C; R_f = 0.06 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.86 (s, 1H, CONH), 7.59–7.25 (m, 6H, Ar), 6.87 (bs, 1H, Ar), 1.59 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.81, 160.55, 159.49, 157.70, 152.21, 148.08, 145.81, 142.91, 135.72, 133.21, 126.20, 124.68, 123.50, 120.30, 117.06, 109.50, 97.76, 92.38, 49.50, 9.07 ppm; IR (KBr): $\bar{\nu}$ = 3333, 3226, 1720, 1681 cm^{-1}: HRMS (ESI): *m/z* calc. for $[M + H]^+$ 417.0835, found 417.0825.

5′-Chloro-8-methylspiro[chromeno[4,3-*b*]isoxazolo[4,5-*e*]pyridine-7,3′-indoline]-2′,6(11*H*)-dione (5d, $C_{21}H_{12}ClN_3O_4$) White solid; yield: 90%; m.p.: 286–290 °C; R_f = 0.08 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.81 (s, 1H, CONH), 8.21 (d, *J* = 7.6 Hz, 1H, Ar), 7.69 (t, *J* = 7.6 Hz, 1H, Ar), 7.46–7.38 (m, 2H, Ar), 7.23–7.22 (m, 2H, Ar), 6.87 (d, *J* = 8.4 Hz, 1H, Ar), 1.60 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.04, 160.27, 159.30, 157.10, 152.19, 145.42, 140.53, 136.92, 133.09, 128.65, 126.28, 124.60, 124.52, 123.37, 117.00, 113.06, 110.71, 98.21, 92.93, 49.69, 8.99 ppm; IR (KBr): $\bar{\nu}$ = 3596, 3198, 1709, 1683 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 406.0595, found 406.0584.

8-Methyl-1′-(prop-2-yn-1-yl)spiro[chromeno[4,3-*b*]isoxazolo[4,5-*e*]pyridine-7,3′-indoline]-2′,6(11*H*)-dione (5e, $C_{24}H_{15}N_3O_4$) White solid; yield: 88%; m.p.: 295–296 °C; R_f = 0.15 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 8.4 Hz, 1H, Ar), 7.69 (t, *J* = 7.6 Hz, 1H, Ar), 7.47–7.29 (m, 3H, Ar), 7.14 (d, *J* = 7.2 Hz, 2H, Ar), 7.01 (t, *J* = 7.6 Hz, 1H, Ar), 4.75–4.70 (m, 1H, CH_2), 4.52–4.48 (m, 1H, CH_2), 3.29 (s, 1H, CH), 1.52 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.66, 160.13, 159.11, 157.25, 152.16, 145.24, 141.11, 134.06, 133.14, 128.82, 124.64, 124.12, 123.37, 123.34, 117.01, 112.92, 108.78, 98.22, 93.15, 77.75, 74.73, 49.13, 29.26, 9.21 ppm; IR (KBr): $\bar{\nu}$ = 3238, 1711, 1683 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 410.1141, found 410.1107.

1′-Allyl-8-methylspiro[chromeno[4,3-*b*]isoxazolo[4,5-*e*]pyridine-7,3′-indoline]-2′,6(11*H*)-dione (5f, $C_{24}H_{17}N_3O_4$) White solid; yield: 89%; m.p.: 266–269 °C; R_f = 0.13 (30% ethyl

acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22 (d, J = 7.6 Hz, 1H, Ar), 7.69 (t, J = 7.6 Hz, 1H, Ar), 7.47–7.37 (m, 2H, Ar), 7.27 (t, J = 7.6 Hz, 1H, Ar), 7.13 (d, J = 6.8 Hz, 1H, Ar), 6.99–6.93 (m, 2H, Ar), 5.89–5.82 (m, 1H, CH), 5.51–5.46 (m, 1H, CH_2), 5.21–5.18 (m, 1H, CH_2), 4.43–4.30 (m, 2H, CH_2), 1.47 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.25, 160.13, 159.10, 157.13, 152.13, 145.20, 142.16, 134.22, 133.10, 131.76, 128.74, 124.61, 123.98, 123.34, 122.93, 118.03, 116.97, 112.93, 108.79, 98.47, 93.25, 49.03, 42.34, 9.08 ppm; IR (KBr): $\bar{\nu}$ = 3142, 1709, 1672 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 412.1297, found 412.1288.

3-Methyl-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione (6a, $C_{22}H_{13}N_3O_4$) Dark red solid; yield: 87%; m.p.: 262 °C; R_f = 0.10 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.72 (s, 1H, CONH), 8.06–8.05 (m, 1H, Ar), 7.81–7.78 (m, 3H, Ar), 7.19–7.17 (m, 1H, Ar), 7.10–7.09 (m, 1H, Ar), 6.91–6.88 (m, 2H, Ar), 1.58 (s, 1H, NH), 1.05–1.01 (m, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.12, 179.24, 178.47, 159.84, 157.23, 141.23, 141.13, 136.06, 135.24, 133.60, 131.56, 130.12, 128.69, 126.26, 125.96, 124.33, 122.23, 115.75, 109.30, 90.00, 49.90, 8.98 ppm; IR (KBr): $\bar{\nu}$ = 3148, 1700, 1658 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 384.0984, found 384.0979.

3-Methyl-5′-nitro-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione (6b, $C_{22}H_{12}N_4O_6$) Dark red solid; yield: 87%; m.p.: 219–221 °C; R_f = 0.01 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.44 (s, 1H, CONH), 8.17–8.02 (m, 3H, Ar), 7.77–7.76 (m, 3H, Ar), 7.10 (d, J = 9.2 Hz, 1H, Ar), 1.61 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.37, 179.11, 179.01, 160.33, 157.07, 147.59, 142.86, 141.93, 136.48, 135.17, 133.70, 131.49, 130.33, 126.32, 126.19, 126.01, 120.42, 114.56, 109.56, 93.03, 49.95, 9.17 ppm; IR (KBr): $\bar{\nu}$ = 3114, 1714, 1658 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 429.0835, found 429.0830.

5′-Chloro-3-methyl-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione (6c, $C_{22}H_{12}ClN_3O_4$) Dark red solid; yield: 84%; m.p.: 224–227 °C; R_f = 0.08 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.8 (s, 1H, NH), 8.07–8.02 (m, 1H, Ar), 7.81–7.75 (m, 3H, Ar), 7.28–7.22 (m, 2H, Ar), 6.92 (d, J = 8.4 Hz, 1H, Ar), 1.68 (s, 1H, NH), 1.63 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.27, 179.21, 178.29, 160.04, 157.15, 141.54, 140.09, 137.77, 135.26, 133.79, 131.57, 130.25, 128.64, 126.30, 124.70, 115.11, 110.80, 93.54, 50.16, 9.09 ppm; IR (KBr): $\bar{\nu}$ = 3490, 3221, 1706, 1690 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 418.0595, found 418.0591.

3-Methyl-1′-(prop-2-yn-1-yl)-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione (6d, $C_{25}H_{15}N_3O_4$) Dark red solid; yield: 84%; m.p.: 246–249 °C; R_f = 0.26 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05–8.01 (m, 1H, Ar), 7.78–7.77 (m, 3H, Ar), 7.35–7.33 (m, 1H, Ar), 7.21–7.14 (m, 2H, Ar), 7.00 (s, 1H, Ar), 4.81–4.76 (m, 1H, –CH), 4.60–4.56 (m, 1H, –CH_2), 3.35 (s, 1H, –CH_2), 1.56 (s, 1H, NH), 1.55 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.07, 179.09, 175.85, 159.90, 157.22, 141.35, 140.61, 135.18, 134.89, 133.63, 131.43, 130.15, 128.78, 126.28, 125.97, 124.33, 123.29, 115.14, 108.80, 93.68, 77.73, 74.84, 49.54, 29.29, 9.26 ppm; IR (KBr): $\bar{\nu}$ = 3277, 1703, 1683, 1676 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 422.1141, found 422.1096.

1′-Allyl-3-methyl-5*H*-spiro[benzo[*g*]isoxazolo[5,4-*b*]quinoline-4,3′-indoline]-2′,5,10(11*H*)-trione (6e, $C_{25}H_{17}N_3O_4$) Dark red solid; yield: 86%; m.p.: 254–256 °C; R_f = 0.28 (30% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07–8.02 (m, 1H, Ar), 7.81–7.76 (m, 3H, Ar), 7.29–7.25 (m, 1H, Ar), 7.18–7.17 (m, 1H, Ar), 7.06–7.04 (m, 1H, Ar), 6.99–6.94 (m, 1H, Ar), 5.98–5.86 (m, 1H, CH), 5.63–5.51 (m, 1H, CH_2), 5.30–5.24 (m, 1H, CH_2), 4.52–4.33 (m, 2H, CH_2), 1.55 (s, 1H, NH), 1.51 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.10, 179.15, 176.47, 159.91, 157.11, 141.68, 141.33, 135.20, 135.09, 133.62, 131.84, 131.49, 130.12, 128.70, 126.27, 126.01, 124.21, 122.91, 118.31, 115.40, 108.83, 93.79, 49.48, 42.41, 9.17 ppm; IR (KBr): $\bar{\nu}$ = 3271, 1706, 1669 cm^{-1}; HRMS (ESI): *m/z* calc. for $[M + H]^+$ 424.1297, found 424.1291.

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