Synthesis of spiro[benzo[*h*]quinoline-7,3'-indolines] via a three-component condensation reaction

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Abstract. An efficient one-pot synthesis of a new series of spiro[benzo[*h*]quinoline-7,3'-indoline] was accomplished simply by the reaction of an isatin, naphthalen-1-amine and a CH-acid (*N,N*-dimethylbarbituric acid, barbituric acid, dimedone or 1,3-indandione) in acetic acid. During this process, the effects of solvent and temperature have been investigated on the yield of reactions.

Keywords. Oxindole; three-component reaction; condensation reaction; spiro compounds.

1. Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process and among the drugs in the clinical market, 68% are heterocycles. Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention.

Multi-component reactions are synthetically important processes in which three or more different starting materials react to give a final product in a one-pot procedure.¹ Such reactions are important tools in modern organic synthesis to generate compound libraries for screening purposes because of their productivity, simple procedures and convergence.² This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in one-pot transformation.

Indole and indoline fragments are important moieties in a large number of natural biologically active compounds,³ and some indolines that are spiroannulated with heterocycles at the 3 position have shown high biological activity.^{4–7} The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.^{8–11} As a result, a number of methods have been reported for the preparation of spirooxindoles.^{12–20}

Among the nitrogen heterocycles, quinoline ring is an important structural motif found in several natural products many of which display biological activities

such as antibacterial, antifungal, antitumour agents,^{21–23} psychotropic,²⁴ antiallergenic,²⁵ antiinflammatory,²⁶ and estrogenic activities.²⁷

Pyrimidine and its derivatives have been studied for over a century for their chemical and biological significance. They have been reported to be antibacterial, antiviral and antitumour agents.²⁸ A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities.^{29–33}

In continuation of our investigations on MCRs,^{34–36} we have developed an efficient method for the synthesis of spiro[benzo[*h*]quinoline-7,3'-indoline] **4** by a one-pot, three-component condensation reaction of naphthalen-1-amine **1** and a CH-acid **2** with isatin **3** in acetic acid at 80°C (scheme 1).

2. Experimental

2.1 Materials and methods

The chemicals used in this work were purchased from Merck, Fluka and Sigma-Aldrich Chemical Companies. Melting points were determined on an Electrothermal 9100 apparatus. IR spectra were recorded on a FT Infrared Spectroscopy instrument JASCO, FT/IR-6300 model as KBr discs. The ¹H NMR and ¹³C NMR, spectra were recorded on a Bruker-AVANCE 400 MHz NMR instrument using DMSO-*d*₆ as solvent and TMS as internal standard. Elemental analyses were performed using a Heraeus CHNS Rapid analyzer.

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Scheme 1. Synthesis of spiro[benzo[*h*]quinoline-7,3'-indoline] **4**.

2.2 General procedure for the synthesis of 8*H*-spiro[benzo[*h*]quinoline-7,3'-indolines] **4a–n**

A solution of an isatin (**3**) (1 mmol), a C-H acid derivative (**2**) (1 mmol), and naphthalen-1-amine (**1**) (1 mmol) was heated at 80°C in acetic acid (5 mL) for 24 h. After completion of the reaction as indicated by TLC (MeOH/AcOEt, 1:4), the residue was filtered and washed successively with gl. acetic acid and CHCl_3 (3 $\times$ 10 mL). The crude product thus obtained was crystallized from MeOH or EtOH and dried at room temperature. The final product was obtained as a powder.

2.2a 9,11-Dimethyl-8*H*-spiro[benzo[*h*]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',10(9*H*)-dione (**4a**): White powder, 0.353 g (86%). M.p. 293–295°C. IR (KBr) cm^{-1} : 3418, 3237, 2959, 1706, 1642, 1535, 1489, 1254, 749. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 2.99 (*s*, 3H, CH_3), 3.64 (*s*, 3H, CH_3), 6.62 (*d*, $^3J = 7.6$ Hz, 1H, CH_{arom}), 6.81–7.19 (*m*, 3H, 3CH_{arom}), 7.35 (*d*, $^3J = 8.0$ Hz, 1H, CH_{arom}), 7.42 (*d*, $^3J = 8.4$ Hz, 1H, CH_{arom}), 7.46–7.56 (*m*, 2H, 2CH_{arom}), 7.84 (*d*, $^3J = 8.4$ Hz, 1H, CH_{arom}), 8.17 (*d*, $^3J = 8.4$ Hz, 1H, CH_{arom}), 9.38 (*s*, 1H, NH_{amine}), 11.14 (*s*, 1H, NH_{amide}) ppm. ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 27.3, 30.2, 48.9, 90.8, 110.4, 119.1, 121.5, 121.6, 122.5, 123.8, 126.4, 128.1, 128.2, 128.3, 132.9, 133.3, 135.1, 136.8, 144.4, 146.4, 150.5, 150.7, 160.3, 181.9 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_3$: C, 70.23; H, 4.42; N, 13.65; Found: C, 70.49; H, 4.31; N, 13.72.

2.2b 5',9,11-Trimethyl-11,12-dihydro-8*H*-spiro[benzo[*h*]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',10(9*H*)-dione (**4b**): White powder. 0.339 g (80%). M.p. 300–303°C. IR (KBr) cm^{-1} : 3284, 3201, 2962, 1712, 1631, 1534, 1504, 750. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 2.02 (*s*, 3H, CH_3), 2.99 (*s*, 3H, CH_3),

3.56 (*s*, 3H, CH_3), 6.43 (*s*, 1H, CH_{arom}), 6.99 (*d*, $^3J = 6.8$ Hz, 1H, CH_{arom}), 7.12 (*d*, $^3J = 8.4$ Hz, 1H, CH_{arom}), 7.28 (*d*, $^3J = 8.4$ Hz, 1H, CH_{arom}), 7.42 (*d*, $^3J = 8.0$ Hz, 1H, CH_{arom}), 7.47–7.57 (*m*, 2H, CH_{arom}), 7.85 (*d*, $^3J = 8.0$ Hz, 1H, CH_{arom}), 8.19 (*d*, $^3J = 8.0$ Hz, 1H, CH_{arom}), 9.29 (*s*, 1H, NH_{amine}), 11.12 (*s*, 1H, NH_{amide}) ppm. ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 20.3, 27.3, 30.1, 52.1, 83.9, 119.1, 121.4, 121.6, 122.6, 125.5, 125.6, 126.2, 128.3, 128.9, 132.6, 132.9, 133.2, 136.9, 150.5, 159.6, 160.3, 181.5, 181.9 ppm. Anal. Calcd for $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_3$: C, 70.74; H, 4.75; N, 13.20; Found: C, 70.41; H, 4.79; N, 13.27.

2.2c 5'-Iodo-9,11-dimethyl-11,12-dihydro-8*H*-spiro[benzo[*h*]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',10(9*H*)-dione (**4c**): White powder. 0.477 g (89%). M.p. 350–353°C. IR (KBr) cm^{-1} : 3408, 3266, 2951, 1709, 1634, 1524, 1478, 752. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 3.09 (*s*, 3H, CH_3), 3.73 (*s*, 3H, CH_3), 6.69–8.29 (*m*, 9H, CH_{arom}), 9.48 (*s*, 1H, NH_{amine}), 11.21 (*s*, 1H, NH_{amide}) ppm. ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 27.4, 30.2, 52.8, 86.65, 119.1, 119.6, 121.4, 121.8, 122.5, 124.1, 125.8, 125.9, 128.4, 132.9, 133.1, 134.1, 135.2, 136.8, 145.2, 145.9, 147.2, 148.8, 150.4, 181.6 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{IN}_4\text{O}_3$: C, 53.75; H, 3.19; N, 10.45; Found: C, 53.81; H, 3.22; N, 10.39.

2.2d 9,11-Dimethyl-5'-nitro-11,12-dihydro-8*H*-spiro[benzo[*h*]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',10(9*H*)-dione (**4d**): White powder. 0.437 g (96%). M.p. 320–323°C. IR (KBr) cm^{-1} : 3408, 3225, 1721, 1689, 1652, 1527, 1410, 1336, 754. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 3.08 (*s*, 3H, CH_3), 3.75 (*s*, 3H, CH_3), 6.71 (*d*, $^3J = 7.2$ Hz, 1H, CH_{arom}), 7.14 (*d*, $^3J = 6.8$ Hz, 1H, CH_{arom}), 7.53 (*d*, $^3J = 8.0$ Hz, 1H, CH_{arom}), 7.61 (*t*, $^3J = 6.4$ Hz, 1H, CH_{arom}), 7.68 (*t*, $^3J = 7.6$ Hz, 1H, CH_{arom}), 7.78 (*s*, 1H, CH_{arom}), 7.87

(d , $^3J = 8.0$ Hz, 1H, CH_{arom}), 8.17 (d , $^3J = 8.8$ Hz, 1H, CH_{arom}), 8.31 (d , $^3J = 8.0$ Hz, 1H, CH_{arom}), 8.99 (s , 1H, NH_{amine}), 11.32 (s , 1H, NH_{amide}). ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 27.5, 30.1, 52.1, 86.1, 109.5, 116.9, 119.2, 122.4, 123.0, 123.1, 124.6, 125.5, 126.4, 127.0, 128.0, 130.3, 132.8, 139.5, 142.6, 147.1, 148.3, 150.7, 160.0, 180.5 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{N}_5\text{O}_5$: C, 63.29; H, 3.76; N, 15.38; Found: C, 63.51; H, 3.82; N, 15.21.

2.2e 8*H*-spiro[benzo[h]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',8,10(9*H*,11*H*,12*H*)-trione (**4e**): Cream powder. 0.309 g (81%). Mp: 280–283°C. IR (KBr) cm^{-1} : 3412, 3330, 3245, 3063, 1726, 1685, 1644, 1553, 1484, 749. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 6.59–7.94 (m , 10H, 10 CH_{arom}), 9.27 (s , 1H, NH_{amine}), 10.11 (s , 1H, NH_{amide}), 10.52 (s , 1H, NH_{amide}), 10.69 (s , 1H, NH_{amide}) ppm. ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 51.7, 85.1, 109.8, 117.5, 120.5, 122.3, 122.4, 123.7, 124.3, 124.5, 127.2, 128.4, 128.9, 129.9, 133.0, 139.5, 141.8, 146.4, 150.2, 162.3, 180.7 ppm. Anal. Calcd for $\text{C}_{22}\text{H}_{14}\text{N}_4\text{O}_3$: C, 69.10; H, 3.69; N, 14.65; Found: C, 68.92; H, 3.70; N, 14.58.

2.2f 10,10-dimethyl-10,11-dihydro-8*H*-spiro[benzo[*c*]acridine-7,3'-indoline]-2',8(9*H*,12*H*)-dione (**4f**): White powder, 0.276 g (70%). Mp: 285–288°C. IR (KBr) cm^{-1} : 3243, 3064, 2951, 2871, 1707, 1599, 1519, 1502, 1384. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 1.04 (s , 3H, CH_3), 1.08 (s , 3H, CH_3), 1.99 (d , $^2J = 16.1$ Hz, 1H, CH_aH_b), 2.13 (d , $^2J = 16.1$ Hz, 1H, CH_aH_b), 2.68 (d , $^2J = 16.6$ Hz, 1H, CH_aH_b), 2.68 (d , $^2J = 16.6$ Hz, 1H, CH_aH_b), 6.67 (d , $^3J = 8.0$ Hz, 1H, CH_{arom}), 6.76–6.82 (m , 2H, 2 CH_{arom}), 6.87 (d , $^3J = 7.6$ Hz, 1H, CH_{arom}), 7.09 (t , $^3J = 7.2$ Hz, 1H, CH_{arom}), 7.37 (d , $^3J = 8.8$ Hz, 1H, CH_{arom}), 7.52 (t , $^3J = 7.2$ Hz, 1H, CH_{arom}), 7.59 (t , $^3J = 8.4$ Hz, 1H, CH_{arom}), 7.78 (d , $^3J = 8.0$ Hz, 1H, CH_{arom}), 8.46 (d , $^3J = 8.4$ Hz, 1H, CH_{arom}), 9.36 (s , 1H, NH_{amine}), 10.40 (s , 1H, NH_{amide}) ppm. ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 18.5, 21.0, 26.9, 28.5, 32.2, 51.6, 105.8, 108.9, 118.6, 121.4, 122.1, 123.1, 124.2, 126.1, 126.3, 127.3, 128.0, 130.2, 132.5, 140.2, 141.2, 152.6, 180.9, 192.6 ppm. Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_2$: C, 79.16; H, 5.62; N, 7.10; Found: C, 79.37; H, 5.69; N, 6.99.

2.2g Spiro[benzo[h]indeno[1,2-*b*]quinoline-7,3'-indoline]-2,8(13*H*)-dione (**4g**): Red powder. 0.308 g (77%). M.p. 289–290°C. IR (KBr) cm^{-1} : 3362, 3240, 1701, 1621, 1591, 1530, 740. ^1H -NMR (400 MHz,

Table 1. One-pot synthesis of 9,11-dimethyl-8*H*-spiro[benzo[h]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',8,10(9*H*,11*H*,12*H*)-trione at different solvents^a.

Entry	Solvent	Yield (%) ^b	Yield (%) ^c
1	Water	11	24
2	Methanol	35	48
3	Acetic acid	64	86
4	Ethyl acetate	23	40
5	Acetonitrile	56	75
6	Dichloromethane	18	29
7	THF	44	69
8	Solvent-free	0	–

^aIsatin (1 mmol), *N,N*-dimethylbarbituric acid (1 mmol), naphthalen-1-amine (1 mmol) in solvent (5 mL), 24 h

^bIsolated yield at rt

^cIsolated yield at reflux conditions

$\text{DMSO}-d_6$) δ : 6.65–8.76 (m , 14H, CH_{arom}), 10.38 (s , 1H, NH_{amine}), 10.68 (s , 1H, NH_{amide}) ppm. ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 50.8, 103.4, 109.6, 119.9, 120.1, 120.6, 121.8, 122.2, 123.4, 124.6, 124.8, 124.9, 126.6, 126.8, 128.2, 128.3, 130.5, 131.3, 131.5, 132.9, 133.7, 136.3, 137.9, 141.4, 156.1, 179.5, 189.2 ppm. Anal. Calcd for $\text{C}_{27}\text{H}_{16}\text{N}_2\text{O}_2$: C, 80.99; H, 4.03; N, 7.00; Found: C, 80.90; H, 4.08; N, 7.12.

2.2h 5'-Methyl spiro[benzo[h]indeno[1,2-*b*]quinoline-7,3'-indoline]-2',8(13*H*)-dione (**4h**): Red powder. 0.290 g (70%). M.p. 295–298°C. IR (KBr) cm^{-1} : 3390, 3263, 2917, 1703, 1624, 1590, 1529, 766. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ : 2.09 (s , 3H, CH_3), 6.66 (d , $^3J = 8.4$ Hz, 1H, CH_{arom}), 6.75 (s , 1H, CH_{arom}), 6.87 (d , $^3J = 7.6$ Hz, 1H, CH_{arom}), 7.01 (d , $^3J = 8.0$ Hz,

Table 2. Effect of temperature and time in one-pot synthesis of 9,11-dimethyl-8*H*-spiro[benzo[h]pyrimido[4,5-*b*]quinoline-7,3'-indoline]-2',8,10(9*H*,11*H*,12*H*)-trione^a.

Entry	Temperature (°C)	Time(h)	Yield (%) ^b
1	100	24	86
2	80	24	86
3	65	24	79
4	50	24	74
5	Rt	24	65
6	80	48	86
7	80	18	80
8	80	12	30
9	80	6	10
10 ^c	80	24	86

^aIsatin (1 mmol), *N,N*-dimethylbarbituric acid (1 mmol), naphthalen-1-amine (1 mmol) in acetic acid (5 mL)

^bIsolated yield

^cIn the presence of *p*-TsOH catalyst (10 mol%)

1H, CH_{arom}), 7.25 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.40 (*t*, ³*J* = 7.6 Hz, 1H, CH_{arom}), 7.53(*d*, ³*J* = 8.0 Hz, 1H, CH_{arom}), 7.55 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.61 (*t*, ³*J* = 7.6 Hz, 1H, CH_{arom}), 7.72 (*t*, ³*J* = 7.6 Hz, 1H, CH_{arom}), 7.86 (*d*, ³*J* = 8.0 Hz, 1H, CH_{arom}), 8.14 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 8.74 (*d*, ³*J* = 8.8 Hz, 1H, CH_{arom}), 10.36 (*s*, 1H, NH_{amine}), 10.57 (*s*, 1H, NH_{amide}) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.4, 50.9, 103.6, 109.3, 120.1, 120.6, 121.8, 123.4, 124.8, 124.9, 125.0, 126.5, 126.8, 128.2, 128.6, 130.4, 131.2, 131.3, 131.5, 132.8, 133.7, 136.3, 138.1, 138.8, 156.0, 179.6, 189.2 ppm. Anal. Calcd for C₂₈H₁₈N₂O₂: C, 81.14; H, 4.38; N, 6.76; Found: C, 81.29; H, 4.41; N, 6.68.

(400 MHz, DMSO-*d*₆) δ: 6.66 (*d*, ³*J* = 8.8 Hz, 1H, CH_{arom}), 6.96 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 7.15 (*s*, 1H, CH_{arom}), 7.27 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.39-7.75 (*m*, 6H, CH_{arom}), 7.89 (*d*, ³*J* = 8.0 Hz, 1H, CH_{arom}), 8.17 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 8.76 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 10.43 (*s*, 1H, NH_{amine}), 10.82 (*s*, 1H, NH_{amide}) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 51.0, 102.8, 111.7, 113.9, 119.2, 120.2, 120.8, 121.9, 123.5, 124.7, 124.9, 126.6, 126.9, 127.3, 128.2, 130.6, 131.2, 131.5, 131.6, 132.9, 133.7, 136.2, 139.9, 140.8, 156.3, 179.2, 189.2 ppm. Anal. Calcd for C₂₇H₁₅BrN₂O₂: C, 67.66; H, 3.15; N, 5.84; Found: C, 68.00; H, 3.16; N, 5.79.

2.2i 5'-Methoxyspiro[benzo[*h*]indeno[1,2-*b*]quinoline-7,3'-indoline]-2',8(13*H*)-dione (**4i**): Orange powder. 0.314 g (73%). Mp: 306–309°C. IR (KBr) cm⁻¹: 3293, 3236, 2834, 1698, 1630, 1593, 1534, 1200, 762. ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 3.60 (*s*, 3H, OCH₃), 6.55 (*s*, 1H, CH_{arom}), 6.66 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 6.80 (*d*, ³*J* = 6.4 Hz, 1H, CH_{arom}), 6.91 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 7.26 (*d*, ³*J* = 6.8 Hz, 1H, CH_{arom}), 7.41 (*t*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.54 (*m*, 2H, CH_{arom}), 7.61 (*t*, ³*J* = 6.8 Hz, 1H, CH_{arom}), 7.72 (*t*, ³*J* = 7.6 Hz, 1H, CH_{arom}), 7.87 (*d*, ³*J* = 8.0 Hz, 1H, CH_{arom}), 8.15 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 8.74 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 10.35 (*s*, 1H, NH_{amine}), 10.48 (*s*, 1H, NH_{amide}) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 51.3, 55.3, 103.4, 110.0, 111.2, 113.2, 119.9, 120.1, 120.6, 121.8, 123.4, 124.7, 124.9, 126.5, 126.8, 128.2, 130.4, 131.3, 131.5, 132.9, 133.8, 134.7, 136.3, 139.1, 155.4, 156.1, 179.4, 189.2 ppm. Anal. Calcd for C₂₈H₁₈N₂O₃: C, 78.13; H, 4.21; N, 6.51; Found: C, 77.90; H, 4.18; N, 6.54.

2.2k 5'-Chloro spiro[benzo[*h*]indeno[1,2-*b*]quinoline-7,3'-indoline]-2',8(13*H*)-dione (**4k**): Orange powder. 0.356 g (82%). M.p. 305–308°C. IR (KBr) cm⁻¹: 3385, 3334, 1706, 1686, 1592, 1527, 736. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 6.65–7.29 (*m*, 5H, CH_{arom}), 7.42 (*t*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.55 (*t*, ³*J* = 7.6 Hz, 2H, CH_{arom}), 7.62 (*t*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.72 (*t*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 7.89 (*d*, ³*J* = 7.6 Hz, 1H, CH_{arom}), 8.17 (*d*, ³*J* = 7.2 Hz, 1H, CH_{arom}), 8.76 (*d*, ³*J* = 8.8 Hz, 1H, CH_{arom}), 10.43 (*s*, 1H, NH_{amine}), 10.82 (*s*, 1H, NH_{amide}) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 51.1, 102.8, 111.1, 119.2, 120.2, 120.8, 121.9, 123.5, 124.6, 124.9, 126.2, 126.6, 126.9, 128.2, 128.3, 130.5, 131.5, 131.6, 132.9, 133.7, 136.2, 139.6, 140.4, 156.3, 179.3, 189.2 ppm. Anal. Calcd for C₂₇H₁₅ClN₂O₂: C, 74.57; H, 3.48; N, 6.44; Found: C, 74.77; H, 3.46; N, 6.40.

2.2j 5'-Bromo spiro[benzo[*h*]indeno[1,2-*b*]quinoline-7,3'-indoline]-2',8(13*H*)-dione (**4j**): Red powder. 0.382 g (80%). M.p. 335–337°C. IR (KBr) cm⁻¹: 3397, 3267, 1708, 1634, 1591, 1528, 718. ¹H-NMR

2.2l 5'-Nitro spiro[benzo[*h*]indeno[1,2-*b*]quinoline-7,3'-indoline]-2',8(13*H*)-dione (**4l**): Red powder. 0.374 g (84%). M.p. 312–315°C. IR (KBr) cm⁻¹: 3489, 3267, 1710, 1665, 1623, 1596, 1532, 1335, 717. ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 6.68 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 7.21 (*d*, ³*J* = 8.4 Hz, 1H, CH_{arom}), 7.27

Scheme 2. One-pot synthesis of 8*H*-spiro[benzo[*h*]quinoline-7,3'-indolines].

Table 3. Synthesis of 8*H*-spiro[benzo[h]quinoline-7,3'-indolines]^a.

Entry	Isatin	CH-acid	Product	Yield(%) ^b
1			4a	86
2			4b	80
3			4c	89
4			4d	96
5			4e	81
6			4f	70
7			4g	77
8			4h	70
9			4i	73

Table 3. (Continued).

Entry	Isatin	CH-acid	Product	Yield(%) ^b
10			4j	80
11			4k	82
12			4l	84
13			4m	65
14			4n	68

^aIsatin (1 mmol), CH-acid (1 m mol) and naphthalen-1-amine (1 m mol) and at 80°C^bIsolated yield

(*d*, $^3J = 6.8$ Hz, 1H, CH_{arom}), 7.43 (*t*, $^3J = 7.2$ Hz, 1H, CH_{arom}), 7.55 (*m*, 2H, CH_{arom}), 7.64 (*t*, $^3J = 7.2$ Hz, 1H, CH_{arom}), 7.73–8.24 (*m*, 5H, CH_{arom}), 8.80 (*d*, $^3J = 8.8$ Hz, 1H, CH_{arom}), 10.53 (*s*, 1H, NH_{amine}), 11.43 (*s*, 1H, NH_{amide}) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ : 50.9, 102.2, 109.9, 118.5, 120.1, 120.3, 121.0, 121.9, 123.5, 124.5, 125.2, 125.9, 126.8, 127.1, 128.3, 130.7, 131.6, 131.7, 133.1, 133.7, 136.2, 138.3, 142.7, 148.1, 156.5, 179.9, 189.2 ppm. Anal. Calcd for C₂₇H₁₅N₃O₄: C, 72.80; H, 3.39; N, 9.43; Found: C, 73.02; H, 3.36; N, 9.40.

2.2m 5',7'-Dimethyl spiro[benzo[h]indeno[1,2-b]quinoline-7,3'-indoline]-2',8(13H)-dione (4m): Red powder. 0.278 g (65%). M.p. 303–306°C. IR (KBr) cm⁻¹: 3439, 3269, 2921, 2861, 1697, 1627, 1591, 1529, 759. ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 2.07 (*s*, 3H, CH₃), 2.31 (*s*, 3H, CH₃), 6.57 (*s*, 1H, CH_{arom}), 6.67

(*d*, $^3J = 8.8$ Hz, 1H, CH_{arom}), 6.83 (*s*, 1H, CH_{arom}), 7.23 (*d*, $^3J = 6.8$ Hz, 1H, CH_{arom}), 7.39 (*t*, $^3J = 7.2$ Hz, 1H, CH_{arom}), 7.50–7.62 (*m*, 3H, CH_{arom}), 7.71 (*t*, $^3J = 7.6$ Hz, 1H, CH_{arom}), 7.86 (*d*, $^3J = 8.0$ Hz, 1H, CH_{arom}), 8.15 (*d*, $^3J = 7.2$ Hz, 1H, CH_{arom}), 8.74 (*d*, $^3J = 8.4$ Hz, 1H, CH_{arom}), 10.34 (*s*, 1H, NH_{amine}), 10.62 (*s*, 1H, NH_{amide}) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ : 16.4, 20.4, 51.1, 103.7, 118.5, 120.1, 120.3, 120.5, 121.8, 122.4, 123.4, 124.7, 125.0, 126.5, 126.7, 128.2, 130.1, 130.3, 131.0, 131.2, 131.5, 132.8, 133.7, 136.3, 137.4, 138.0, 155.9, 180.0, 189.2 ppm. Anal. Calcd for C₂₉H₂₀N₂O₂: C, 81.29; H, 4.70; N, 6.54; Found: C, 81.35; H, 4.62; N, 6.61.

2.2n 1'-Acetyl spiro[benzo[h]indeno[1,2-b]quinoline-7,3'-indoline]-2',8(13H)-dione (4n): Orange powder. 0.301 g (68%). M.p. 310–312°C. IR (KBr) cm⁻¹: 3352, 3051, 1719, 1689, 1631, 1593, 1528, 1260, 761.

Scheme 3. Mechanism for the formation of the 8*H*-spiro[benzo[*h*]quinoline-7,3'-indolines] **4**.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ : 2.63 (*s*, 3H, CH_3), 6.78–8.83 (*m*, 14H, CH_{arom}), 10.59 (*s*, 1H, NH_{amine}) ppm. $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ : 26.3, 51.3, 103.4, 115.6, 119.3, 120.4, 121.2, 122.0, 123.4, 124.8, 125.2, 125.4, 125.8, 126.8, 127.2, 128.3, 128.6, 130.8, 131.4, 131.8, 133.0, 133.4, 135.8, 136.0, 138.8, 155.9, 170.8, 178.8, 189.2 ppm. Anal. Calcd for $\text{C}_{29}\text{H}_{18}\text{N}_2\text{O}_3$: C, 78.72; H, 4.10; N, 6.33; Found: C, 78.81; H, 4.08; N, 6.40.

3. Results and discussion

Using the synthesis of **4a** as a model reaction, the reaction conditions were optimized with respect to the solvents, reaction temperature and the presence or absence of the catalyst. This study showed that among the investigated solvents, gl. Acetic acid was found to be the best (table 1), the yields were better when the reactions were done at 80°C for 24 h (table 2), and the use of *p*-TsOH to catalyse the reaction was ineffective.

Then, to find out the scope of this approach various C-H acids such as *N,N*-dimethyl barbituric acid (**2a**), barbituric acid (**2b**), dimedone (**2c**) and 1,3-indandione (**2d**) and isatin derivatives **3a–h** were used in the presence of naphthalen-1-amine (scheme 2). Corresponding 8*H*-spiro[benzo[*h*]pyrimido[4,5-*b*]quinoline-7,3'-indolines] **4a–n** were synthesized by the one-pot, three component condensation in good yields at 80°C

temperature in acetic acid for 24 h. The yields and product structures have been given in table 3.

The structures of products **4a–n** were deduced from their IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. For example, the IR spectrum of **4a** showed absorptions at 3418, 3237 (NH), 2953 (CH_3), 1726, 1706, 1642 (C=O), 1535 (C=C), 1489 and 1254 (C-N) cm^{-1} , indicating the presence of the functional groups in the proposed structure. The $^1\text{H-NMR}$ spectrum of **4a** exhibited two singlet signals for two CH_3 groups at δ 2.99 and 3.64 ppm. Signals of eight aromatic H-atoms appeared at δ 6.62–8.17 ppm. The signals for the H-atoms of the NH amine and amide groups appeared as two singlet at δ 9.38 and 11.14 ppm. The ^1H -decoupled $^{13}\text{C-NMR}$ spectrum of **4a** showed 24 distinct resonances in agreement with the suggested structures.

Although we have not established an exact mechanism for the formation of the 8*H*-spiro[benzo[*h*]quinoline-7,3'-indolines] **4** but a reasonable possibility is shown in scheme 3.

4. Conclusion

In summary, a simple and efficient three-component condensation reaction for the synthesis of 8*H*-spiro[benzo[*h*]quinoline-7,3'-indolines], having two or three important heterocyclic parts, using easily available starting materials has been developed. The

one-pot nature, good yield and easy work-up procedure are among the advantages of this new method.

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