J. Biol. Chem. Chron. **2019**, **5***(1)*, 52-60
ISSN (Print): 2454 – 7468
ISSN (Online): 2454 – 7476
www.eresearchco.com/jbcc/

Ultrasound Assisted Regioselective Synthesis of Polyhydrospiro [indoline-3,3'-pyrrolizine]-2-one Library via Multicomponent Cycloaddition Reaction

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(Received 30 Jan, 2019; Accepted 01 Mar, 2019; Published 12 Mar, 2019)

ABSTRACT: Present work demonstrates the ultrasound mediated synthesis of new Hexahydrospiro[indoline-3,3'-pyrrolizine]-2-one derivatives in excellent yields via [3+2] cycloaddtion reaction in regioselective manner under ultrasonic irradiation. Multicomponent reaction of substituted 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-one, isatin, L-proline was utilized for synthesis of spiro framework in regioselective manner at room temperature. All the synthesized hexahydrospiro molecules were characterized by ^{1}H and ^{13}C NMR, IR spectra, mass spectra and elemental analysis. Regioselective nature of reaction was explained on the basis of secondary orbital interactions. We have developed a very simple and facile methodology that has great importance in synthetic chemistry.

Keywords: Spiropyrrolidine; Ultrasonic irradiation; Dehydroacetic acid; Isatin; L-Proline; Multicomponent reaction and Cycloaddition.

INTRODUCTION: In continuation of work from our research group in field of multicomponent reaction towards synthesis of biologically active nucleus, this time we have reported a facile method for synthesis of new spirooxindole analogues under ultrasonic irradiation.[1-4] Spiro compounds fused with indole nucleus is an important object of investigation due to 1) Its structural diversity 2) Diverse biological activities related with the prototype 3) Its Structural complexity in molecule to provide an attractive target for synthetic chemist. We have earlier reported the several methodologies involving multicomponent reaction for synthesis of antidiabetic molecules.[5] Spiro compounds with attached indole moiety having all carbon quaternary stereogenic center has attracted synthetic organic chemists due to its fascinating structure and biological importance.[6] Spiroindoles and their derivatives have structural similarity with the core unit of many naturally occurring molecules (Figure 1) that possess significant biological activities, which include spasmolitic, diuretic, anticoagulant, anticancer, and antianaphylactic activities.[7-10] In the past several years, significant advances have been achieved on the development of new synthetic methods to access spirooxindole derivatives.[11-13] One carbon atom which common to two rings in spirocyclic systems is chiral and spiro carbon is one of the important criteria of the biological activities.[14-15] The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[16] The spirooxindole ring system forms the core structure of many pharmacological agents and alkaloids.[17] For example, spirotryprostatin (Fig. 1), a natural product isolated from the fermentation of *Aspergillus funigatus*, has been identified as a novel inhibitor of microtubule assembly. Natural product isopteropodine (Fig. 1) has been shown to modulate the function of muscarinic and serotonin receptors. It has been observed that incorporation of more than one bioactive heterocyclic moiety into a single framework may result into the production of novel heterocycles with enhanced bioactivity.[18] Spirooxindoles have been identified to posses as aldose reductase, poliovirus and rhinovirus 3C-proteinase inhibitors.[19-20] All these excellent pharmacological properties and structurally complex nature of these spiro compounds, prompted us to describe green synthesis of new bioisosetric analogues of natural spiropyrrolidines via [3+2] cycloaddition reaction under ultrasonic reaction condition.

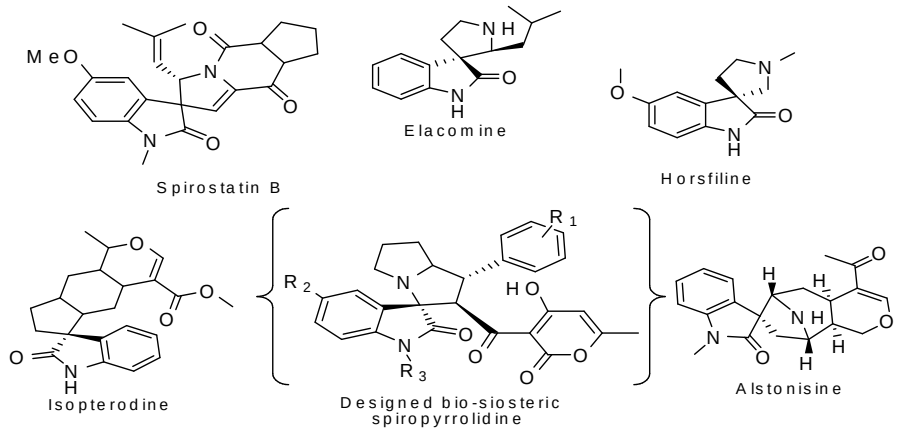


Figure 1: Representatives of spiroindole containing compounds.

MATERIALS AND METHODS: All the reactions were carried out at room temperature, under ultrasounic irradiation. Unless otherwise specified, all the reagents were purchased from Sigma-Aldrich Chemical Co, and were used directly without further any purification. NMR spectra were obtained using the Brucker DRX 300MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were taken on VARIAN FT-IR spectrometer as KBr pellets (when solid). Elemental analysis was performed using a Perkin Elmer Autosystem XL Analyzer. Melting points were measured using a COMPLAB melting-point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

General procrdure for synthesis of compounds (4a-y) (method A): Isatin (147mg, 1.0 mmol), L-proline (115mg, 1.0 mmol), and chalcone derivatives (1.0 mmol) were mixed with 10 ml ethanol and placed in ultrasonic bath at room temperature upto completion of reaction. Progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated under reduced pressure and precipitated by adding in ice water. Solid residue was filtered through buchner funnel under vacuum and recrystallized in absolute ethanol.

Analytical data:

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(3-methoxyphenyl)-1-propyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4a): White solid; mp= 180^{0}C; ν_{max}(KBr) 3621, 3020, 2971, 1720, 1604, 1216, 1043 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.97 (s, 1H), 7.21 (s, 1H), 7.20-7.04 (m, 4H), 6.80-6.72 (m, 3H), 5.68 (s, 1H), 4.91 (d,1H, J = 9.4 Hz), 4.57 (t, 1H, J = 8.14 Hz), 4.48 (t, 1 H, J = 9.9 Hz), 3.79 (s, 3H), 3.64 (t, 2H, *J* = 7.5 Hz), 2.58 (t, 1 H, J = 7.62 Hz,), 2.28 (s, 3H), 2.14-1.73 (m, 5H), 1.22-1.15 (m, 2H), 1.00 (t, 3H, *J* = 4.3 Hz); ^{13}C NMR (75MHz, $CDCl_3$,): 13.7, 20.9, 22.5, 23.2, 25.3, 33.4, 38.9, 41.6, 47.4, 49.7, 51.2, 55.8, 57.4, 63.4, 65.8, 72.3, 101.5, 103.1, 111.5, 114.8, 116.1, 122.5, 126.6, 129.2, 134.4, 140.9, 144.3, 157.8, 163.2, 184.7, 204.4; MS (ES): m/z (%) = 529.1(100) $[M+1]^+$. Anal. Calcd for $C_{31}H_{32}N_2O_6$ C, 70.44; H, 6.10; N, 5.30% Found: C, 70.02; H, 6.05; N, 5.20.

1-Benzyl-1'-(2-chlorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4b): Yellow solid; mp= 191^{0}C %.; ν_{max}(KBr) 3424, 3059, 2953, 1722, 1605, 1234, 1075 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.02 (s, 1H), 8.21 (d, 1H, *J* = 7.4 Hz,), 7.43-7.38 (m, 2H), 7.36-7.26 (m, 5H), 7.16-7.03 (m, 3H), 6.80 (t, 1H, *J* = 7.5 Hz), 6.61 (d, 1H, *J* = 7.8 Hz), 5.71 (s, 1H), 5.22-4.76 (m, 3H), 4.42-4.47 (m, 1H), 3.31 (q, 1H, *J* = 8.7 Hz,), 2.66 (t, 1H, *J* = 8.2 Hz), 2.17 (s, 1H), 2.06 (s, 3H), 2.04-1.97 (m, 3H), 1.91-1.67 (m, 1H). ^{13}C (75 MHz $CDCl_3$) 20.4, 24.3, 27.3, 44.6, 47.4, 49.7, 67.3, 72.3, 73.8, 101.2, 101.5, 109.3, 121.6, 125.6, 126.1, 127.3, 127.5, 128.4, 128.8, 129.2, 129.7, 130.3, 134.2, 136.5, 139.2, 145.9, 169.2, 179.5, 180.4, 205.4; MS (ES): m/z (%) = 581 (100) $[M+1]^+$. Anal. Calcd for $C_{34}H_{29}ClN_2O_5$ C, 70.28; H, 5.03; N, 4.82 Found: C, 70.14; H, 5.01; N, 4.96 .

1'-(4-Fluorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4c): Yellow solid; mp= 184^{0}C ν_{max}(KBr) 3439, 3031, 2779, 1726, 1659, 1231, 1035 cm^{-1}. ^{1}H (300 MHz, $CDCl_3$): 10.94 (s, 1H), 7.55 (d, 1H, J = 7.36 Hz), 7.20 (d, 2H, J = 6.6 Hz), 7.07 (t, 2H, J = 5.78 Hz), 6.67-6.63 (m, 3H), 5.90 (s, 1H), 5.61 (t, 1H, J = 11.4

Hz), 5.01 (q, 1H, J = 7.38 Hz), 4.32 (d, 1H, J = 7.36 Hz), 3.15-3.11 (m, 1H), 2.82 (t, 1H, J = 7.38 Hz), 2.27(s, 3H), 2.05-1.75 (m, 3H), 1.60-1.25 (m, 2H). ^{13}C (75 MHz $CDCl_3$) 19.6, 20.9, 21.6, 22.4, 24.1, 25.2, 28.5, 49.3, 51.7, 63.3, 72.6, 102.1, 108.6, 114.7, 115.6, 116.9, 122.2, 131.3, 133.4, 133.8, 134.6, 144.8, 152.9, 161.3, 184.6, 205.4; MS (ES): m/z (%) = 475 (100) $[M+1]^+$. Anal. Calcd for $C_{27}H_{23}FN_2O_5$ C, 68.35; H, 4.89; N, 5.90 Found: C, 68.21; H, 4.72; N, 5.97 %.

1'-(4-Fluorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1-propyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4d): White solid; mp= 181^{0}C ν_{max}(KBr) 3437, 3020, 1720, 1607, 1512, 1216, 1043 cm^{-1}; ^{1}H (300 MHz $CDCl_3$) 10.96 (s, 1H), 7.58 (d, 1H, J = 7.3Hz), 7.25 (t, 2H, J = 8.07 Hz,), 7.11-7.01 (m, 2H), 6.67 (t, 2H, J = 8.5 Hz,), 6.63 (d, 1H, J = 7.74 Hz,), 5.91 (s, 1H), 5.70 (t, 1H, J = 9.24 Hz,), 5.05 (q, 1H, J = 7.6 Hz,), 4.32 (d, 1H, *J* = 11.7 Hz), 3.81-3.62 (m, 1H), 3.21-3.17 (m, 2H), 2.83 (t, 1H, J = 6.4 Hz), 2.28 (s, 3H), 2.18-1.89 (m, 3H), 1.41-1.27 (m, 3H), 0.64 (t, 3H, J = 7.41 Hz,). ^{13}C (75 MHz $CDCl_3$):19.7, 22.7, 23.9, 27.9, 27.5, 29.7, 33.5, 46.3, 49.2, 55.1, 64.3, 102.4, 108.7, 115.2, 116.4, 121.7, 126.4, 129.7, 132.4, 133.7, 138.2, 144.4, 148.3, 153.3, 176.9, 183.5, 205.1; MS (ES): m/z (%) = 517 (100) $[M+1]^+$. Anal. Calcd for $C_{30}H_{29}FN_2O_5$ C, 69.75; H, 5.66; N, 5.42 Found: C, 69.63; H, 5.42; N, 5.61 %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(4-methoxyphenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4e): Yellow solid; mp= 186^{0}C ν_{max}(KBr) 3432, 3020, 2970, 1727, 1606, 1410, 1216, 1034 cm^{-1}; ^{1}H (300 MHz $CDCl_3$) 11.04 (s, 1H), 8.10 (d, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 7.95 Hz), 7.44-7.34 (m, 2H), 7.15-6.93 (2 H, m), 6.74-6,67 (m, 2H), 6.31 (s, 1H), 5.64 (t, 1H, J = 8.4 Hz), 5.21 (d, 1H, J = 7.94 Hz), 4.96 (d, 1H, J = 6.5 Hz), 3.61 (s, 3H), 3.22-3.13 (m, 2H), 2.30 (s, 3H), 1.90-1.70 (m, 3H), 1.23-1.05 (m, 2H); ^{13}C (75 MHz $CDCl_3$): 21.4, 23.5, 28.4, 32.4, 42.9, 44.9, 47.9, 53.3, 59.7, 61.9, 67.4, 72.5, 107.4, 108.3, 117.5, 118.7, 123.6, 125.2, 126.1, 127.2, 127.7, 155.8, 178.6, 204.1; MS (ES): m/z (%) = 487 (100) $[M+1]^+$. Anal. Calcd for $C_{28}H_{26}N_2O_6$ C, 69.12; H, 5.39; N, 5.76%.; Found: C, 69.18; H, 5.47; N, 5.62 %.

1-Butyl-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(3-hydroxyphenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4f): White solid; mp= 167^{0}C ν_{max}(KBr) cm^{-1}. ^{1}H (300 MHz $CDCl_3$) 11.03 (s, 1H), 8.20 (d, 1H, J = 11.6 Hz), 7.99 (s, 1H), 7.59-7.55 (m, 2H), 7.06-6.88 (m, 2H), 6.85 (d, 2H, J = 9.4 Hz), 5.78 (s, 1H), 4.77 (d, 1H, J = 9.0 Hz), 4.63-4.55 (m, 1H), 4.10 (t, 1H, J = 8.7 Hz), 3.79 (q, 2H, J = 7.6 Hz), 3.18-3.06 (m, 1H), 2.29 (s, 3H), 2.09-1.79 (m, 3H), 1.75-1.47 (m, 3H), 1.04 (t, 4H, J = 9.2 Hz), 0.93-0.85 (m, 3H). ^{13}C (75 MHz $CDCl_3$): 11.8, 13.3, 20.8, 22.7, 25.3, 28.7, 31.2, 34.1, 34.4, 36.3, 51.5, 53.2, 59.4, 74.2, 74.9, 101.2, 105.4, 109.3, 112.2, 112.8, 118.0, 121.2, 126.7, 130.8, 132.6, 133.2, 146.2, 149.8, 165.4, 185.2, 208.0; MS (ES): m/z (%) = 529 (100) $[M+1]^+$. Anal. Calcd for $C_{31}H_{32}N_2O_6$ C, 69.12; H, 5.39; N, 5.76 Found: C, 69.02; H, 5.28; N, 5.81 %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(2-methoxyphenyl)-1-propyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4g): White solid; mp= 182^{0}C; ν_{max}(KBr) 3448, 3057, 2951, 1718, 1643, 1241, 1144 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.98 (s, 1H), 7.93 (d, 1H, J = 6.2 Hz), 7.28-7.14 (m, 3H), 7.01 (t, 1H, J = 9.6 Hz), 6.86-6.75 (m, 3H), 5.70 (s, 1H), 5.00 (d, 1H, J = 9.2 Hz), 4.71 (t, 1H, J = 6.3 Hz), 4.61-4.52 (m, 1H), 3.83 (s, 3H), 3.69 (q, 2H, J = 6.2 Hz), 3.43-3.31 (m, 1H), 3.24-3.16 (m, 1H), 2.18 (s, 3H), 2.06-2.02 (m, 3H), 2.01-1.77 (m, 3H), 1.04 (t, 3H, J = 7.4 Hz); ^{13}C (75 MHz, $CDCl_3$) 12.3, 16.4, 21.1, 23.4, 24.8, 42.7, 49.3, 53.9, 57.4, 59.1, 68.4, 101.5, 108.4, 116.1, 118.2, 118.3, 119.6, 120.2, 121.2, 121.7, 123.6, 133.9, 134.1, 134,2, 138.1, 146.3, 158,1, 163.2, 174.3, 196.8; MS (ES): m/z (%) = 543 (100) $[M+1]^+$. Anal. Calcd for $C_{31}H_{32}N_2O_6$ C, 70.44; H, 6.10; N, 5.30 Found: C, 70.35; H, 5.99; N, 5.38. %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(4-nitrophenyl)-1-propyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4h): White solid; mp= 163^{0}C; ν_{max}(KBr) 3621, 3020, 2972, 1718, 1604, 1216, 1041 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.97 (s, 1H), 8.19 (d, 2H, J = 8.7 Hz), 8.15 (d, 2H, J = 8.6 Hz), 7.26-7.20 (m, 1H), 7.04 (d, 1H, *J* = 7.4 Hz), 6.81 (t, 2H, J = 8.2 Hz), 5.72 (s, 1 H), 4.91 (d, 1H, J = 9.2 Hz), 4.73-4.61 (m, 1H), 4. 17 (t, 1H, J = 9.4 Hz), 3.69 (t, 2H, J = 7.5 Hz), 3.28-3.12 (m, 1H), 2.65 (t, 1H, J = 6.3 Hz), 2.05 (s, 3H), 1.80-1.62 (m, 4H), 1.25-1.20 (m, 2H), 1.04 (t, 3H, J = 7.4 Hz). ^{13}C (75 MHz $CDCl_3$) 15.3, 18.2, 21.3, 25.6, 27.7, 28.7, 28.9, 33.1, 33.4, 38.2, 46.5, 49.2, 56.4, 69.7, 73.9, 108.1, 108.8, 110.7, 113.8, 114.6, 119.0, 123.2, 123.7, 128.1, 131.2, 136.2, 140.7, 148.2, 163.3, 189.2, 208.5; MS (ES): m/z (%) = 544 (100) $[M+1]^+$. Anal. Calcd for $C_{30}H_{29}N_3O_7$ C, 66.29; H, 5.38; N, 7.73 Found: C, 66.32; H, 5.41; N, 7.66 %.

1'-(3,4-Dimethoxyphenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1-propyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4i): White solid; mp= 174^{0}C; ν_{max}(KBr) 3622, 3021, 2970, 1719, 1602, 1216, 1035 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.02 (s, 1H), 7.26-7.19 (m, 2H), 7.14-7.07 (m, 3H), 6.84-6.74 (m, 3H), 5.69 (s, 1H), 4.93 (d, 1H, J = 9.3 Hz), 4.53-4.41 (m, 1H), 4.04-3.98 (m, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.67 (t, 2H, J = 7.5 Hz), 3.21 (q, 1H, J = 8.5 Hz), 2.61 (t, 1H, J = 7.4 Hz), 2.05 (s, 3H), 1.82-1.75 (m, 2H), 1.25-1.20 (m, 3H), 1.03 (t, 3H, J = 6.9 Hz); ^{13}C (75 MHz $CDCl_3$) 14.3, 21.6, 22.3, 24.9, 26.6, 28.3, 40.1, 49.6, 53.4, 64.6, 71.9, 101.6, 103.5, 117.9, 119.4, 121.1, 124.6, 135.1, 138.1, 143.3, 144.3, 145.8, 147.3, 152.4, 152.8, 163.5, 183.3, 203.6; MS (ES): m/z (%) = 559 (100) [M+1]$^+$. Anal. Calcd for $C_{32}H_{34}N_2O_7$ C, 66.80; H, 6.13; N, 5.01 Found: C, 66.63; H, 6.02; N, 5.14 %.

1-Benzyl-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(3-methoxyphenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4j): Yellow solid; mp= 169^{0}C; ν_{max}(KBr) 3436, 3024, 2972, 1717, 1615, 1410, 1216, 1034 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.01 (s, 1H), 7.46-7.34 (m, 3H), 7.12-7.01 (m, 5H), 6.80-6.76 (m, 2H), 6.60-6,54 (m, 3H), 5.92 (s, 1H), 5.24-5.03 (m, 2H), 4.80 (d, 1H, J = 12 Hz), 4.62-4.33 (m, 2H), 4.06 (t, 1H, J = 9.4 Hz), 3.27-3.12 (m, 2H), 2.69-2.45 (m, 1H), 2.29 (s, 3H), 1.63-1.31 (m, 3H), 0.87-0.75 (m, 2H). ^{13}C (75 MHz $CDCl_3$) 20.4, 20.7, 24.2, 30.4, 49.4, 51.0, 54.3, 55.5, 64.6, 66.6, 70.2, 72.3, 101.5, 109.5, 113,2, 120.9, 121.5, 126.3, 126.6, 127.1, 127.9, 128.6, 128.7, 129.4, 130.3, 132.4, 134.7, 138.1, 144.7, 146.5, 148.4, 153.2, 164.3, 183.1, 201.3; MS (ES): m/z (%) = 577 (100) [M+1]$^+$. Anal. Calcd for $C_{35}H_{32}N_2O_6$ C, 72.90; H, 5.59; N, 4.86 Found: C, 72.82; H, 5.51; N, 4.92 %.

1-Ethyl-1'-(4-fluorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4k): White solid; mp= 182^{0}C; ν_{max}(KBr) 3422, 3020, 2976, 1707, 1612, 1216, 1044 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.96 (1 H, s), 7.58 (d, 2H, J = 7.4 Hz), 7.27-7.16 (m, 2H), 7.12-7.00 (m, 2H), 6.69 (t, 2H, J = 8.5 Hz), 5.91 (s, 1H), 5.70-5.61 (m, 1H), 4.31 (d, 1H, J = 11.6 Hz), 3.70-3.63 (m, 1H), 3.21-3.04 (m, 2H), 2.86-2.51 (m, 2H), 2.05 (s, 3H), 2.06-1.78 (m, 4H), 1.62-1.48 (m, 3H). ^{13}C (75 MHz $CDCl_3$) 20.7, 22.7, 27.9, 28.5, 29.7, 30.5, 46.1, 48.2, 55.1, 64.3, 101.3, 108.1, 114.4, 114.7, 121.4, 126.4, 129.7, 130.4, 133.6, 138.1, 142.4, 146.3, 153.2, 176.2, 183.1, 204.1; MS (ES): m/z (%) = 503 (100) [M+1]$^+$. Anal. Calcd for $C_{29}H_{27}FN_2O_5$ C, 69.31; H, 5.42; N, 5.57 Found: C, 69.25; H, 5.38; N, 5.61 %.

1-Butyl-1'-(4-fluorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4l): White solid; mp= 186^{0}C; ν_{max}(KBr) 3460, 3057, 2963, 1720, 1612, 1226, 1002 cm^{-1}. ^{1}H (300 MHz, $CDCl_3$) 10.98 (s, 1H), 7.59 (d, 2H, J = 7.4 Hz), 7.28 (t, 2H, J = 8.2 Hz), 7.13 (t, 1H, J = 6.8 Hz), 6.75-6.63 (m, 3H), 5.96 (s, 1H), 5.67 (t, 1H, J = 7.1 Hz), 5.11-4.98 (m, 1H), 4.34 (d, 1H, J = 12.1 Hz), 3.67-3.60 (m, 2H), 3.44-3.37 (m, 3H), 3.23 (m, 2H), 2.28 (t, 1H, J = 6.8 Hz), 2.29 (s, 3H), 2.19-1.97 (m, 2H), 1.45-1.43 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz) ^{13}C (75 MHz $CDCl_3$) 13.3, 14.3, 23.9, 26.7, 28.7, 31.7, 31.9, 32.1, 32.3, 34.3, 49.5, 53.1, 58.9, 72.7, 72.9, 103.2, 106.1, 108.0, 114.1, 114.8, 115.0, 120.7, 123.7, 128.1, 131.2, 133.3, 148.9, 149.8, 169.3, 183.2, 204.0; MS (ES): m/z (%) = 531 (100) [M+1]$^+$. Anal. Calcd for $C_{31}H_{31}FN_2O_5$ C, 70.17; H, 5.89; N, 5.28 Found: C, 70.03; H, 5.80; N, 5.32 %.

1-(3-Hydroxy-4-methoxyphenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4m): Yellow solid; mp= 206^{0}C; N, 5.57 %; ν_{max}(KBr) 3625, 3020, 2973, 1725, 1607, 1216, 1039 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.96 (s, 1H), 7.64 (s, 1H), 7.45-7.39 (m, 2H), 7.07-7.03 (m, 2H), 6.97 (d, 1H, J = 7.68 Hz), 6.81 (d, 1H, J = 8.76 Hz), 5.91 (s, 1H), 5.04 (s, 2H), 4.91-4.88 (m, 1H), 4.43-4.39 (m, 1H), 4.15 (t, 1H, J = 9.6 Hz), 3.33-3.21 (m, 1H), 2.63 (t, 1H, J = 7.4 Hz), 2.28 (s, 1H), 2.01 (s, 3H), 1.81-1.75 (m, 2H), 1.29-1.23 (m, 2H), 0.89-0.84 (m, 2H). ^{13}C (75 MHz $CDCl_3$) 21.4, 23.2, 27.8, 29.3, 49.7, 52.1, 57.2, 62.8, 72.1, 101.6, 108.3, 114.2, 116.3, 116.4, 118.6, 123.1, 124.6, 128.1, 132.7, 133.3, 139.4, 149.1, 149.6, 153.2, 162.4, 183.6, 208.1; MS (ES): m/z (%) = 503 (100) [M+1]$^+$. Anal. Calcd for $C_{28}H_{26}N_2O_7$ C, 66.92; H, 5.22Found: C, 66.74; H, 5.13; N, 5.69 %.

1-Ethyl-1'-(3-hydroxy-4-methoxyphenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4n): White solid; mp= 201^{0}C; ν_{max}(KBr) 3355, 2932, 1711, 1621, 1275, 1029 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.94 (s, 1H), 7.27-7.16 (m, 3H), 7.10 (d, 1H, J = 7.5Hz), 7.01 (d, 1H, J = 11.6 Hz), 6.84-6.76 (m, 3H), 5.94 (s, H), 4.90 (d, 1H, J = 9.3 Hz), 4.49 (t, 1H, J = 6.1 Hz), 3.97 (s, 3H), 3.86-3.73 (m, 2H), 3.20 (q, 1H, J = 7.2 Hz), 2.27 (s, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.85-1.78 (m, 2H), 1.33 (t,

3H, J = 7.2 Hz). ^{13}C (75 MHz $CDCl_3$) 12.3, 14.2, 26.8, 27.1, 29.3, 29.7, 30.1, 32.3, 35.3, 49.5, 52.1, 56.4, 70.2, 72.9, 101.1, 101.4, 108.7, 111.1, 114.6, 115.0, 121.7, 122.7, 126.1, 129.2, 133.2, 144.7, 147.2, 169.4, 181.2, 201.0; MS (ES): m/z (%) = 531 (100) $[M+1]^+$. Anal. Calcd for $C_{30}H_{30}N_2O_7$ C, 67.91; H, 5.70; N, 5.28 Found: C, 67.84; H, 5.61; N, 5.31 %;

1'-(4-Chlorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4o): Yellow solid; mp= 176^{0}C; ν_{max}(KBr) 3420, 3020, 1540, 1423, 1216, 1044 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.97 (s, 1H), 7.49 (d, 2H, J = 8.9 Hz), 7.21-7.01 (m, 3H), 6.97-6.79 (m, 1H), 6.63 (d, 2H, J = 8.0 Hz), 5.98 (1 H, s), 5.62-5.51 (1 H, m), 4.95-4.65 (1 H, m), 4.26 (1 H, d, J 11.8 Hz), 3.65 (1 H, q, J 7.02 Hz), 3.34 (t, 1H, J = 4.75 Hz), 2.16 (s, 3H), 2.02-1.93 (m, 1H), 1.86-1.68 (m, 3H), 1.20-1.14 (m, 1H). ^{13}C (75 MHz $CDCl_3$) 20.5, 22.1, 23.1, 24.8, 49.2, 53.6, 63.1, 74.6, 101.3, 103.4, 116.7, 123.3, 128.3, 129.3, 129.8, 130.6, 133.2, 134.8, 144.9, 152.8, 162.6, 164.1, 169.3, 183.2, 206.8; MS (ES): m/z (%) = 491 (100) $[M+1]^+$. Anal. Calcd for $C_{27}H_{23}ClN_2O_5$ C, 66.06; H, 4.72; N, 5.71 Found: C, 66.09; H, 4.76; N, 5.66 %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(3-hydroxyphenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4p): Yellow solid; mp= 181^{0}C; ν_{max}(KBr) 3413, 3020, 1844, 1419, 1216, 1044 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.04 (s, 1H), 7.18-7.11 (m, 4H), 7.06 (d, 1H, J = 7.29 Hz), 6.94 (d, 1H, J = 7.47 Hz), 6.84-6.71 (m, 2H), 5.78 (s, 1H), 4.90 (d, 1H, J = 9.51 Hz), 4.42 (q, 1H, J = 7.02 Hz), 3.34 (t, 1H, J = 4.75 Hz), 3.11-3.03 (m, 2H), 2.16 (s, 3H), 2.23 (s, 3H), 2.02-1.93 (m, 2H), 1.38-1.32 (m, 1H); ^{13}C (75 MHz $CDCl_3$) 17.1, 20.3, 24.5, 26.3, 38.4, 40.9, 45.3, 46.8, 53.3, 58.4, 62.9, 67.2, 70.3, 107.4, 108.3, 118.5, 118.7, 124.2, 124.6, 126.1, 126.3, 126.6, 155.8, 175.6, 201.4; MS (ES): m/z (%) = 473 (100) $[M+1]^+$. Anal. Calcd for $C_{27}H_{24}N_2O_6$ C, 68.63; H, 5.12; N, 5.93 Found: C, 68.55; H, 5.03; N, 6.08 %.

1'-(4-Fluorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4q): Yellow solid; mp= 186^{0}C; ν_{max}(KBr) 3444, 2925, 2856, 1717, 1609, 1231 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.98 (s, 1H), 7.57 (d, 1H, J = 7.3 Hz), 7.55 (s, 1H), 7.28-7.03 (m, 3H), 6.73 (t, 2H, J = 8.7 Hz), 6.62 (d, 1H, J = 7.83 Hz), 5.91 (s, 1H), 5.67-5.55 (m, 1H), 5.11-4.94 (m, 1H), 4.32 (d, 1H, J = 11.76 Hz), 3.31-3.18 (m, 1H), 2.93 (s, 3H), 2.83 (t, 1H, J = 6.4 Hz), 2.28 (s, 3H), 2.19-1.73 (m, 2H), 1.41-1.37 (m, 2H); ^{13}C (75 MHz $CDCl_3$) 14.1, 20.7, 22.6, 25.4, 26.9, 28.1, 29.6, 31.2, 50.2, 50.5, 55.0, 64.3, 101.2, 108.2, 114.7, 121.3, 123.8, 125.6, 129.4, 129.6, 130.6, 134.2, 144.9, 169.5, 183.4, 204.2; MS (ES): m/z (%) = 489 (100) $[M+1]^+$. Anal. Calcd for $C_{28}H_{25}FN_2O_5$ C, 68.84; H, 5.16; N, 5.73 Found: C, 68.76; H, 5.09; N, 5.82 %.

1-Benzyl-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4r): Yellow solid; mp= 197^{0}C; ν_{max}(KBr) 3424, 3020, 1718, 1517, 1453, 1216, 1104 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.02 (s, 1H), 8.36-8.15 (m, 5H), 7.95-7.78 (m, 4H), 7.22 (t, 1H, J = 7.1 Hz), 7.08 (d, 1H, J = 8.31 Hz), 6.83 (q, 2H, J = 7.5 Hz), 6.01 (s, 1H), 5.73 (s, 2H), 4.86 (d, 1H, J = 9.2 Hz), 4.61-4.55 (m, 1H), 4.23 (t, 1H, J = 8.41 Hz), 3.36-3.14 (m, 2H), 2.67 (t, 1H, J = 9.2 Hz), 2.31 (s, 3H), 2.05-1.88 (m, 2H), 1.25-1.14 (m, 1H). ^{13}C (75 MHz $CDCl_3$) 20.4, 22.3, 26.5, 27.7, 45.2, 48.3, 63.2, 70.4, 101.4, 108.3, 120.4, 122.1, 124.4, 124.7, 128.1, 129.3, 129.8, 130.1, 132.1, 133.0, 134.1, 146.2, 170.5, 180.3, 204.1; MS (ES): m/z (%) = 592 (100) $[M+1]^+$. Anal. Calcd for $C_{34}H_{29}N_3O_7$ C, 69.03; H, 4.94; N, 7.10 Found: C, 68.91; H, 4.87; N, 7.14 %.

1'-(2-Chlorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4s): Yellow solid; mp= 188^{0}C; ν_{max}(KBr) 3532, 3020, 2970, 1718, 1606, 1410, 1217, 1031 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.95 (s, 1H), 8.17 (d, 1H, J = 8.31 Hz), 7.35-7.09 (m, 5H), 6.86-6.75 (m, 2H), 5.71 (s, 1H), 4.94-4.88 (m, 2H), 4.48-4.36 (m, 1H), 3.46-3.38 (m, 1H), 3.27 (s, 3H), 2.68 (t, 1H, J = 8.61 Hz), 2.05 (s, 3H), 1.97-1.62 (m, 2H), 1.24-1.22 (m, 2H). ^{13}C (75 MHz $CDCl_3$) 20.4, 23.8, 26.4, 26.8, 46.3, 49.7, 66.6, 71.8, 73.5, 100.5, 101.7, 108.2, 121.1, 124.9, 126.8, 127.6, 127.7, 129.1, 129.3, 130.6, 134.8, 138.5, 145.5, 160.6, 168.8, 179.7, 180.2, 205.2; MS (ES): m/z (%) = 505 (100) $[M+1]^+$. Ana. calcd. for $C_{28}H_{25}ClN_2O_5$: C, 66.60; H, 4.99; N, 5.55 Found: C, 66.51; H, 4.88; N, 5.61 %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(2-methoxyphenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4t): Yellow solid; mp= 159^{0}C; ν_{max}(KBr) 3621, 3020, 2923, 1721, 1216, 1042 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.02 (s, 1H), 7.84 (d, 1H, J = 7.2 Hz), 7.22-7.09 (m, 3H), 7.00 (t, 2H, J = 7.4 Hz), 6.88-6.78 (m, 3H), 5.76 (s, 1H), 5.01 (d, 1H, J = 9.42 Hz), 4.70 (t,

1H, J = 9.7 Hz), 4.48 (t, 1H, J = 7.7 Hz), 3.83 (3 H, s), 3.36-3.67 (m, 2H), 2.65 (t, 1H, J = 4.6 Hz), 2.19 (s, 3H), 2.01-1.79 (m, 2H), 1.26-0.86 (m, 1H). ^{13}C (75 MHz $CDCl_3$) 17.7, 21.4, 24.5, 28.4, 33.8, 40.9, 46.2, 46.9, 53.3, 58.7, 62.9, 67.4, 70.3, 107.4, 108.2, 118.5, 118.7, 124.1, 124.2, 126.1, 126.6, 126.7, 155.8, `178.6; MS (ES): m/z (%) = 487 (100) $[M+1]^+$. Anal. Calcd for $C_{28}H_{26}N_2O_6$ C, 69.12; H, 5.39; N, 5.76 Found: C, 68.08; H, 5.21; N, 5.84 %.

1-Butyl-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-5-nitro-1'-p-tolyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4u): White solid; mp= 186^{0}C; ν_{max}(KBr) 3422, 3020, 2927, 1724, 1609, 1216, 1077 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.00 (s, 1H), 8.20 (d, 1H, J = 12.6 Hz), 7.96 (d, 1H, J = 3.36 Hz), 7.15 (d, 2H, J = 12 Hz), 7.03 (d, 1H, J = 11.5 Hz), 6.85 (d, 1H, J = 10.53 Hz), 6.71-6.67 (m, 2H), 5.76 (s, 1H), 4.79 (d, 1H, J = 14.04 Hz), 4.51-4.44 (m, 2H), 4.05 (t, 1H, J = 15.3 Hz), 3.64 (q, 2H, J = 11.5 Hz), 3.19-3.11 (m, 2H), 2.62-2.54 (m, 2H), 2.28 (s, 3H), 2.19 (s, 3H), 1.81-1.64 (m, 2H), 1.45-1.34 (m, 2H). 0.91 (t, 3H, J = 7.81 Hz), ^{13}C (75 MHz, $CDCl_3$) 14.2, 18.7, 21.7, 25.4, 25.8, 27.9, 28.5, 31.7, 33.5, 44.1, 50.2, 54.1, 68.0, 101.4, 108.2, 114.7, 116.1, 123.4, 127.4, 130.3, 133.3, 133.8, 138.3, 146.4, 148.3, 156.3, 175.2, 184.1, 205.5 ppm. MS (ES): m/z (%) = 572 (100) $[M+1]^+$. Anal. Calcd for $C_{32}H_{33}N_3O_7$ C, 67.24; H, 5.82; N, 7.35 Found: C, 67.14; H, 5.71; N, 7.42 %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-(4-hydroxyphenyl)-1-propyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4v): White solid; mp= 159^{0}C; ν_{max}(KBr) 3621, 3020, 2923, 1721, 1216, cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.97 (s, 1H), 7.23-7.04 (m, 5H), 6.85-6.71 (m, 3H), 5.71 (s, 1H), 4.92 (d, 1H, J = 9.8 Hz), 4.28-4.17 (m, 2H), 4.02 (t, 1H, J = 7.4 Hz), 3.65 (t, 2H, J = 7.2 Hz), 3.27-3.14 (m, 3H), 2.63 (t, 1H, J = 6.42 Hz), 2.06 (s, 3H), 2.03-1.74 (m, 4H), 1.02 (t, 3H, J = 9.6 Hz), ^{13}C (75 MHz $CDCl_3$) 13.2, 18.7, 21.7, 23.4, 27.6, 28.0, 31.0, 33.0, 44.1, 51.2, 54.1, 66.3, 101.3, 108.1, 114.27, 118.4, 123.4, 129.4, 129.7, 133.3, 133.7, 138.1, 146.4, 148.3, 152.3, 175.2, 183.6, 205.4; MS (ES): m/z (%) = 515 (100) $[M+1]^+$. Anal. Calcd for $C_{30}H_{30}N_2O_6$ C, 70.02; H, 5.88; N, 5.44 Found: C, 69.94; H, 5.72; N, 5.53 %.

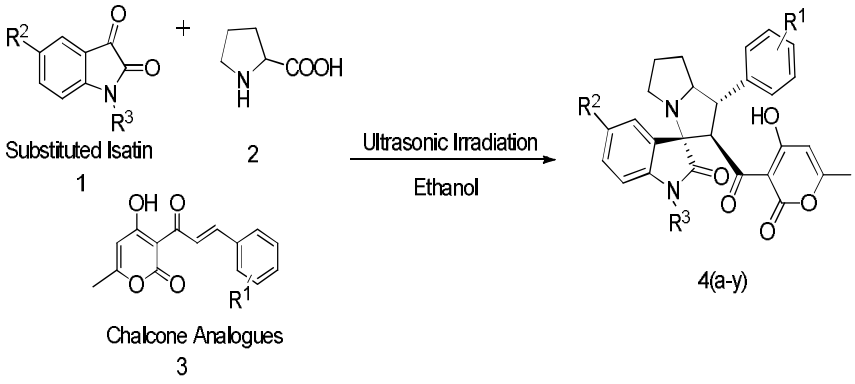
1'-(3-Chlorophenyl)-2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4w): Yellow solid; mp= 184^{0}C; ν_{max}(KBr) 3642, 3120, 2970, 1718, 1626, 1452, 1207, 1031 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 10.97 (s, 1H), 8.20 (d, 1H, J = 8.31 Hz), 7.32-7.07 (m, 5H), 6.88-6.79 (m, 2H), 5.73 (s, 1H), 4.92-4.86 (m, 2H), 4.46-4.34(m, 1H), 3.48-3.40 (m, 2H), 2.66 (t, 1H, J = 8.61 Hz), 1.99 (s, 3H), 1.95-1.60 (m, 3H), 1.23 (s, 1H). ^{13}C (75 MHz $CDCl_3$) 21.7, 24.8, 27.3, 47.3, 50.7, 67.6, 72.9, 74.5, 101.9, 102.7, 109.2, 122.1, 125.9, 127.8, 128.3, 128.7, 130.3, 130.7, 131.6, 135.8, 139.5, 146.5, 161.3, 169.8, 170.7, 181.2, 206.2; MS (ES): m/z (%) = 491 (100) $[M+1]^+$. Anal. Calcd for $C_{27}H_{23}ClN_2O_5$ C, 66.06; H, 4.72; N, 5.71 Found: C, 65.97; H, 4.61; N, 5.80 %.

2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1-methyl-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4x): White solid; mp= 181^{0}C; ν_{max}(KBr) 3641, 3050, 2982, 1718, 1624, 1217, 1031 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.01 (s, 1H), 8.21 (d, 2H, J = 8.7 Hz), 8.19 (d, 2H, J = 8.6 Hz), 7.23-7.17 (m, 2H), 7.01 (d, 1H, J = 7.4 Hz), 6.78 (t, 2H, J = 8.2 Hz), 5.69 (s, 1H), 4.88 (d, 1H, J = 9.2 Hz,), 4.73-4.61 (m, 1H), 4. 17 (t, 1H, J = 9.4 Hz), 3.28-3.12 (m, 1H), 2.62 (t, 1H, J = 6.3 Hz), 2.04 (s, 3H), 1.77-1.59 (m, 2H), 1.25-1.20 (m, 4H),. ^{13}C (75 MHz, $CDCl_3$): 21.3, 24.1, 28.7, 27.2, 27.7, 32.1, 32.3, 37.2, 47.5, 50.2, 57.4, 70.2, 74.9, 109.2, 110.1, 111.7, 112.1, 113.0, 118.0, 122.2, 122.7, 127.1, 130.2, 135.3, 141.7, 147.8, 162.3, 188.2, 207.5; MS (ES): m/z (%) = 516 (100) $[M+1]^+$. Anal. Calcd for $C_{28}H_{25}N_3O_7$ C, 66.24; H, 4.89; N, 8.15 Found: C, 66.15; H, 5.80; N, 7.72%. %.

2'-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4y): Yellow solid; mp= 147^{0}C; ν_{max}(KBr) 3429, 3041, 2789, 1726, 1659, 1227, 1035 cm^{-1}. ^{1}H (300 MHz, $CDCl_3$): 10.98 (s, 1H), 7.48 (d, 2H, J = 7.36 Hz), 7.24 (d, 2H, J = 6.6 Hz), 7.11 (t, 2H, J = 5.78 Hz), 6.68-6.61 (m, 3H), 5.95 (s, 1H), 5.58 (t, 1H, J = 11.4 Hz), 4.97 (q, 1H, J = 7.38 Hz), 4.36 (d, 1H, J = 7.36 Hz), 3.19-3.14 (m, 1H), 2.79 (t, 1H, J 7.38 Hz), 2.28 (s, 3H), 2.02-1.78 (m, 3H), 1.64-1.31 (m, 2H). ^{13}C (75 MHz $CDCl_3$) 19.8, 21.9, 22.4, 22.9, 23.1, 24.7, 26.5, 46.1, 51.7, 64.8, 73.8, 108.1, 108.3, 115.7, 115.9, 116.0, 122.1, 131.3, 133.1, 133.8, 134.6, 144.8, 146.9, 163.1, 183.4, 204.2; MS (ES): m/z (%) = 457 (100) $[M+1]^+$. Anal. Calcd for $C_{27}H_{24}N_2O_5$ C, 71.04; H, 5.30; N, 6.14 Found: C, 70.92; H, 5.19; N, 6.21 %.

RESULTS AND DISCUSSION: We used different substituted 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-one (Chalcone analogues) as substrate for preparation of spiro derivatives. All the chalcone de-

rivatives used were synthesized by condensation of dehydroacteic acid and substituted benzaldehydes via claisen-schmidt condensation reaction by our earlier reported protocol.[21-22] Then we make our efforts to develop a greener synthetic protocol for synthesis of spirooxindole analogues. Our first objective was to find optimum reaction condition. We started our study in search of best solvent for synthesis of spiropyrrolidines (4a-y). To achieve this goal the reaction of (E)-4-hydroxy-3-(3-(2-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (3a), isatin (1) and L-proline (2) was taken as the model reaction. Various solvents as methanol, dichloromethane, ethanol, acetonitrile, chloroform, benzene and DMSO were explored to check the feasibility of reaction. We found product 4a was formed in excellent yield in ethanol under ultrasonic conditions. Whereas yield of product was not satisfactory with other solvents, even at refluxing condition and prolonged reaction time. Hence ethanol was chosen as the solvent for reaction. The results are summarized in table 1.



Scheme 1: Synthesis of new Spirooxindole under ultrasonic irradiation.

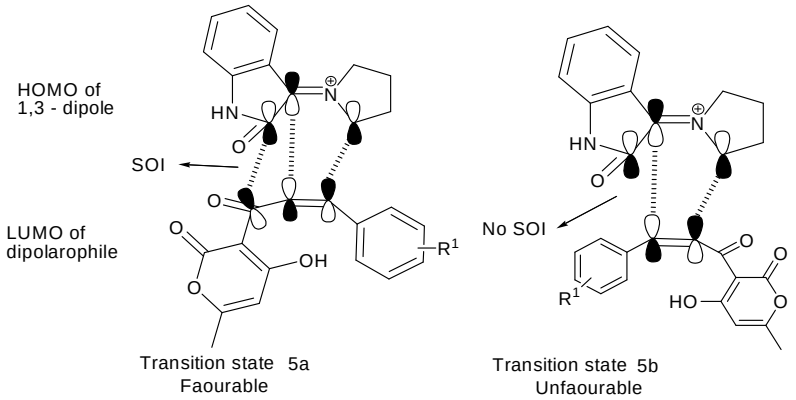


Figure 2: Plausible transition states for 1,3-dipolar cycloaddition reaction.

After optimizing appropriate solvent for reaction, to verify general procedure for synthesis of spirooxindole we carried out reaction with different 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-one derivatives (3a-y), isatin (1) and L-proline (2) under ultrasonic reaction conditions to afford a series of new spiroindoles (4a-y) in excellent yields. Results are summarized in Table 1.

The structures of products were confirmed by spectroscopic methods (^{1}HNMR, ^{13}C NMR, IR, Mass spectroscopy and elemental analysis). All the spectral details were in good support with the illustrated structure of spiroindole derivatives. This cycloaddition reaction proceeds via intermediate formation of azomathine ylide (Figure 2). The regioselectivity of synthesized spiroindole derivatives were explained on the basis of secondary orbital interaction. It is evident from figure 2 that the approach of ylide to dipolarophile can lead to formation of transition state 5a and 5b leading to product 4(a-y), but predominantly forms transition state 5a. This can be attributed to considering regioselective approach of HOMO of dipole to the LUMO of dipolarophile in path-A with secondary orbital interaction (SOI) between orbital of carbonyl group in dipolarophile with those of dipole. This secondary orbital interaction is not possible in other path-B due to opposite orientation of phenyl ring. Hence there was predominant formation of product 5a is more favorable in comparison to 5b.

After characterizing the synthesized spirooxindole derivatives, to explore the effect of substituent on the reactivity of the cycloaddition reaction we used various substitutions at phenyl ring of Isatins to prepare a 25 member library of spirooxindole analogues. In process of synthesis of compound library it was found that the substituent with negative inductive effect tends to facilitate the reaction. As with the methoxy groups at the R^1 position decrease the reaction rate to such a extent that reaction does not complete even after prolonged reaction time and product formed in low yield. Whereas with electron withdrawing groups such as nitro and halogens at that positions activates the reaction and it completed within 3 hrs at room temperature.

Table 1: Synthesis of hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one derivatives.

S. No.	Compound	R^1	R^2	R^3	Room Temperature (under ultrasonic radiation)		M.P. (^oC)
					Time (hrs)[c]	Yield (%)[b]	
1	4a	3-OMe	H	$(CH_2)_2CH_3$	3	81	180
2	4b	2-Cl	H	CH_2Ph	2.5	86	191
3	4c	4-F	H	H	2	90	184
4	4d	4-F	H	$(CH_2)_2CH_3$	2	88	181
5	4e	4-OMe	H	H	2	92	186
6	4f	3-OH	H	$(CH_2)_3CH_3$	2	81	167
7	4g	2-OMe	H	$(CH_2)_2CH_3$	2	83	182
8	4h	4-NO_2	H	$(CH_2)_2CH_3$	1.5	84	163
9	4i	3,4-$(OCH_3)_2$	H	$(CH_2)_2CH_3$	2.5	88	174
10	4j	3-OMe	H	CH_2Ph	2	87	169
11	4k	4-F	H	CH_2CH_3	2	94	182
12	4l	4-F	H	$(CH_2)_3CH_3$	2	94	186
13	4m	3-OH,4-OCH_3	H	H	2.5	92	206
14	4n	3-OH,4-OCH_3	H	CH_2CH_3	2.5	86	201
15	4o	4-Cl	H	H	2.5	90	176
16	4p	3-OH	H	H	3	82	181
17	4q	4-F	H	CH_3	2	92	186
18	4r	4-NO_2	H	CH_2Ph	2.5	94	197
19	4s	2-Cl	H	CH_3	2.5	91	188
20	4t	2-OMe	H	H	3	90	159
21	4u	4-Me	NO_2	$(CH_2)_3CH_3$	5	84	186
22	4v	4-OH	H	$(CH_2)_2CH_3$	3.5	87	159
23	4w	3-Cl	H	H	3	94	184
24	4x	4-NO_2	H	CH_3	2	84	181
25	4y	H	H	H	2.5	86	147

Method A= reaction at room temperature under ultrasonic irradiation

CONCLUSION: Our investigation provides an easy and ecofriendly access to 22 member library of hexahydrospiro[indoline-3,3'-pyrrolizine]-2-one derivatives via [3+2] cycloaddition using isatin and L-proline and a pyran-2-one moiety in regioselective manner at room temperature under ultrasonic reaction condition. This method is an easy synthesis of the novel five member heterocyclic frameworks in regioselective manner, which are major building blocks and active phrmacophores of several natural products and may become a potential pharmacologically active nucleus in near future.

ACKNOWLEDGMENT: Authors are thankful to CSIR New Delhi for financial support. Authors also acknowledge SAIF-CDRI for providing the spectral and analytical data and necessary laboratory facilities.

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