Heterocyclic Letters
Vol. 10| No.2|267-279|Feb–April | 2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

MICROWAVE MEDIATED REGIOSELECTIVE SYNTHESIS OF SPIRO INDOLINONE LIBRARY VIA MULTICOMPONENT REACTION

Vishwa Deepak Tripathi[1]* Akhilesh Kumar Singh[2], Anand Mohan Jha[2]

[1]*Department of Chemistry, M. K. College, (Lalit Narayan Mithila University, Darbhanga), Bihar. 846003. India.*
[2]*Department of Chemistry, M. L. T. College, Saharsa, (B. N. Mandal University Madhepura), Bihar. 852201. India.*
E-mail: vishwadeepak66@gmail.com

Abstract :
This work explains an easy synthetic methodology to create a 25 member library of Hexahydrospiro[indoline-3,3'-pyrrolizine]-2-one derivatives under microwave irradiation. Spiro nucleus was synthesized via microwave mediated three component reaction of Isatin, L-proline and chalcone analogues in regioselective manner. A possible explanation for regioselectivity of present reaction was made by the discussion of secondary orbital interaction present in transition sate. Prepared spiroindolinone library were well characterized using all the spectroscopic data and elemental analysis. Thus we have developed a green and methodology that has great importance in synthetic chemistry.

Keywords: Microwave, Spiropyrrolidine, Dehydroacetic acid, Isatin, L-Proline, Multicomponent reaction, Cycloaddition.

Introduction

Billions of people die due to various health ailments like pathothogenic or lifestyle diseases every year worldwide. The development of resistance and multidrug resistances in pathogen make this situation more critical and crucial. So the Scientists and Chemists involved in drug discovery research and Medicinal Chemistry programme have tremendous burden of developing new therapeutics to combat this situation. As a result a number of new synthetic molecules are being synthesized everyday in order to get molecules of better biological property. This creates huge environmental trouble as the conventional chemical synthetic protocols end with hazardous chemical and by product to pollute the environment. Therefore, there is urgent need to develop environmentally benign and green synthetic protocols for synthesis of therapeutically important molecules or nucleus. This situation lead to the development of various methods like using Green Solvents, Green Catalysts, Ultrasound Medium, Microwave reaction medium and many other synthetic procedures. Microwave mediated organic synthesis provides an easy and green alternative for the synthesis of small organic molecules [I]. This method has its significance both from

environmental as well as economic perspective. The main advantages of this technology are highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product [II]. MW heating usually employs reusable reaction media and eco-friendly solvents, or even under solvent less conditions [III]. As a consequence, not only the problem of pollution can be overcome but the risk of overpressure and explosions can also be avoided.

Multicomponent reactions have posse's special place in organic synthesis due to the beauty of forming multiple bonds in single step. They produce an alternative which is sustainable, cost effective, efficient and less wasteful then the conventional methods of synthesis of small molecules [IV]. Since this methodology consumes very less time and efforts, therefore it becoming an attractive protocol for medicinal chemists as can generate a library of small molecules within very short span of time. Our group is working on multicomponent synthesis of small compounds since several years and we have reported synthesis of spiro framework and polyhydroquinoline derivatives with antidiabetic and antibacterial potential [V-VIII]. 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 ecofriendly and cost effective for synthesis of new spirooxindole analogues under ultrasonic irradiation. 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 [IX]. Spiro framework mixed with indole scaffold containing quaternary stereogenic centre is a fascinating target for synthetic organic chemists due to its attractive structure and pharmacological properties [X]. Spiroindoles and its analogues posses structural resemblance with the core unit of various natural products (Figure **1**) with significant biological activities, which include spasmolitic, diuretic, anticoagulant, anticancer, and antianaphylactic activities [XI-XIV]. A careful literature review reveals that a lot of work has been done in search of new synthetic methods for synthesis of spirooxindole derivatives [XV-XVII]. The common carbon atom between two rings in spirocyclic systems is chiral and this structural property is reported to be one of the chief criterions of the excellent pharmacological properties [XVIII-XIX]. The existence of the quaternary constrained carbon in spiro structure in a variety of natural products also adds to the interest in the investigations of spiro compounds [XX]. Spirooxindole moiety is main part of the core structure found in various biological active agents and alkaloids [XXI] (Fig. **1**). In the field of medicinal chemistry and drug discovery, the incorporation of two or more bioactive heterocyclic moiety into a single compound may result into the construction of novel heterocycles with better biological activity [XXII]. Spirooxindoles have been identified to posses as aldose reductase, poliovirus and rhinovirus 3C-proteinase inhibitors [XXIII-XXIV]. In continuation of our work of developing novel for developing new sustainable synthetic process and inspired by these outstanding pharmacological properties of spirooxindole compounds, we wish to describe here green and cost effective synthesis of new bioisosetric analogues of natural spiropyrrolidines via [3+2] cycloaddition reaction under Microwave irradiation reaction condition [XXV-XXVII].

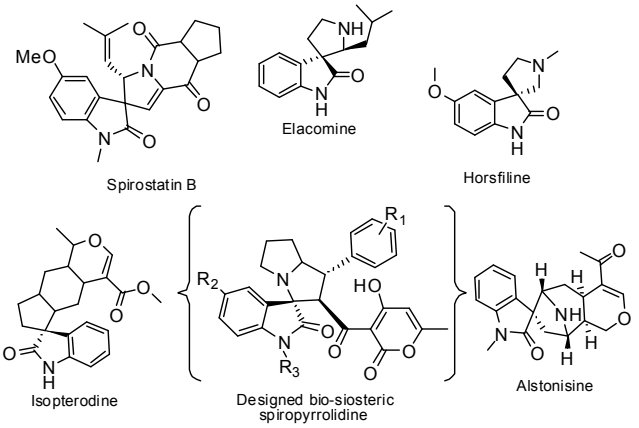


Figure 1. Representatives of spiroindoles of therapeutic interest.

Experimental

All the reactions were carried out under Microwave irradiation. 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 preformed 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 5 ml ethanol in sealed Microwave tube and placed in reactor 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 to afford desired spiro compound as solid powder.

3.4.4 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= 180^0C; 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= 191^0C %.; 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= 186^0C; 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= 159^0C; 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= 184^0C; 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. %.

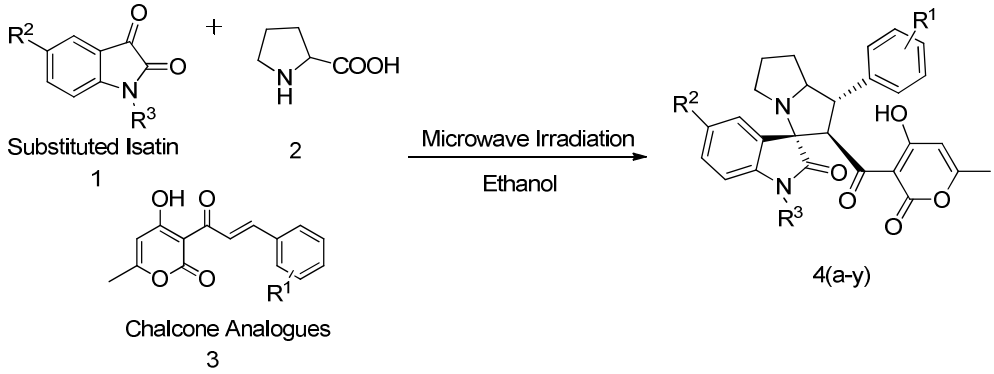
2'-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-1-methyl-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4x): White solid; mp= 181^0C; ν_{max}(KBr) 3641, 3050, 2982, 1718, 1624, 1217, 1031 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 11.01 (s, 1H), 8.21 (d, 2H, J = 8.7 Hz), 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= 147^0C; 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 synthesized spiro nucleus using chalcone derivative, Isatin and L-proline. Various substituted 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-one derivatives (Chalcone analogues) used as substrate for preparation of spiro derivatives. All the chalcone derivatives used were synthesized by reaction of dehydroacteic acid and substituted benzaldehydes via claisen-schmidt condensation reaction by our earlier reported protocol [XVIII-XXX]. Then we make our efforts to develop a greener synthetic protocol for synthesis of spirooxindole analogues. Firstly we focus our attention to find out most favorable reaction condition. We begin with an objective to find out best solvent for synthesis of spiropyrrolidines (4a-y). We screened various solvents as methanol, dichloromethane, ethanol, acetonitrile, chloroform, benzene and DMSO for the cycloaddition reaction of reaction of (E)-4-hydroxy-3-(3-(2-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (**3a**), isatin (**1**) and L-proline (**2**) for which result are summarized in Table **1**. We end up with conclusion that compound 4a was formed in excellent yield in ethanol under Microwave irradiation. While product yield was not suitable with other solvents, even at higher temperature and prolonged reaction time. So, we decided to use ethanol as green solvent for reaction.



Scheme 1. Synthesis of new Spirooxindole under Microwave Irradiation.

After having appropriate solvent in hand for reaction, we moved forward to prove general procedure under Microwave irradiation for synthesis of spirooxindole. In order to achieve this goal we carried out reaction by substituted chalcone derivatives (**3a-y**), isatin (**1**) and L-proline (**2**) under Microwave irradiation to get a series of new spiroindoles (**4a-y**) in excellent yields. Results are summarized in Table **1.**

Synthesized spiroindole structures 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. From the mechanistic perspective we proposed that this cycloaddition reaction proceeds through intermediate formation of azomethine ylide (**Figure 2**). The explanation for regioselectivity is based on the preferential formation of one of the azomethine ylide due to presence of secondary orbital interaction. Figure **2** clearly shows that the approach of ylide to dipolarophile may lead to formation of both transition state **5a** and **5b** resulting in the formation of corresponding

spiroindole derivatives **4**(**a-y**), but predominantly forms transition state **5a**. This behavior is explained by considering regioselective approach of HOMO of dipole to the LUMO of dipolarophile in path-A, where secondary orbital interaction (SOI) between orbital of carbonyl group in dipolarophile with those of dipole is present. Whereas the secondary orbital interaction (SOI) does not present in other path-B because of opposite orientation of phenyl ring. Hence there was predominant formation of product **5a** is more favorable in comparison to **5b**.

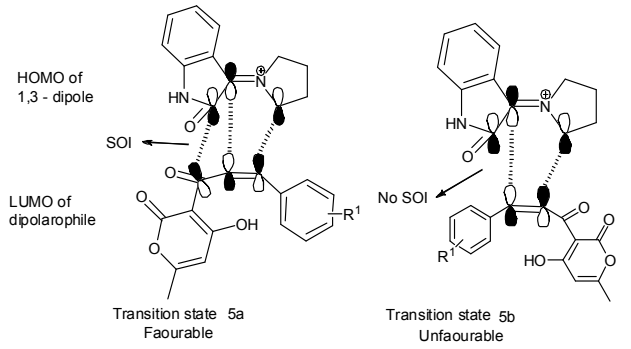


Figure 2. Plausible transition states for 1,3-dipolar cycloaddition reaction

Once we developed the process and characterized the prepared spiro derivatives then in order to analyze the substituent effect on the reactivity of the cycloaddition reaction, we prepared a 25 member library of spirooxindole analogues by using various substitutions on phenyl ring. During the synthesis of spirooxindole library we observed that the electron withdrawing group attached on phenyl ring tends to facilitate the rate of reaction, while electron donating substances retarded the reaction. As with the N,N-dimethyl group at the R1 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. While with substituent with negative inductive effects 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	(Under Microwave irradiation)		M.P. (^oC)
					Time (min)[c]	Yield (%)[b]	
1	4a	3-OMe	H	$(CH_2)_2CH_3$	27	81	180
2	4b	2-Cl	H	CH_2Ph	25	83	191
3	4c	4-F	H	H	38	85	184
4	4d	4-F	H	$(CH_2)_2CH_3$	25	84	181
5	4e	4-OMe	H	H	25	80	186
6	4f	3-OH	H	$(CH_2)_3CH_3$	30	78	167
7	4g	2-OMe	H	$(CH_2)_2CH_3$	27	69	182
8	4h	4-NO_2	H	$(CH_2)_2CH_3$	20	78	163
9	4i	3,4-$(OCH_3)_2$	H	$(CH_2)_2CH_3$	30	72	174
10	4j	3-OMe	H	CH_2Ph	27	76	169
11	4k	4-F	H	CH_2CH_3	35	80	182
12	4l	4-F	H	$(CH_2)_3CH_3$	35	83	186
13	4m	3-OH,4-OCH_3	H	H	30	75	206
14	4n	3-OH,4-OCH_3	H	CH_2CH_3	30	73	201
15	4o	4-Cl	H	H	25	80	176
16	4p	3-OH	H	H	30	69	181
17	4q	4-F	H	CH_3	25	81	186
18	4r	4-NO_2	H	CH_2Ph	20	79	197
19	4s	2-Cl	H	CH_3	25	81	188
20	4t	2-OMe	H	H	30	76	159
21	4u	4-Me	NO_2	$(CH_2)_3CH_3$	30	76	186
22	4v	4-OH	H	$(CH_2)_2CH_3$	30	71	159
23	4w	3-Cl	H	H	27	80	184
24	4x	4-NO_2	H	CH_3	20	81	181
25	4y	H	H	H	30	84	147

Conclusion

In summary we described a sustainable 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 under Microwave reaction condition. Our methodology 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.

Acknowledgments

Authors are thankful to CSIR New Delhi for financial support and Lalit Narayan Mithila University Darbhanga for providing necessary support. Authors also acknowledge SAIF-CDRI for providing the spectral and analytical data and necessary laboratory facilities.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

References

I. Hügel H. M., Molecules 14, (**2009**) 4936-4972.
II. Wang S. L., Zhang G., Jie D., Jiang B., Wang X. H., Tu S. J., Combinatorial Chemistry & High Throughput Screening, *15,* (**2012)** 400-410.
III. Gawande M. B., Shelke S. N., Zboril R., Varma R. S., Acc. Chem. Res., *47*, **(2014)** 1338−1348
IV. J. J. Shah, Mohanraj K., *Indian J Pharm Sci.* (**2014)** Jan-Feb; 76(1): 46–53.
V. Kumar A., Sharma S., Tripathi V. D., Maurya R. A., Srivastava S. P., hatia G., Tamrakar A. K., Srivastava A. K., Bioorganic & Medicinal Chemistry**,** *18*, (**2010)** 4138–4148
VI. Tripathi V. D., Shukla A. K., and Mohammed H. S., Asian Journal of Chemistry; 31, (**2019)** 613-616.
VII. Kumar A., Kumar P., Tripathi V. D. and Srivastava S., RSC Advances,*2*, (**2012)** 11641–11644.
VIII. Kumar A., Tripathi V. D., Kumar P., Gupta L. P., Akanksha, Trivedi R., Bid H., Nayak V. L., Siddiqui J. A., Chakravarti B., Saxena R., Dwivedi A., Siddiquee M. I., Siddiqui U., Konwar R., Chattopadhyay N., Bioorganic & Medicinal Chemistry , *19*, (**2011),** 5409–5419.
IX. Marti C., Carreira E. M., Eur. J. Org. Chem., **(2003)** 2209. (b) C. J. Douglas L. E., Proc. Natl. Acad. Sci. U.S.A., 101, (**2004)** 5363. (c) Trost B. M., Jiang C., Synthesis, (**2006)** 369.
X. Wei Q., and Gong, L. Z., Org. Lett., *12*, (**2010)** 1009.
XI. Pandey G., Banerjee P, Gadre S. R., Chem. Rev., *106*, (**2006)** 4484.
XII. Wang, Z. P., Xiang S., Shao P. L., He Y.; J. Org. Chem., *83*, (**2018)** 10995.
XIII. Jayashankaran J., Manian R., Venkatesan R, and Raghunathan R., Tetrahedron, *61*, (**2005)** 5595.
XIV. P. Shanmugam, B Viswambharan, K. Selvakumar, S. Madhavan, Tetrahedron Lett., *49*, (**2008)** 2611.
XV. Toru Y., Kayo Y, Harushisa K., Yukihiko K, Alison A.W, Robert J. N, George W. J. F., Naoki A., J. Nat. Prod., *65*, **(2002)**1875.
XVI. Daly J. W., Spande T. W., Whittaker N., Highet R. J., Feigl D., Noshimori N., Tokuyama

T., Meyers C. W., J. Nat. Prod., *46*, (**1986)** 210.
XVII. Moldoveanu C. C., Jones P. G., Mangalagiu L. L., Tetrahedron Lett, *50*, (**2009)** 7205.
XVIII. Kobayashi J., Tsuda M., Agemi K., Shigemori H., Ishibashi M., Sasaki T., Mikami Y., Tetrahedron, *47*, **(1991)**6617.
XIX. James D. M., Kunze H. B., Faulkner D. J., J. Nat. Prod., *54*, **(1991)** 1137.
XX. Periyasami G., Raghunatha R. N, Surendiran G., Mathivanan N., Eur. J. of Med. Chem , *44*, (**2009)** 959.
XXI. Miyamoto H., Okawa Y., Nakazaki A., Kobayashi S., Angew. Chem., Int. Ed., *45*, (**2006)** 2274.
XXII. Dounay A. B., Overman L. E., Chem. Rev., *103*, (**2003)** 2945.
XXIII. Hilton S. T., Ho T. C., Pljevalijcic G., Jones K., Org. Lett. (**2000)**, *17*, 2639.
XXIV. (a) S. N. Pandeya, D. Sriram, G. Nath, E. De Clercq, Indian J. Pharm. Sci., *61*, **(1999)** 358. (b) S.N. Pandeya, D. Sriram, G. Nath, E. De Clercq, Sci. Pharm., *67*, **(1999)** 103.
XXV. Murugan R., Anbazhagan S., Narayanan S., Eur. J. Med. Chem, , 44, (2009) 3272.
XXVI. Borthwick A. D., Weingarte G., Haley T. M., Tomaszewski M., Wang W., Hu Z., Bedard J., Jin H., Yuen L., Mansour T. S., Bioorg. Med. Chem. Lett., *8*, (**1998)** 365.
XXVII. Kumar R. R., Perumal S., Senthilkumar P., Yogeeswari P., Sriram D., Eur. J. of Med. Chem, , *44*, (**2009)** 3821–3829.
XXVIII. Bazgir A., Tisseh Z. N., Mirzaei P., Tetrahedron Lett., *49*, (**2008)** 5165–5168.
XXIX. Tripathi V. D., Shukla A. K., Asian J. Org. Med. Chem., *3*, (**2018)** 164-170.
XXX. V. D. Tripathi, A. M. Jha, J. Bio. Chem. Chron., *4*, (**2018)** 59-64.

Received on May 5, 2020.