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ARTICLE

An anti-Michael route for the synthesis of indole-spiro (indene-pyrrolidine) by 1,3-cycloaddition of azomethineylide with indole-derivatised olefins

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Abstract

One-pot three-component reaction for indole-spiro (indene-pyrrolidine) highly strained molecules were synthesized with moderate yield by 1,3-cycloaddition of unsymmetrical dipolarophiles, prepared from indol-3-yl and 1-acetyl-1*H*-indol-3-yl derivative with azomethineylide generated through decarboxylative addition of amino acid sarcosine and ninhydrine, which is confirmed by NOESY. Our method is to demonstrate an efficient path in the preparation of strained organic spiro compound, an atom-economical process and eco-friendly toward environment. Viability gives an access to prepare of various spiro pharmaceutical drug molecules.

1 | INTRODUCTION

The indole scaffold represents a "privileged" structural design, well distributed in pharmaceutical drugs and natural products.[1] Due to their promising and wide biological application, its derivatives are important and applicable in the pharmaceutical field. As a result, new approaches need to be adopted for synthesis of many indole derivatives to find out the lead compound. Particularly, C-3-substituted indole derivatives are significant in building blocks for the preparation of various biologically active compounds such as antimalarial, inhibitors of HIV-1, antimicrobial, antioxidant, anticancer, cytotoxic, inhibitors of hepatitis C virus, antidiabetic, and neuro protective activities, conversely, nitrogen and C-3-substituted indole derivatives possessed important role in biologically active compounds, chiefly with anti-inflammatory, anticancer, antinociceptive, and antipsychotic activities.[2]

A spiro compounds are one in which same atom is bonded and bridged to support two or more rings, due to steric strain in the molecule they always exist in the twisted form.[3] The common junction atom called spiro atom could be carbon or any other hetero atom/s like silicon, nitrogen, and other atoms.[4] If all the atoms in the rings are carbon then it is carbocyclic and if it contains any one or more hetero atoms then it is said to heterocyclic.[5]

The design of new spirocyclic compounds is attractive due to their unique nonplanar structure and enormous ability to bind with biomolecules because of their inherent rigid chiral structure.[6] Spiro [indolo-pyrans] is found to be recognized as good muscle relaxants, anti-inflammatory agents and also, as pesticides, similarly, number of spiro [indole-pyrrolidines] exhibits local anesthetic and anticonvulsant activities, spiro [indole-pyran/imidazoles] have been used in treating complication of diabetes or galactosemia.[7]

1,3-Dipolar cycloaddition, which is also known as the Huisgen reaction,[8] is one of the significant approaches for the synthesis of five-membered heterocycles[9] present in various natural products.[10] Pyrrolidine-based natural products are being used in preventing and treating rheumatoid arthritis, asthma, and allergies; and also possess anti-influenza virus and anticonvulsant activities.[11] The azomethineylide represents the most reactive and versatile classes of 1,3-dipoles and is readily trapped by a range of dipolarophiles forming substituted pyrrolidines.[12]

The 1,3-dipolar cycloaddition of azomethineylides, generated in situ via decarboxylative condensation of

ninhydrine and sarcosine with different olefinicdipolarophiles, represents a key approach for the regioselective and stereo-selective construction of a various complex spiro-indoles. Recently, this route has become significant in combinatorial chemistry due to its process simplicity, atomic economy, and extension of the scope of substrates.

In the present work, we report the synthesis of indole-spiro (indene-pyrrolidine) by using 1,3-dipolar cycloaddition of indole-derivatised olefins with azomethineylide, in situ via decarboxylative condensation of ninhydrine and sarcosine in a three-component fashion. Indole-derivatised olefins were prepared from indole-3-carboxaldehyde and active methylene compounds through Knoevenagel reaction followed by acetylation. All the synthesized compounds were characterized by ^{1}H-NMR, LC-MS, FT-IR, and UV-visible spectrophotometer.

2 | RESULT AND DISCUSSION

Equimolar mixture of three component system such as indole-derivatised olefins, sarcosine and ninhydrine monohydrate afforded the indole-spiro (indene-pyrrolidine) **2a-2h** (Scheme 1) in low to moderate yields (Table 1).

The formation of low to moderate yields is due to the formation of highly strained spiro compounds for different moieties. It has been found that indole-derivatised olefins diethylcarboxylate without acetyl **2b** and with acetyl **2f** substituent was found to give moderate yield where as in case of indole-derivatised olefins dimethylcarboxylate without acetyl **2d** and with acetyl **2g** substituent were low to moderate yield, respectively. Low to moderate yields were observed in indole-derivatised olefins ethyl nitrocarboxylate without acetyl **2c** and with acetyl **2h** substituent; same observation was noticed, in case of indole-derivatised olefins nitromethane without acetyl **2a** and with acetyl **2e** substituent. The least yield has observed in indole-derivatised olefin nitromethane **2a** without acetyl substituent and best moderate in indole-derivatised olefin dimethylcarboxylate with acetyl substituent **2g** (Figure 1).

TABLE 1 Synthesis of Indole-spiro (indene-pyrrolidine) derivatives

Sl. no	R	R_1	R_2	Product	% Yield
1.	NO_2	H	H	**2a**	20
2.	CO_2Et	CO_2Et	H	**2b**	61
3.	CO_2Et	NO_2	H	**2c**	23
4.	CO_2Me	CO_2Me	H	**2d**	30
5.	NO_2	H	MeCO	**2e**	44
6.	CO_2Et	CO_2Et	MeCO	**2f**	45
7.	CO_2Me	CO_2Me	MeCO	**2g**	62
8.	CO_2Et	NO_2	MeCO	**2h**	47

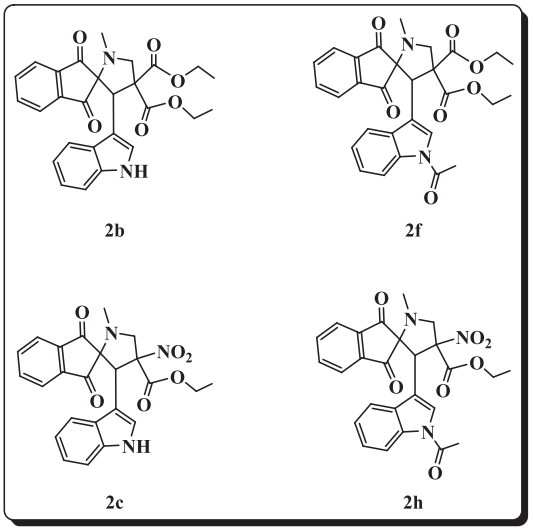
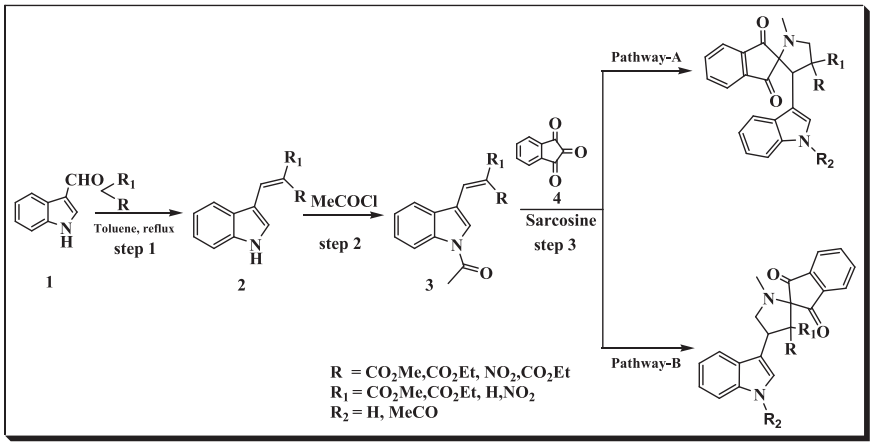


FIGURE 1 Structure of the molecules 2b, 2c, 2f, and 2h



SCHEME 1 Synthetic route for the synthesis of indole-spiro (indene-pyrrolidine) derivatives

1,3-cycloaddition of unsymmetrical dipolarophiles such as indole-derivatised olefins with azomethineylide can occur via two pathways **A** and **B** by Michael addition and anti-Michael addition fashion, respectively, leading to the formation of regioisomers **5** and **5′** as depicted in Scheme 2. All novel cyclo-adducts obtained by the above method were confirmed by ^{1}H-NMR and NOESY.

Inclusively, 3′-(1-acetyl-1H-indol-3-yl)-1′-methyl-4′-nitrospiro [indene-2,2′-pyrrolidine]-1, 3-dione had been selected as a role model to confirm which regioisomer exists, either 5 or 5′. The ^{1}H-NMR shows three peaks at 5.84 ppm (*m*, 1H), 4.91 ppm (*d*, $J = 9.2$ Hz, 1H), and 3.99 ppm (*d*, $J = 7.2$ Hz, 2H) for the proton bonded to pyrolidine ring at C_3, C_2, and C_4, respectively, as depicted in Figure 2.

But for further confirmation NOESY had been taken (Figure 3). There was correlation signal at 5.84 ppm (x-axis) corresponds to 3.99 ppm (y-axis) and 4.91 ppm (y-axis), similarly a signal at 4.91 ppm (x-axis) and 3.99 ppm (x-axis) correlated to 5.84 ppm (y-axis). Signal at 5.84 ppm (x-axis) was due to proton of C3 which is adjacent to C2 and C4 protons of pyrolidine ring of **5**, whereas signals at 4.91 ppm (x-axis) and 3.99 ppm (x-axis) were due to protons of C2 and C4, respectively, adjacent to C3 protons of pyrolidine ring **5**. Apart from the above signals, there were other correlation signals which were insignificance to assist in confirming the isomers. The above results reveal that the indene moiety is attached to the pyrolidine ring at C_1 and thus isomer 5 exists.

The mechanism of azomethineylide formation by a decarboxylative route has been repeatedly described by number of authors and is depicted as in Scheme 3.[13,14]

Ninhydrine (**structure-4a**) contains two hydroxyl groups bonded to the carbon atom 2 of cyclopentane ring in between the two adjacent oxa groups, would undergo dehydration during heating and form keto group (**structure-4**). The three oxa groups of ninhydrine (**structure-4**) are electrophilic in nature, but the oxa group at carbon-2 is most electrophilic due to presence of same species at either sides. Sarcosine contains secondary amino group, which is basic and nucleophilic in nature due to its lone pair of electron. The amino group with its lone pair of electrons attacks on oxa group at carbon-2 of ninhydrine (**structure-4**) and forms amino alcohol (**structure-4b**) which is unstable and undergoes further reaction. The alcoholic part of **structure-4b** attacks internally at its carboxylic group to form cyclic oxazolidine ring (**structure-4c**) and ring opening and closing exist at equilibrium. The two oxa groups on the ninhydrine ring assist (by –I effect) the oxazolidine ring to undergo ring opening by decarboxylation to form azomethineylide (**structure-4d**). By 1,3-cycloaddition reaction, the carbon anion of azomethine acts as nucleophile and attacks at one of the olefinic carbon of indole derivative by anti-Michael addition (confirmed by

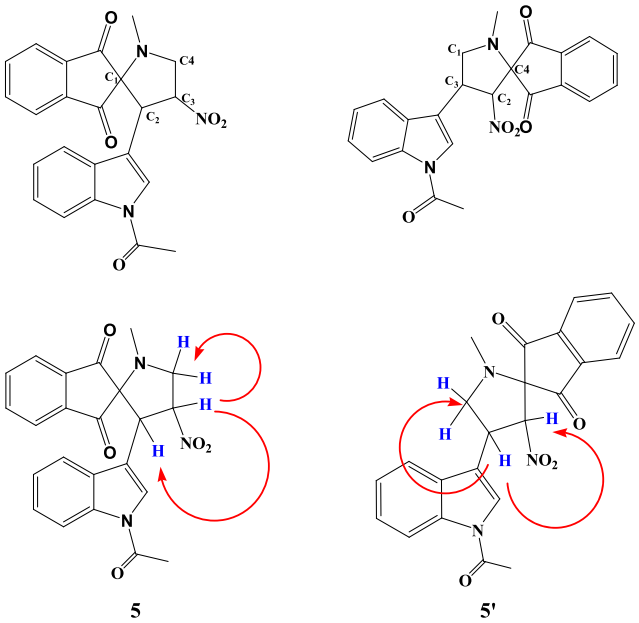
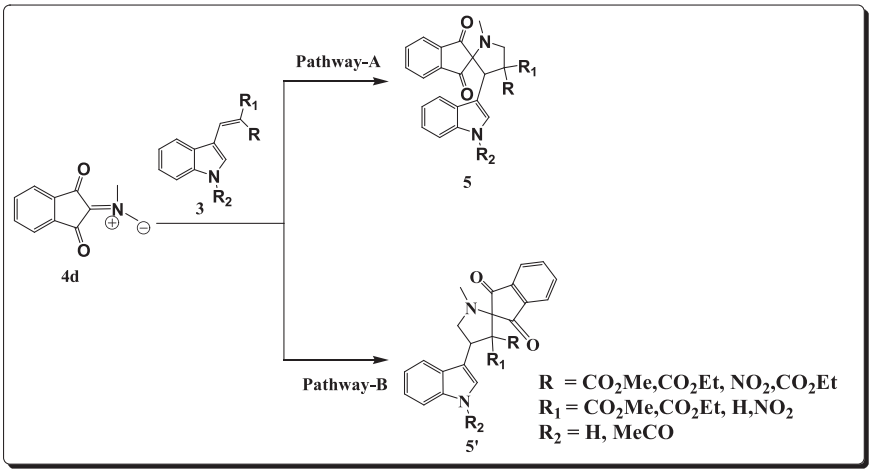


FIGURE 2 NOESY correlation H-H interactions



SCHEME 2 Synthetic route for the conversion of azomethineylide to indole-spiro (indene-pyrrolidine)

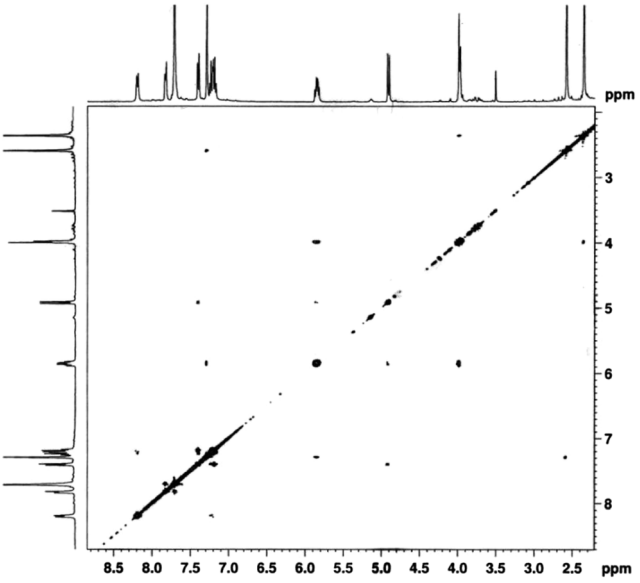
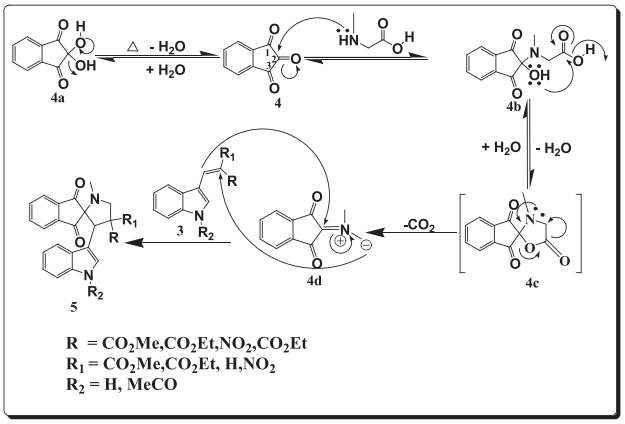


FIGURE 3 NOESY for 3′-(1-acetyl-1H-indol-3-yl)-1′-methyl-4′-nitrospiro [indene-2, 2′-pyrrolidine]-1, 3-dione



SCHEME 3 Tentative synthetic mechanism for the synthesis of indole-spiro (indene pyrrolidine) derivatives

NOESY) and simultaneously the other olefinic carbon which carries π-electrons attacks at the iminocarbon (electron deficient carbon due to adjacent oxa groups and amino group) and eventually, rearranges to affords indolyl-spiro (indene-pyrrolidine).

3 | CONCLUSION

A new protocol for the preparation of novel indole-spiro (indene-pyrrolidine) derivatives has been developed. The reaction of secondary amino-acid sarcosine and ninhydrine afforded azomethineylide, a highly reactive unstable intermediate generated in situ by decarboxylative addition, which underwent 1,3-cycloaddition reaction with indol-3-yl and 1-acetyl-1*H*-indol-3-ylderivatives to form the desired product. All synthesized products had undergone anti-Michael addition route which was confirmed by ^{1}H-NMR and NOESY experiment on selected molecule 3′-(1-acetyl-1*H*-indol-3-yl)-1′-methyl-4′-nitrospiro [indene-2,2′-pyrrolidine]-1,3-dione as a role model. Various functional groups are tolerated giving excess to a wide range of substituted indole-spiro (indene-pyrrolidine). Our exclusive synthetic procedure is quite efficient and provides an easy access to various pharmaceutical drug molecules. Prepared derivatives can be used in various therapeutic applications.

3.1 | Experimental

All the chemical reagents used for synthesis were purchased from Sigma Aldrich, Merck, Avra Synthesis Pvt. Ltd., and SDFCL. Progress of the reaction was evaluated by thin layer chromatography (TLC) by using petroleum ether and ethyl acetate as co-solvent mixture.

3.2 | Instrumentation

^{1}H and ^{13}C NMR spectra were recorded on JEOL Eclipse, (Peabody, MA) and Eclipse plus spectrometers at 400 MHz using either deuterated chloroform (CDCl3) or hexadeuterated dimethyl sulphoxide (DMSO-d_6) as solvents. Chemical shifts (δ) are given in ppm versus TMS (^{1}H-NMR) as an internal reference. Coupling constants are given in Hertz (Hz). Spectra of HR-MS were recorded on ESI-^{Q}TOF machine. Infrared (IR) spectra were measured on Agilent FT-IR spectrometer over the range of 400 to 4000 per cm. Absorption spectra were carried out on Shimadzu UV-1800 series. Melting points of all synthesized compounds were determined by open capillary tubes using Toshiba-melting point apparatus, expressed in °C and are uncorrected. Column chromatography was carried out by using silica gel 60 to 120 and 230 to 400 mesh.

3.3 | General procedure for synthesis

3.3.1 | Indole-3-yl (step 1) derivatives

To the round-bottomed flask connected with dean stark apparatus contained a suspension of indole-3-carboxaldehyde (1 eq.) in toluene (15 v/w) was added active methylene compound or nitromethane (1.2 eq.)

at room temperature followed by pipyridine (0.05 eq.), and acetic acid (0.05 eq.); and heated to reflux for 6 hours. Reaction mixture was cooled to room temperature and toluene was removed by rotavapor. Water (4 v/w of starting material) was added to the crude compound, resulted solid was filtered, washed with water, methanol and dried to yield compound-**2** (Scheme 1) as a solid.[15]

3.3.2 | 1-acetyl-1H-indol-3-yl (step 2) derivatives

Triethyl amine (1.5 eq.) was added to the solution of compound-**2** (1 eq.) in anhydrous dichloromethane (20 v/w) at room temperature under nitrogen atmosphere and cooled to 0°C. Acetyl chloride (1.2 eq.) was added drop wise to the reaction mixture and left stirring at room temperature for 2 hours. Reaction mixture was quenched with crushed-ice (20 w/w) and separated the biphasic layers. Aqueous layer was extracted with dichloromethane (20 v/w). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield compound-**3** (Scheme 1) as a solid.[15]

3.3.3 | Indole-spiro (indene-pyrrolidine) (step 3) derivatives (2a-h)

A mixture of compound **2** or **3** (1 equiv.), sarcosine (1.2 equiv.), and ninhydrine (1.2 equiv.) in anhydrous toluene (50 v/w) was heated to reflux for 16 hours. Dark brownish reaction mixture was cooled to room temperature and toluene was removed by concentration under vacuo. Crude compound was purified by column chromatography over silica gel 230 to 400 mesh by using ethyl acetate in petroleum ether as an eluent to afford compound-**5** (Scheme 1) as a solid.[16]

*3′-(1H-indol-3-yl)-1′-methyl-4′-nitrospiro [indene-2,2′-pyrrolidine]-1,3-dione (**2a**)*

Yield: 20%; mp: 169-171°C; ^{1}H NMR (400 MHz, CDCl3) δ[ppm]: 8.04 (*s*, 1H), 7.84-7.78 (*m*, 1H), 7.63-7.62 (*m*, 3H),7.42 (*d*, J = 7.6, 1H), 7.07-6.99 (*m*, 3H), 5.87 (*q*, J = 7.2 Hz), 5.00 (*d*, J = 8.0 Hz, 1H), 4.00 (*d*, J = 7.2 Hz, 2H), 2.39 (*s*, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 203.0, 199.6, 142.1, 140.3, 137.0, 136.5, 135.9, 129.0, 125.1, 123.8, 123.6, 123.3, 121.3, 119.2, 116.5, 114.7, 87.4, 76.32, 57.4, 47.2, 36.0; ESI-MS$^+$: exact mass calculated for $C_{21}H_{17}N_3O_4$ [M + H]$^+$: 375.1219, found: 398.1115 (M + Na); IR (cm^{-1}): 3279 (N-H), 2963 (=C-H), 1700 (C=0), 1550 (-NO2), 1258 (C-N); UV-visible (nm): 397, 234, 214.

*Diethyl 3′-(1H-indol-3-yl)-1′-methyl-1,3-dioxo-1,3-dihydrospiro [indene-2,2′-pyrrolidine]-4′,4′-dicarboxylate (**2b**)*

Yield: 61%; mp: 154-156°C; ^{1}H NMR (400 MHz, CDCl3) δ [ppm]: 8.06 (*s*, 1H), 7.86-7.84 (*m*, 1H), 7.69-7.66 (*m*, 3H), 7.57 (*d*, J = 8 Hz, 1H), 7.17 (*d*, J = 1.2 Hz, 1H), 7.06-6.97 (*m*, 3H), 5.36 (*s*, 1H), 4.56 (*d*, J = 10 Hz, 1H), 4.38-4.22 (*m*, 2H), 3.77 (*d*, J = 10 Hz, 1H), 3.73-3.65 (*m*, 1H), 3.43-3.35 (*m*, 1H), 2.39 (*s*, 3H), 1.27 (*t*, J = 7.2 Hz, 3H), 0.47 (*t*, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 200.2, 199.4, 168.3, 167.8, 140.9, 140.1, 136.1, 135.0, 133.5, 130.1, 125.6, 124.5, 123.0, 122.7, 121.8, 118.2, 115.0, 114.8, 78.4, 64.2, 62.0, 61.1, 59.2, 46.8, 35.4, 13.3, 12.2; ESI-MS$^+$: exact mass calculated for $C_{27}H_{26}N_2O_6$ [M + H]$^+$: 474.1791, found: 497.1688 (M + Na). IR (cm^{-1}): 3252 (N-H), 2933 (=C-H), 2820 (-C-H), 1704 (C=0), 1592 (C-O), 1347 (C-N); UV-visible (nm): 350, 232, 216.

*Ethyl-3′-(1H-indole-3-yl)-1′-methyl-4′-nitro-1,3-dioxo-1,3-dihydrospiro[indene-2,2′-pyrolidine]-4′-carboxylate (**2c**)*

Yield: 23%; mp: 182-184°C; ^{1}H NMR (400 MHz, CDCl3) δ[ppm]: 8.06 (*s*, 1H), 7.87-7.86 (*m*, 1H), 7.72-7.69 (*m*, 3H), 7.65 (*d*, *J*=6.8 Hz, 1H), 7.19-7.18 (*m*, 1H), 7.11-7.02 (*m*, 3H), 5.78 (*s*, 1H), 4.85 (*d*, J = 11.6 Hz, 1H), 4.07 (*d*, J = 11.6 Hz, 1H), 3.76-3.71 (*m*, 1H), 3.61-3.57 (*m*, 1H), 2.36 (*s*, 3H), 0.50-0.47 (*m*, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 201.3, 199.5, 164.0, 141.6, 141.2, 136.5, 136.0, 134.5, 127.7, 125.3, 123.5, 122.6, 122.5, 120.2, 118.7, 110.6, 106.2, 102.2, 78.3, 62.7, 62.5, 48.8, 35.4, 12.7; ESI-MS$^+$: exact mass calculated for $C_{24}H_{21}N_3O6$ [M + H]$^+$: 447.1430, found: 470.1328 (M + Na); IR (cm^{-1}): 2930(=C-H), 2842 (C-H aliphatic), 1706 (C=0), 1593 (C-O), 1347 (C-N), 1072 (C-O); UV-visible (nm): 257, 234, 214.

*Dimethyl-3′-(1H-indol-3-yl)-1′-methyl-1,3-dioxo-1,3dihydrospiro [indene-2,2′-pyrrolidine]-4′,4′-dicarboxylate (**2d**)*

Yield: 30%; mp: 180-182°C; ^{1}H NMR (400 MHz, CDCl3) δ[ppm]: 8.01 (*s*, 1H), 7.83 (*d*, J = 4.5 Hz, 1H), 7.65 (*m*, 3H), 7.57 (*d*, J = 7.5 Hz, 1H), 7.16 (*d*, J = 7.9 Hz, 1H), 7.09-6.99 (*m*, 3H), 5.37 (*s*, 1H), 4.59 (*d*, J = 10.1 Hz, 1H), 3.88-3.62 (*m*, 4H), 3.11 (*s*, 3H), 2.49 (*s*, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 201.3, 200.9, 171.3, 169.1, 141.8, 141.1, 136.0, 135.6, 134.5, 127.8, 124.7, 122.3, 122.0, 121.7, 119.8, 118.7, 110.5, 108.4, 79.1, 63.7, 60.9, 53.4, 52.2, 48.5, 35.9; ESI-MS$^+$: exact mass calculated for $C_{25}H_{22}N_2O_6$ [M + H]$^+$: 446.1478, found: 469.1375 (M + Na); IR (cm^{-1}): 3279 (N-H), 2963 (=C-H), 1700 (C=0), 1550 (-NO2), 1258 (C-N); UV-visible (nm): 286, 260, 234.

3′-(1-acetyl-1H-indol-3-yl)-1′-methyl-4′-nitrospiro [indene-2,2′-pyrrolidine]-1, 3-dione ***(2e)***

Yield: 44%; mp: 164-166°C; ^{1}H NMR (400 MHz, CDCl3) δ [ppm]: 8.10 (*d*, *J* = 7.2 Hz, 1H), 7.83-7.81 (*m*, 1H), 7.71-7.69 (*m*, 3H), 7.39 (*d*, *J* = 7.6 Hz, 1H), 7.28 (*s*, 1H), 7.24-7.16 (*m*, 2H), 5.84 (*m*, 6.0 Hz, 1H), 4.91 (*d*, *J* = 9.2 Hz, 1H), 3.99 (*d*, *J* = 7.2 Hz, 2H), 2.58 (*s*, 3H), 2.36 (*s*,3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 203.3, 199.3, 168.3, 141.8, 140.4, 136.9, 136.6, 135.3, 128.7, 125.9, 123.9, 123.7, 123.4, 122.3, 118.9, 116.2, 114.5, 86.8, 77.96, 57.3, 47.6, 36.3, 24.0; ESI-MS$^+$: exact mass calculated for $C_{23}H_{19}N_3O_5$ [M + H]$^+$: 417.1325, found: 440.1220 (M + Na); IR (cm^{-1}): 2925 (=CH), 2823 (-C-H), 1703 (C=0), 1549 (-NO2), 1331 (C-N); UV-visible (nm): 299, 292, 234.

Diethyl-3′-(1-acetyl-1H-indol-3-yl)-1′-methyl-1,3-dioxo-1,3 dihydrospiro [indene-2,2′-pyrrolidine]-4′, 4′-dicarboxylate ***(2f)***

Yield: 45%; mp: 108-110°C; 1 H NMR (400 MHz, CDCl3) δ [ppm]: 8.27 (*d*, *J* = 8.0 Hz, 1H), 7.90-7.89 (*m*, 1H), 7.78-7.69 (*m*, 3H), 7.52 (*d*, *J* = 7.6 Hz, 1H), 7.36 (*s*, 1H), 7.25-7.14 (*m*, 2H), 5.23 (*s*, 1H), 4.48 (*d*, *J* = 10 Hz, 1H), 4.39-4.24 (*m*, 2H), 3.80 (*d*, *J* = 10 Hz, 1H), 3.77-3.67 (*m*, 1H), 3.44-3.36 (*m*, 1H), 2.73 (*s*, 3H), 2.39 (*s*, 3H), 1.29 (*t*, *J* = 7.2 Hz, 3H), 0.48 (*t*, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 199.7, 199.1, 169.3, 167.7, 167.2, 140.6, 139.6, 135.4, 135.0, 133.2, 129.6, 125.1, 124.2, 122.5, 122.3, 121.5, 117.8, 115.0, 114.3, 77.5, 64.1, 61.3, 60.3, 59.3, 46.1, 34.7, 23.0, 12.9, 11.9; ESI-MS$^+$: exact mass calculated for $C_{29}H_{28}N_2O_7$ [M + H]$^+$: 516.1897, found: 539.1792 (M + Na); IR (cm^{-1}): 3289 (N-H), 2978 (=C-H), 1705 (C=0), 1558 (-NO2), 1247 (C-N); UV-visible (nm): 303, 295, 233.

Dimethyl-3′-(1-acetyl-1H-indol-3-yl)-1′-methyl-1,3-dioxo-1,3 dihydrospiro [indene-2,2′-pyrrolidine]-4′,4′-dicarboxylate ***(2g)***

Yield: 62%; mp: 103-105°C; ^{1}H NMR (400 MHz, CDCl3) δ [ppm]: 8.28 (*d*, *J* = 8.0 Hz, 1H), 7.90-7.88 (*m*, 1H), 7.77-7.70 (*m*, 3H), 7.52 (*d*, *J* = 7.6 H, 1H), 7.35 (*s*, 1H), 7.24-7.18 (*m*, 2H), 5.21 (*s*, 1H), 4.51 (*d*, *J* = 10.0 Hz, 1H), 3.86-3.81 (*m*, 4H), 3.12 (*s*, 3H), 2.60 (*s*, 3H), 2.40 (*s*, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 202.4, 202.2, 173.8, 172.4, 169.7, 142.2, 140.3, 136.6, 135.0, 133.0, 128.0, 124.4, 121.5, 121.0, 120.5, 119.6, 117.9, 109.8, 108.3, 77.7, 63.6, 61.4, 54.0, 53.3, 47.8, 36.2, 23.6; ESI-MS$^+$: exact mass calculated for $C_{27}H_{24}N_2O_7$ [M + H]$^+$: 488.1584, found: 511.1479 (M + Na); IR (cm^{-1}): 2930 (=C-H), 2842 (C-H aliphatic), 1706 (C=0), 1593 (C-O), 1347 (C-N), 1072 (C-O); UV-visible (nm): 293, 233.

Ethyl-3′-(1-acetyl-1H-indole-3-yl)-1′-methyl-4′-nitro-1,3-dioxo-1,3-Dihydrospiro[indene-2,2′-pyrolidine]-4′-carboxylate ***(2h)***

Yield: 47%; mp: 181-183°C; ^{1}H NMR (400 MHz, CDCl3) δ [ppm]: 8.28-8.25 (*m*, 1H), 7.92-7.86 (*m*, 1H), 7.80-7.78 (*m*, 3H), 7.61-7.57 (*m*, 1H), 7.31 (*s*, 1H), 7.24-7.23 (*m*, 1H), 7.22-7.17 (*m*, 1H), 5.65-5.42 (*m*, 1H), 4.81-4.73 (*m*, 1H), 4.38-4.33 (*m*, 1H), 4.12-3.98 (*m*, 1H), 3.80-3.61 (*m*, 1H), 2.68-2.55 (*m*, 3H), 2.41-2.35 (*m*, 3H), 0.57-0.53 (*m*, 3H); ^{13}C NMR (100 MHz, CDCl3) δ[ppm]: 201.5, 200.2, 168.6, 164.4, 142.0, 141.3, 136.8, 136.1, 134.4, 128.3, 125.4, 123.6, 123.1, 122.8, 120.7, 119.3, 111.2, 106.0, 102.8, 78.1, 63.4, 63.2, 48.5, 36.0, 23.7, 12.8; ESI-MS$^+$: exact mass calculated for $C_{26}H_{23}N_3O_7$ [M + H]$^+$: 489.1536, found: 512.1433 (M + Na); IR (cm^{-1}): 3263 (N-H), 2948 (=C-H), 2816 (-C-H), 1702 (C=0), 1584 (C-O), 1341 (C-N); UV-visible (nm): 230, 291, 299.

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