An expedient synthesis of pyrrolidinyl spirooxindole grafted 3-nitrochromanes through 1,3-dipolar cycloaddition reaction of azomethine ylides

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Graphical abstract

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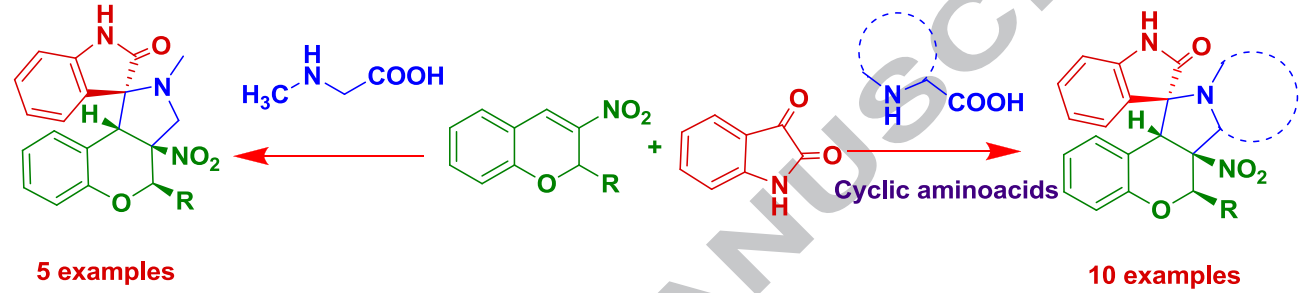

An expedient synthesis of pyrrolidinyl spirooxindole grafted 3-nitrochromanes through 1,3-dipolar cycloaddition reaction of azomethine ylides

J. Naga Siva Rao and R. Raghunathan*
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai-600 025, India.

Abstract:

A facile one-pot synthesis of pyrrolidinyl-spirooxindole grafted 3-nitrochromanes has been accomplished by 1,3-dipolar cycloaddition (1,3-DC) reaction of 3-nitrochromenes with azomethine ylides generated *in situ* from isatin and secondary amino acids. The regio- and stereochemical outcome of the cycloaddition reaction was ascertained by X-ray crystallographic analysis.

Keywords: 1,3-dipole, cycloaddition, azomethine ylide, pyrrolidinyl-spirooxindole, 3-nitrochromenes.

The 1,3-dipolar cycloaddition reaction employing an azomethine ylide as a 1,3-dipole has been used extensively to construct complex heterocycles from relatively simple precursors.[1] This type of cycloaddition simultaneously forms two carbon-carbon bonds to construct complex ring systems with regio-and stereocontrol.[2] Synthesis of polycyclic compounds incorporating pyrrolidine and pyrrolizidine rings has been center of attraction for the past several decades since it constitutes significant class of substances with highly pronounced biological activities.[3] Among the different synthetic strategies, The 1,3-dipolar cycloaddition of azomethine ylide is the most convenient method for the construction of highly substituted pyrrolidine and pyrrolizine rings.[4]

Corresponding author E-mail: ragharaghunathan@yahoo.com.(R.Raghunathan)

Phone: +91-44-22202811; Fax: +91-44-22300488

In recent years much attention has been focused on synthesis of 3,3'-pyrrolidinyl-spirooxindole frame work as it forms core structure of numerous alkaloids with strong bioactivity such as horsifiline, spirotryprostatine A and B, pteropodine, isopteropodine *etc*.[5-7] It is an important structural motif which acts as potent non-peptide inhibitor of the p53–MDM2 interaction.[8]

Chromane derivatives have received special attention in medicinal chemistry due to their significant biological property [9] and frequent occurrence in nature.[10] Recently several studies have demonstrated that benzopyranopyrrolidine derivatives S33084[11] and S33138[12] (Figure 1) act as antagonists of the dopamine D3 receptor and potential antipsychotic medicaments, while benzopyranopyrrolidine **I** is an antagonist of 5-HT_{2C} receptors with respect to 5-HT_{2A}.[13] Similarly fiduxosin **II** is an α_1 adrenoreceptor antagonist and shows an α_{1a} /α_{1b} selectivity for adrenoreceptors. It is suggested as a promising pharmaceutical agent for the treatment of benign prostatic hyperplasia (Figure 1).[14]

Figure 1

Encouraged by the reports on the structural features and biological activity of these molecules, we plan to fuse structurally unique pyrrolidinyl-spirooxindole motifs with benzopyran derivatives, with the expectation that this will lead to a new class of heterocycles with potential biological activities. To the best of our knowledge, there is no report in the literature on the synthesis of spirooxindole grafted 3-nitrochromanes through 1,3-dipolar cycloaddition reaction.

As part of our own interest in 1,3-dipolar cycloaddition of azomethine ylide[15] herein we report the facile synthesis of title compounds *via* [3+2] cycloaddition of 3-nitrochromenes with

azomethine ylides generated *in situ* from thermal decarboxylative condensation of isatin and secondary aminoacids (Figure 2) .

Figure 2

The 3-nitrochromenes containing 1-napthyl, ferrocenyl,[16] *N*-methyl-3-indole,[17] phenyl and 4-methoxy phenyl at 2-position utilized for 1,3-dipolar cycloaddition were prepared by the treatment of *β*-nitroalkenes with salicylaldehyde in the presence of DABCO under solvent-free conditions in a single step by modification of the method reported by Yao[18] (Scheme 1).

Scheme 1

Initially, we investigated the reaction of 2-napthyl-3-nitro chromene (3a) as dipolarophile with azomethine ylide generated *in situ* from isatin and sarcosine in refluxing toluene under Dean–Stark reaction conditions. [3+2] cycloaddition reaction occured smoothly to afford the cycloadduct **6**[19] in good yields (83%) with high regio- and stereoselectivity after 20 h (Scheme 2).

Scheme 2

The structure of the product was confirmed by spectroscopic analysis**.** A single product was isolated and no trace of the other isomer was observed even after prolonged reaction time. The crude ^{1}H NMR spectra of the product confirmed the formation of single regio and stereoisomer. The ^{1}H NMR spectrum of compound **6** exhibited a characteristic singlet at δ 2.11corresponding to *N*-methyl protons. The H_a proton of pyrrolidine ring attached to chromane core appeared as singlet at δ 4.42, and H_b proton of chromane ring and NH proton of oxindole resonated as singlets at δ 6.93 and δ 9.74,which clearly proved the incorporation of spiropyrrolidine oxindole ring in 2-napthyl-3-nitrochromane. Furthermore the characteristic singlet at δ 4.42 corresponding to H_a proton proved the formation of regio isomer **6.** If the other regioisomer **6A** had formed, the H_a proton would have appeared as a multiplet in the ^{1}H NMR spectrum. The amide carbonyl carbon

of oxindole showed characteristic peak at 176.9 ppm in ^{13}C NMR spectrum. Further the *N*-methyl carbon of pyrrolidine ring and carbons attached to H_a, H_b protons appeared at 34.2, 52.1 and 74.4 ppm respectively in ^{13}C NMR spectrum. The pyrrolidine methylene carbon, resonated at 56.6 ppm, and was confirmed by DEPT-135 NMR spectroscopy. These observed chemical shift values are in good agreement with the structure of the compound **6**. The reaction was found to be highly regioselective leading to the formation of only one product **6** (Figure 3, path A) and the formation of the other possible regioisomer **6A** (Figure 3, path B) was not observed. This may be due to the high polarized charge of dipole and dipolarophile. The regio- and stereochemical outcome of the cycloaddition reaction was clearly determined by single-crystal X-ray analysis of the cycloadduct **6** [20] (Figure 4).

Figure 3

Figure 4

To optimize the reaction conditions, the reaction was carried out in different solvents such as benzene, acetonitrile, methanol, DMF, and 1,4 dioxane. It was found that toluene was the best to get the maximum yield of the products. To expand the scope of the reaction, we treated different 3-nitrochromenes containing ferrocenyl, *N*-methyl-3-indole, phenyl and 4-methoxy phenyl at 2-position with azomethine ylide generated *in situ* from isatin and sarcosine under optimized reaction conditions. The reaction smoothly proceeded through [3+2] cycloaddition to give the corresponding cycloaddition products in good yields (Table 1).

Table 1

Encouraged by these results, we further investigated similar type of reaction of structurally diverse 3-nitrochromenes **(3a-e)** with different 1,3-dipoles generated *in situ* from decarboxylative

condensation of isatin and cyclic aminoacids such as proline and pipacolinic acid, under optimized conditions. These reactions successfully led to the formation of desired cycloadducts in good yields (Schemes 3).

Scheme 3

The results are summarized in Table 2. The cycloaddtion was found to be regioselective in all cases. The ^{1}H NMR spectrum of compound **12** showed a characteristic broad singlet at δ 7.39 corresponding to NH proton of isatin. The H_a proton of pyrrolizidine ring attached to chromane core and H_b proton of chromane ring appeared as singlets at δ 4.89 and δ 5.25 respectively. The characteristic singlet at δ 4.89 corresponding to H_a proton proved the formation of regioisomer **12**. If the other regioisomer had formed, the H_a should have appeared as doublet which we did not observe in any of the cases. The ^{1}H NMR spectra of the crude and column purified products showed identical which confirm the stereoselective nature of the reaction.

The X-ray crystal structure analysis of compound **19**[21] showed that the relative stereochemistry (Figure 5) of the H_a proton and NO_2 group in the vicinal positions is *cis*. Similarly the phenyl group at 2-position of chromane and NO_2 group in the vicinal positions also have *cis* orientation.

Figure 5

In conclusion, we have demonstrated a simple and efficient protocol for the synthesis of pyrrolidinyl-spirooxindole grafted 3-nitrochromanes through 1,3-dipolar cycloaddition methodology. This multicomponent reaction offers high yield of the products, with simple experimental procedure and formation of single regioisomer. The biological activities of the

synthesized compounds are currently under investigation, and further work in this direction is in progress.

Acknowledgment

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16. To a solution of salicylaldehyde (2 equiv) and (E)-(2-nitrovinyl) ferrocene (1 equiv) was added 1,4 diazabicyclo[2.2.2]octane (DABCO) (0.5 equiv) respectively. In the absence of solvent the reaction mixture was stirred at 90°C for 2h. After completion of the reaction as indicated by TLC, the crude product was extracted with ethylacetate. The organic layer was dried with anhydrous sodium sulphate and concentrated in *vacuo.* Then the crude product was purified by column chromatography using hexane/EtOAc (9:1) as eluent.

17. To a solution of salicylaldehyde (2 equiv) and (E)-1-methyl-3-(2-nitrovinyl)-1H-indole (1 equiv) was added 1,4 diazabicyclo[2.2.2]octane (DABCO) (0.5 equiv). In the absence of solvent the reaction mixture was stirred at 90 °C for 5h. After completion of the reaction as indicated by TLC, the crude product was extracted with ethylacetate. The organic layer was dried with anhydrous sodium sulphate and concentrated in *vacuo.* Then the crude product was purified by column chromatography using hexane/EtOAc (7:3) as eluent.

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19. **General Procedure for synthesis of pyrrolidinyl-spirooxindole fused 3-nitrochromanes:** To a solution of isatin (1.0 mmol) and cyclic or acyclic secondary amino acid (1.5 mmol) in dry toluene, were added 3-nitrochromenes **(3a-e)** under nitrogen atmosphere. The solution was refluxed for 24 h in Dean-Stark apparatus to give the cycloadducts. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure. The crude product obtained was purified by column chromatography using hexane/EtOAc (8:2) as eluent.

Spectroscopic Data for Selected Compounds

Compound 6: White solid, (83%), Mp: 280-282 ˚C, IR (KBr): 1728, 1619, 3410, 1321, 1529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+ DMSO-d_6): δ 2.11 (s, 3H), 3.83-3.95 (m, 2H), 4.42 (s, 1H), 6.44 (d, J = 7.8 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.93 (s,1H), 6.95-6.98 (m, 2H), 7.09-7.18 (m, 2H), 7.32-7.42 (m, 2H), 7.49-7.54 (m, 2H), 7.57-7.63 (m, 2H), 7.89-7.93 (m, 2H), 8.66 (d, J = 8.4 Hz, 1H), 9.74 (s, 1H).^{13}C NMR (75MHz, $CDCl_3$+ DMSO-d_6): δ 34.2, 52.1, 56.6, 74.4, 76.6, 95.8, 110.2, 117.4, 118.9, 121.8, 122.9, 123.0, 124.0, 125.0,125.1, 125.5, 126.1, 126.5, 127.8, 128.0, 128.6, 129.5, 129.9, 130.6, 131.2, 133.4, 142.3, 154.6, 176.9. m/z: 477.52. Anal. Calc. For $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.80%. Found: C, 72.98; H, 4.81; N, 8.85%.

Compound 12: Brown solid, (84%), Mp: 180-182˚C, IR (KBr):1734, 1618, 3410, 1325, 1547 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.02-1.21 (m, 2H), 1.77-2.03 (m, 2H), 2.24-

2.31 (m, 1H), 2.76-2.82 (m, 1H), 4.18-4.18 (m, 1H), 4.24-4.26 (m, 1H), 4.28 (s, 5H), 4.56-4.57 (m, 1H), 4.67-4.72 (m, 2H), 4.89 (s, 1H), 5.25 (s, 1H), 6.44 (d, *J* = 7.5 Hz, 1H), 6.75-6.80 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.28-7.33 (m, 1H), 7.39 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$): δ 24.2, 26.2, 42.8, 62.0, 67.7, 67.9, 68.10, 69.1, 69.3, 69.8, 71.9, 77.2, 83.6, 97.8, 109.6, 117.3, 122.7, 122.7, 123.1, 125.3, 126.5, 128.7, 129.0, 129.6, 141.1, 155.8, 176.5. m/z: 561.93. Anal. Calc. For $C_{31}H_{27}FeN_3O_4$: C, 66.32; H, 4.85; N, 7.48%. Found: C, 66.39; H, 4.91; N, 7.53%.

Compound 19: White solid, (87%), Mp: 250-252 ˚C, IR (KBr): 1705, 1620, 3441, 1327, 1543 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96-1.08 (m, 1H), 1.19-1.39 (m, 2H), 1.50-1.53 (m, 1H), 1.63-1.66 (m, 1H), 1.74-1.77 (m, 1H), 2.23-2.24 (m, 1H), 2.52-2.56 (m, 1H), 4.14-4.18 (m, 1H), 4.93 (s, 1H), 5.88 (s, 1H), 6.41 (d, *J* = 7.8Hz, 1H), 6.65-6.70 (m, 1H), 6.85 (t, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 7.3Hz, 1H), 7.20-7.25 (m, 1H), 7.35-7.39 (m, 4H), 7.45-7.48 (m, 2H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.66 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 24.8, 28.8, 46.3, 50.4, 64.3, 75.2, 80.0, 98.1, 109.8, 117.8, 120.2, 122.3, 123.8, 124.9, 126.2, 127.7, 127.9, 128.4, 128.6, 128.9, 130.0, 135.8, 141.5, 154.5, 177.1. m/z: 468.20. Anal. Calc. For $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99%. Found: C, 71.98; H, 5.33; N, 8.94%.

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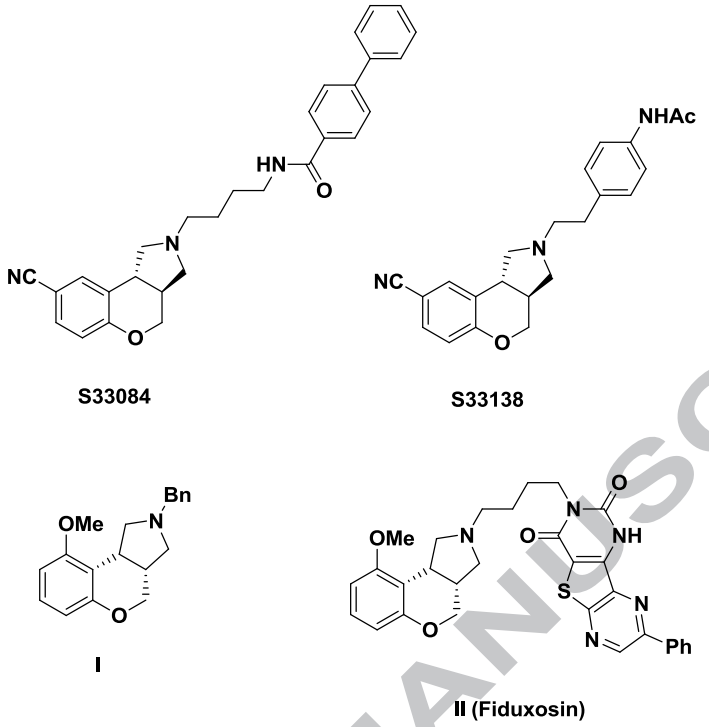


Figure 1 Biologically active benzopyranopyrrolidines

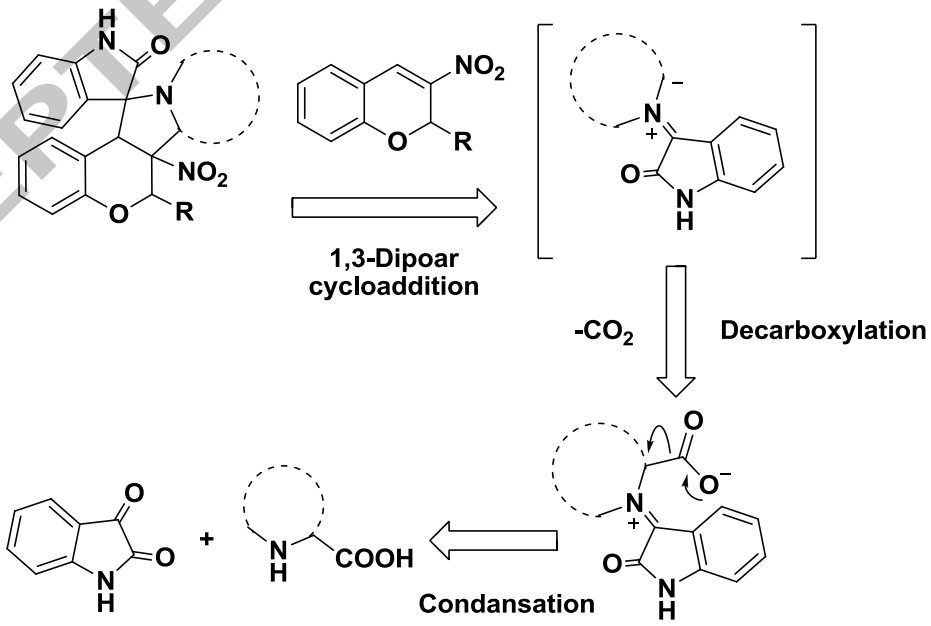
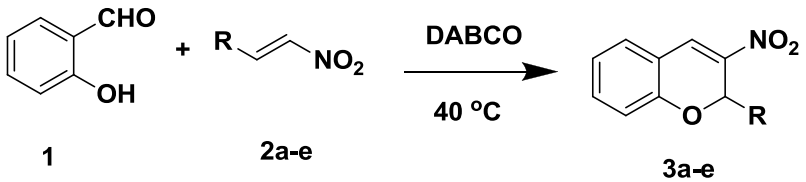


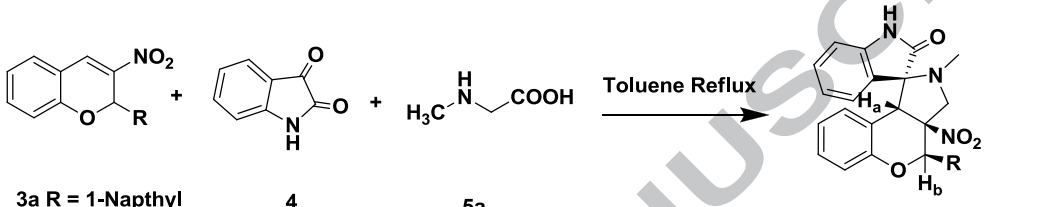
Figure 2 Synthetic plan for synthesis of spirooxindoles fused benzopyrans



1 2a-e 3a-e

R = 1-Napthyl, Ferrocenyl, N-Methyl 3-indole, Ph, 4-OMe-ph

Scheme 1 Synthesis of 3-nitrochromene derivatives



3a R = 1-Napthyl
3b R = Ferrocenyl
3c R = N-Methyl 3-indole
3d R = Ph
3e R = 4-OMe-ph

4

5a

6 R = 1-Napthyl
7 R = Ferrocenyl
8 R = N-Methyl 3-indole
9 R = Ph
10 R = 4-OMe-ph

Scheme 2 Synthesis of spiropyrrolidine oxindole fused 3-nitrochromanes

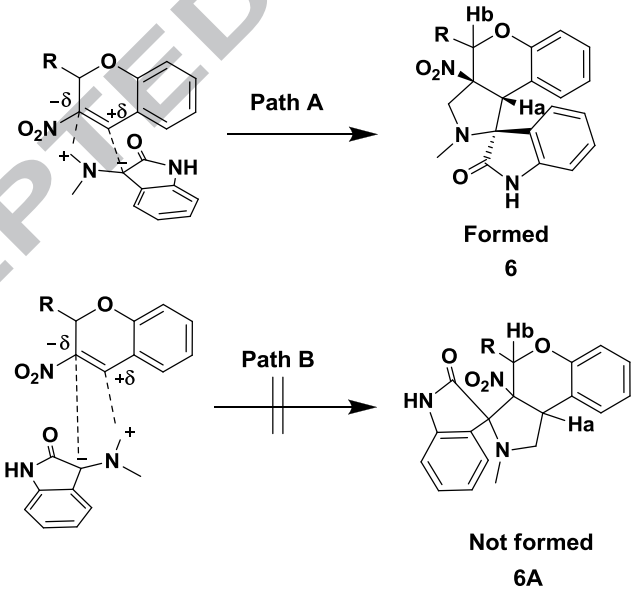


Figure 3: The possible regio chemical mode of approach of azomethine ylide to the dipolarophile

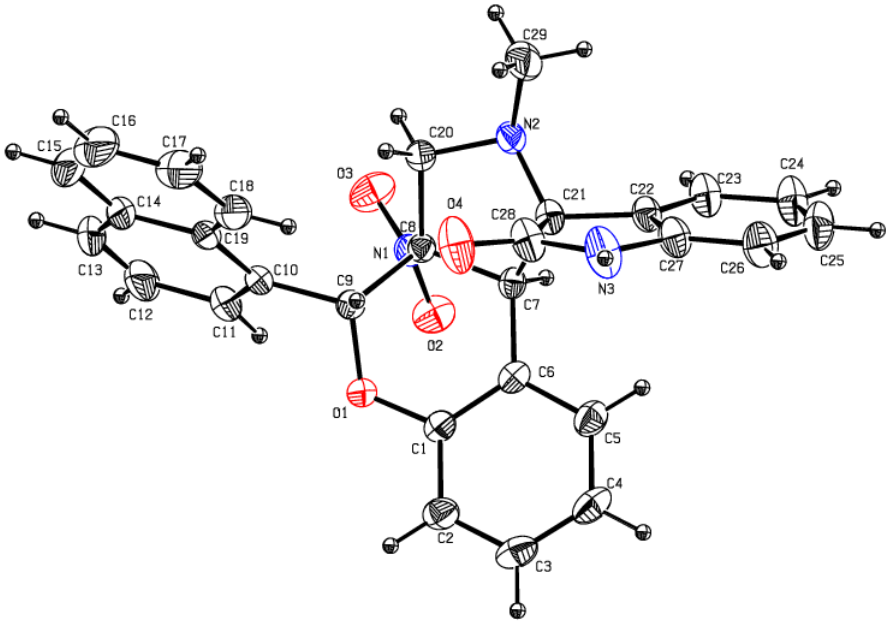
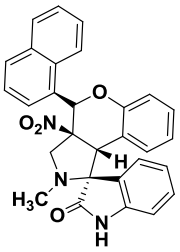
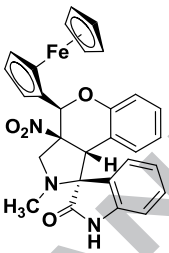
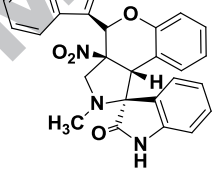
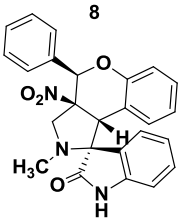
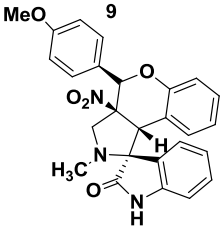


Figure 4: ORTEP diagram of compound **6**

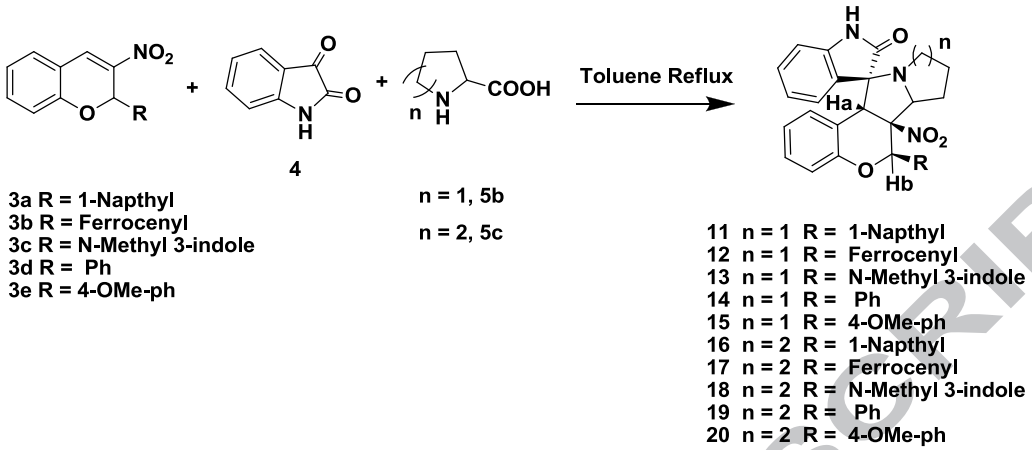
Table 1: Synthesis of spiropyrrolidine oxindole fused 3-nitrochromanes

Entry	Substrate	Time (h)a	Product [b]	yield (%) [c]
1	3a	20	 6	83
2	3b	16	 7	85
3	3c	24	 8	75
4	3d	20	 9	81
5	3e	20	 10	78

[a] Completion of the reaction based upon TLC analysis.

[b] The products were characterized by IR, NMR, MS and elemental analysis.

[c] Isolated yield after purification.



Scheme 3 Synthesis of spiropyrrolizidine/spiroindolizidine oxindole fused 3-nitrochromanes

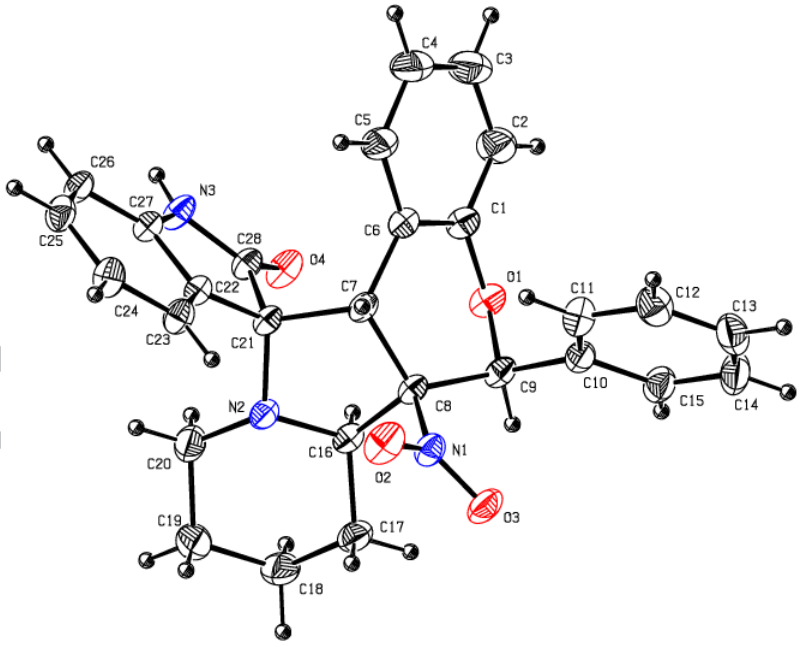
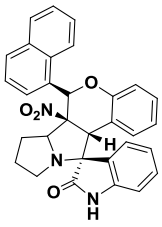
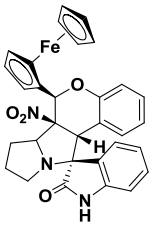
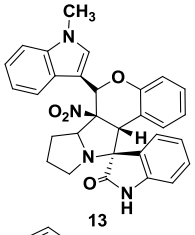
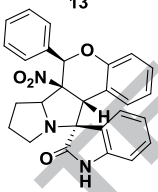
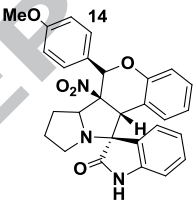
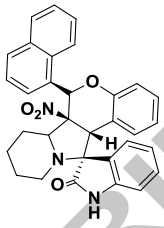
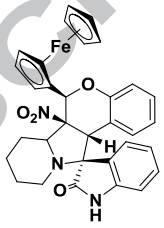
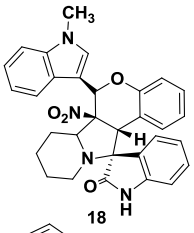
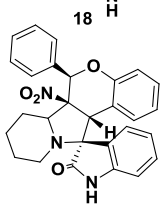
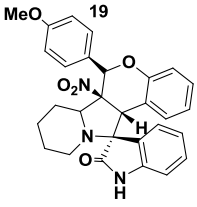


Figure 5: ORTEP diagram of compound **19**

Table 2: Syntheis of spiro pyrrolizidine/spiro indolizidine oxindole fused 3-nitrochromanes

Entry	Substrate	Time (h)[a]	Product [b]	yield (%) [c]
11	3a	20	 11	81
12	3b	16	 12	84
13	3c	24	 13	79
14	3d	20	 14	85
15	3e	20	 15	77
16	3a	20	 16	85
17	3b	16	 17	87
18	3c	24	 18	81
19	3d	20	 19	87
20	3e	20	 20	82

[a] Completion of the reaction based upon TLC analysis.

[b] The products were characterized by IR, NMR, MS and elemental analysis.

[c] Isolated yield after purification.