5.1 INTRODUCTION

5.1.1 Spiropyrrolidine-oxindoles

Oxindoles are an important class of heterocyclic compounds contained in the core structure of many natural products as well as pharmaceutically active compounds. There are a number of oxindole containing compounds that are currently used in the treatment of medical conditions. Ropinirole 1 manufactured by Glaxo-Smithkline is used in the treatment of Parkinson’s disease and restless leg syndrome. Ropinirole acts as an agonist at the D2, D3, and D4 dopamine receptors.\(^1\) Before the patent on ropinirole expired in 2008, it was listed as one of the top 100 drugs based on sales in the United States. Compounds 2, 3 and 4 are all represent a class of oxindole containing compounds known as spirooxindoles. Spirooxindole 4, a synthetic compound containing a cyclopropyl ester is known to inhibit the replication of HIV and possess potent anti-viral activity against other types of viruses.\(^2\) Almost 50 oxindoles are also present in the core of many natural products including welwitindolinone A, isonitrile 3 and hapalindolinone B 4. Welwitindolinone A, isolated from blue-green algae\(^3\), is found to have anti-fungal properties and the ability to reverse P-glycoprotein mediated multiple drug resistance.\(^4\)

![Figure 5.1: Some naturally occurring oxindoles.](image-url)
The hapalindolinone compounds are found to be useful in the treatment of diseases involving vasopressin including congestive heart failure, hypertension and edema.\textsuperscript{5}

Spirooxindole frameworks are commonly found in natural products and bioactive pharmaceutically relevant compounds. As a result, structure variation of this “privileged” pharmacophore has received much attention over the last decade. A variety of three, four, five and six-membered carbo- and heterocyclic ring systems were successfully incorporated at the C3 position of the oxindolic architecture as a result of the possible application of these scaffolds in medicinal chemistry or in the synthesis of complex heterocycles. In particular, extensive research effort has been devoted to the construction of spirooxindoles with multiple stereogenic centers. In this context, the mono- and bi-spirooxindole scaffolds were recently attracted considerable interest because of its unique structure and stereochemical diversity. However, only limited examples have been reported to date, probably because of the challenges associated with the assembly of the highly sterically congested spirocyclic moiety and multiple stereogenic centers.

### 5.1.2 Chromones and its importance

The chromone moiety forms an important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin. Many of them have useful medicinal applications. Consequently, chromone chemistry continues to draw considerable attention of synthetic organic and medicinal chemists.\textsuperscript{6}

Chromones are widely distributed in nature, especially in the plant kingdom, and a wide spectrum of useful properties of biological importance are associated with them.\textsuperscript{7} Chromone derivatives have been of special interest to organic chemists due to
their biological activities including antimicobacterial, antifungal, anticonvulsant, antimicrobial and mushroom tyrosinase inhibition activities. These derivatives also serve as intermediates to many products of fine chemical industries such as pharmaceuticals, agrochemicals and dyestuffs.

The natural products with annulated chromone nuclei are an emerging class of metabolites. In recent years, members like 6-methoxycomapavin\textsuperscript{9} 5, isonigerone\textsuperscript{10} 6, and pluramycin\textsuperscript{11} 7 have gained enormous attention due to their antitumor, antibacterial and enzyme inhibitory activities.

![Figure 5.2: Representative structures of naturally occurring annulated chromones.](image)

More specifically, 5-hydroxychromones, annulated to a quinone represented by topopyrone 8 have begun to receive attention due to their promising topoisomerase inhibitory activity\textsuperscript{12}.

![Figure 5.3: Naturally occurring annulated chromones.](image)
5.1.3 Literature survey

Our research group has been largely involved in the synthesis of spiropyrrrolidine-oxindole by intermolecular 1,3-dipolar cycloaddition reaction. We have carried out a comprehensive study on the synthesis of these moieties.

Yan et al.\textsuperscript{13} have developed an efficient synthesis of multicyclic spirooxindoles from readily available isatylidene malononitriles and curcumins. Curcumins work as multifunctional nucleophiles and electrophiles in this transformation.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{image}};
\end{tikzpicture}
\end{center}

Basavaiah et al.\textsuperscript{14} have developed a simple, convenient and one pot atom economical stereoselective synthesis of spiro-oxindoles via the titanium tetrachloride catalyzed coupling (aldol reaction) of 2-acetyl-6-methyl-2,3-dihydro-4H-pyran with various isatins and acenaphthoquinone derivatives involving tandem construction of C–C and C–O bonds.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{image}};
\end{tikzpicture}
\end{center}

Shi et al.\textsuperscript{15} have described a simple one-pot three component reaction involving phthalhydrazide, isatin and malononitrile (cyanoacetic ester) for the synthesis of spiro[indoline-pyrazolo[1,2-b]phthalazine] derivatives.
Wang et al.\textsuperscript{16} described a highly efficient bifunctional thiourea catalyzed asymmetric Michael addition/cyclization reaction of isothiocyanato oxindoles to synthesize functionalized 3,2’-pyrrolidinyl spirooxindole derivatives.

The cinchona alkaloids catalyzed all carbon-[4+2] cyclization of \( \alpha,\beta \)-unsaturated acyl chlorides with electron-deficient alkenes derived from oxindole was developed by Ye et al.\textsuperscript{17} to give the corresponding spirocarbocyclic oxindoles in good yields with high diastereo- and enantio-selectivities.

Zhu et al.\textsuperscript{18} have developed a novel palladium-catalyzed, domino spirocyclization process for the formation of biologically relevant spiropyrrolidine-3,3’-oxindoles.
Zhong et al.\textsuperscript{19} have developed an efficient organocatalytic [3+2]-cycloaddition reaction for the direct construction the 3,3’-pyrrolidonyl spirooxindole motif common to many bioactive molecules through the rational design of α-isothiocyanato imides as dienophiles.

Wang et al.\textsuperscript{20} synthesized 2’-alkyl-4’ aryl-1H-spiro[indole-3,3’-pyrrolidin]-2-ones by 1,3 dipolar cycloaddition reaction.
5.2 RESULTS AND DISCUSSION

5.2.1 Synthesis of thioproline based spirooxindoles

The chromone framework represents an important structural component in a number of biologically active and natural compounds such as alkaloids, flavonoids, tocopherols and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of biomedical chemistry.

As part of our endeavour to synthesize new spiropyrrolidine derivatives containing spiro carbons, we herein report the incorporation of chromone moiety into them. In order to establish the generality of this cycloaddition reaction to synthesize the desired spirooxindoles, we have initiated the reaction of various isatins, amino acids and dipolarophile in diverse solvents, say protic and aprotic solvents. A mixture of isatin (1.0 mmol), thioproline (1.0 mmol) and a dipolarophile (E)-3-(4-chloro-2H-chromen-3-yl)-2-(1H-indole-3-carbonyl) acrylonitrile (1.0 mmol) in various solvents (10 mL) was refluxed for about 2 h (Table 5.1).

![Scheme 5.1: 1,3-Dipolar cycloaddition method for the synthesis of substituted spirooxindoles.](image_url)

The reaction proceeds by generating an azomethine ylide by the reaction of isatin with thioproline. The formed 1,3-dipole subsequently undergoes a cycloaddition reaction with the dipolarophile (E)-3-(4-chloro-2H-chromen-3-yl)-2-(1H-indole-3-carbonyl) acrylonitrile to afford a series of novel spiropyrrolidine-oxindoles in good
to moderate yields (Scheme 5.1). Better results were obtained when we have refluxed
the reaction mixture in methanol with high yield of product and purity without
involving tedious workup and column chromatography. In general, protic solvents
provide better yield compared to aprotic solvents. When toluene was used as a
solvent, it provided about 65% of yield (Table 5.1).

Table 5.1:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl₃</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>2</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl acetate</td>
<td>1.5</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>2.5</td>
<td>65</td>
</tr>
</tbody>
</table>

Having achieved inspiring result using methanol as a solvent, we have
attempted to react various isatin derivatives, thioproline with dipolarophile refluxed in
methanol for about 2 h to afford the desired product. The ratios of the reactants under
the optimized condition was isatin 10a-f (1.0 mmol), dipolarophile 9 (1.1 mmol) and
thioproline 11 (1.1 mmol) under reflux in ethanol for 2-3h (Scheme 5.1). After the
reaction was completed (monitored by TLC), the reaction mixture was allowed to
room temperature for a while and then poured into cold water, filtered off and the
resulting crude was recrystallized using ethanol to afford 79-94 % pure
spiropyrrolidine-oxindole derivatives 13a-f as shown in the Table 5.2.
Table 5.2:
Synthesis of spiropyrrolidinex-oxindole from thioproline 13a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield(%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>H</td>
<td>H</td>
<td><img src="image" alt="13a" /></td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>Allyl</td>
<td>H</td>
<td><img src="image" alt="13b" /></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>Benzyl</td>
<td>H</td>
<td><img src="image" alt="13c" /></td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>Propargyl</td>
<td>H</td>
<td><img src="image" alt="13d" /></td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>10e</td>
<td>H</td>
<td>F</td>
<td><img src="image" alt="13e" /></td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>10f</td>
<td>H</td>
<td>NO₂</td>
<td><img src="image" alt="13f" /></td>
<td>79</td>
</tr>
</tbody>
</table>

<sup>a</sup>All products were characterized by NMR and mass spectrometry. <sup>b</sup>Isolated yield

Though we have expected two products from the reaction (Scheme 5.3), only one spirooxindole was formed predominantly. This can be explained as follows. The two possible regio approaches of dipolarophile and diene were shown in Figure 5.4. The transition state formed by path A stabilized by secondary orbital interaction
between oxindole carbonyl groups of diene and dipolarophile, whereas there is no such secondary orbital interaction in path B. Hence, only path A spiropyrrolidine-oxindoles (13a-f) were formed.

![Diagram](image)

**Figure 5.4:** Mode of approach of azomethine ylide towards the dipolarophile.

![1H spectrum](image)

**Figure 5.5:** $^1$H spectrum of compound 13b.
The products were characterized on the basis of their elemental analysis as well as $^1$H NMR, $^{13}$C NMR and mass spectral analysis as illustrated for compound 13b. In the $^1$H NMR (Figure 5.5), chemical shifts in the range of δ 6.85-7.38ppm confirms aromatic protons. The diastereotopic -CH$_2$ protons adjacent to-NCH appeared as a doublet at 6.47 (1H, d, J=13.5 Hz) and 5.98 (1H, d, J=13.5 Hz). The broad signals at δ 5.98 and 4.98 ppm for two protons showed the presence of pyrrolidine ring –CH$_2$ group. Moreover, a singlet at 6.2 ppm showed the presence of proton attached to the indole ring.

In the $^{13}$C NMR (Figure 5.6), the shifts at δ 75.3 correspond to a spiro carbon and the resonances at 164.2, and 164.8 ppm show the presence of two amide carbonyl carbons.

![Figure 5.6: $^{13}$C spectrum of compound 13b.](image-url)
A distinguishing peak observed at m/z: 619.68 [M+H]+ (Figure 5.7) in the mass spectrum further confirms the product 13b.

**Figure 5.7: Mass spectrum of compound 13b.**

### 5.2.2 Synthesis of proline based spirooxindoles

We have extended the methodology for the synthesis of spiropyrrolidine-oxindoles by reacting various substituted isatins (1.0 mmol) 10a-f, dipolarophile (1.1 mmol) 9 and proline (1.1 mmol) 15 refluxed in methanol as a solvent for about 3 h as shown in **Scheme 5.2**. The reaction provided the products in the range of 73-89 % and the results were summarized in **Table 5.3**.

**Scheme 5.2: Synthesis of spirooxindole derivatives 16 a-f via 1,3 Dipolar cycloaddition**
Table 5.3:
Synthesis of proline based spiropyrrolidine-oxindoles 16a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>H</td>
<td>H</td>
<td><img src="image" alt="16a" /></td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>Allyl</td>
<td>H</td>
<td><img src="image" alt="10b" /></td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>Benzyl</td>
<td>H</td>
<td><img src="image" alt="16c" /></td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>Propargyl</td>
<td>H</td>
<td><img src="image" alt="16d" /></td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>10e</td>
<td>H</td>
<td>F</td>
<td><img src="image" alt="16e" /></td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>10f</td>
<td>H</td>
<td>NO₂</td>
<td><img src="image" alt="16f" /></td>
<td>73</td>
</tr>
</tbody>
</table>

<sup>a</sup> All products were characterized by NMR and mass spectrometry.  <sup>b</sup> Isolated yield

The structure of spirooxindole derivatives synthesized was elucidated with the help of various techniques such as <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass data. The details are given in the experimental section 5.3.3.
5.2.3 Synthesis of sarcosine based spiropyrrolidine-oxindoles

To enhance the scope of the above methodology, we have reacted various substituted isatins 10a-f (1.0 mmol), dipolarophile 9 (1.1 mmol) and sarcosine 17 (1.1 mmol) in methanol. The reaction mixture was refluxed until the completion of the reaction as mentioned in Scheme 5.3. The completion of the reaction is often monitored by TLC and afforded the corresponding spiropyrrolidine-oxindole products 18 a-f in good to excellent yields (76-91%). The results were summarized in Table 5.4.

![Scheme 5.3: Synthesis of spiropyrrolidine-oxindole derivatives 18 a-f.]

Table 5.4:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>H</td>
<td>H</td>
<td><img src="image" alt="18a" /></td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>Allyl</td>
<td>H</td>
<td><img src="image" alt="18b" /></td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>Benzyl</td>
<td>H</td>
<td><img src="image" alt="18c" /></td>
<td>81</td>
</tr>
</tbody>
</table>
The structure of spirooxindole derivatives synthesized was elucidated with the help of various techniques such as $^1$H NMR, $^{13}$C NMR and mass spectral data. The details are given under experimental section 5.3.4.
5.3 EXPERIMENTAL SECTION

5.3.1 Materials and methods

All the chemicals were purchased from Aldrich and were used as received. The $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ and DMSO-d$_6$ using TMS as internal standard with JEOL 500MHz and Bruker 500MHz high resolution NMR spectrometer. Multiplicities were abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br). The mass spectra were recorded using a Electrospray Ionisation Method (ESI) with Thermo Finnigan mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using Thermo Finnigan FLASH EA 1112 CHN instrument.

5.3.2 Syntheses of spirooxindoles using thioproline

A mixture of various substituted isatins (10a-f) (1.0 mmol), dipolarophile 9 (1.1 mmol) and thioproline 11 (1.1 mmol) in methanol was refluxed until the completion of the reaction as mentioned in Table 5.4 and the mixture cooled to room temperature. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure products 13a-f in good yields (79-94%).
(3S,6'S,7'S)-6'-(4-Chloro-2H-chromen-3-yl)-7'-(1H-indole-3-carbonyl)-2-oxo-3',6',7',7a'-tetrahydro-1'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-7'-carbonitrile (13a):

$^1$H NMR (500 MHz, DMSO-d$_6$): δ 3.21 (1H, dd, $J_1$=3Hz, $J_2$=3Hz), 3.86 (2H, t, $J$=12Hz), 3.88 (1H, d, $J$=11Hz), 3.93 (1H, d, $J$=7Hz), 4.17 (1H, dd, $J_1$=5Hz, $J$=7Hz), 6.61 (1H, d, $J$=8.5Hz), 6.91-7.11 (2H, m), 7.16 (1H, t, $J$=9.5Hz), 7.20-7.27 (4H, m), 7.35 (1H, t, $J$=9.5 Hz), 7.41 (1H, d, 10Hz), 7.47 (1H, s), 7.90 (1H, d, $J$=9.5 Hz), 8.31 (1H, d, $J$=9Hz), 8.43 (1H, s) and 9.85 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 34.2, 42.1, 43.4, 53.1, 66.2, 75.1, 109.5, 111.4, 114.7, 115.9, 120.2, 121.7, 122.3, 122.9, 123.0, 123.5, 124.6, 125.6, 126.8, 126.9, 127.4, 130.5, 130.7, 130.9, 132.1(2), 135.0(2), 144.5, 154.1, 172.4 and 180.5.

ESI Mass: Molecular Weight: 578.89; m/z: 579.56 [M+H]$^+$: Anal. calcd for C$_{32}$H$_{23}$ClN$_4$O$_5$S; C, 66.37; H, 4.00; Cl, 6.12; N, 9.68; O, 8.29 and S, 5.54.

(3S,6'S,7'S)-1-Allyl-6'-((4-chloro-2H-chromen-3-yl)-7'-(1H-indole-3-carbonyl)-2-oxo-3',6',7',7a'-tetrahydro-1'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-7'-carbonitrile (13b):

$^1$H NMR (500 MHz, DMSO-d$_6$): δ 3.27 (1H, dd, $J_1$=3Hz, $J_2$=3Hz), 3.82 (2H, t, $J$=12Hz), 3.86 (1H, d, $J$=11Hz), 3.90 (1H, d, $J$=7Hz), 4.07 (1H, dd, $J_1$=5Hz, $J$=7Hz), 4.96-5.06 (4H, m), 5.16-5.28 (1H, m), 5.43 (1H, d, $J$=17Hz), 5.63 (1H, dd, $J$=5Hz, $J$=4.5Hz), 6.62 (1H, d, $J$=8.5Hz), 6.93-7.01(2H, m), 7.18 (1H, t, $J$=9.5Hz), 7.21-7.28 (4H, m), 7.33(1H, t, $J$=9.5 Hz), 7.45 (1H, d, 10Hz), 7.49 (1H, s), 7.92(1H, d, $J$=9.5 Hz), 8.33 (1H, d, $J$=9Hz) and 8.49 (1H, s).
\(^{13}\text{C}\) NMR (125 MHz, DMSO-d\(_6\)): δ 34.8, 42.0, 43.68, 53.30, 65.0, 66.6, 75.3, 109.0, 111.1, 114.1, 115.79, 117.70, 120.0, 121.9, 122.5, 122.8, 123.2, 123.7, 124.1, 125.7, 126.2, 126.4, 126.5, 129.5, 130.37, 130.6, 130.9, 132.7(2), 135.0(2), 144.5, 154.8, 172.8 and 180.4.

ESI Mass: Molecular Weight: 618.87; m/z: 619.68 [M+H]\(^{+}\): Anal. calcd for C\(_{33}\)H\(_{29}\)ClN\(_2\)O\(_3\)S; C, 67.90; H, 4.40; Cl, 5.73; N, 9.05; O, 7.75 and S, 5.18.

\((3S,6'S,7'S)-1\text{-Benzy1-6'-}(4\text{-chloro-2H-chromen-3-yl})\text{-7'}-(1H-indole-3-carbonyl)-2\text{-oxo-3',6',7',7a'-tetrahydro-1'\text{-H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-7'}-carbonitrile (13c):}\)

\(^{1}\text{H}\) NMR (500 MHz, DMSO-d\(_6\)): δ 3.25 (1H, dd, \(J_1=3\)Hz, \(J_2=3\)Hz), 3.71(2H, t, \(J=12\)Hz), 3.88 (1H,d, \(J=11\)Hz), 3.87(1H, d, \(J=7\)Hz), 4.11(1H, dd, \(J_1=5\)Hz, \(J=7\)Hz.), 4.64-4.71(1H, m), 4.77(1H, d, \(J=12.5\)Hz), 6.65 (1H, d, \(J=8.5\)Hz), 6.81-6.99 (2H, m), 7.13(1H,t, \(J=9.5\)Hz), 7.22-7.29 (4H, m), 7.33(1H, t, \(J=9.5\) Hz),7.39 (1H, d, 10Hz), 7.44(1H, s), 7.61-7.67 (3H, t, \(J=8.0\) Hz), 7.81-7.86 (2H, m), 7.92 (1H, d, \(J=9.5\) Hz), 8.33 (1H, d, \(J=9\)Hz) and 8.40 (1H, s).

\(^{13}\text{C}\) NMR (125 MHz, DMSO-d\(_6\)): δ 34.1, 42.7, 43.2, 49.0, 53.5, 66.7, 75.3, 109.4, 110.7, 114.3, 115. 6, 120.7, 121.9, 122.3, 122.6, 123.1, 123.9, 124.4, 125.3, 126.4, 126.7, 126.9 (2), 127.0, 129.7(2) 130.3, 130.8, 131.2, 132.7(2), 134.7(2), 137.2, 144.1, 154.0, 171.9 and 180.7.

ESI Mass: Molecular Weight: 669.19; m/z: 670.25 [M+H]\(^{+}\): Anal. calcd for C\(_{39}\)H\(_{29}\)ClN\(_2\)O\(_3\)S; C, 70.00; H, 4.37; Cl, 5.30; N, 8.37; O, 7.17 and S, 4.79.
(3S,6'S,7'S)-6'-(4-Chloro-2H-chromen-3-yl)-7'-(1H-indole-3-carbonyl)-2-oxo-1-(prop-2-ynyl)-3',6',7',7a'-tetrahydro-1'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-7' carbonitrile (13d):

$^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 2.81-2.90 (1H, m), 3.25 (1H, dd, $J_1$=3Hz, $J_2$=3Hz), 3.63 (1H, d, $J$=12Hz), 3.80 (2H, t, $J$=12Hz), 3.84 (1H, d, $J$=11Hz), 3.87 (1H, d, $J$=7Hz), 4.14 (1H, dd, $J_1$=5Hz, $J$=7Hz), 4.65 (1H, d, $J$=17Hz), 6.71 (1H, d, $J$=8.5Hz), 6.90-7.12 (2H, m), 7.16 (1H, t, $J$=9.5Hz), 7.20-7.26 (4H, m), 7.31 (1H, t, $J$=9.5 Hz), 7.43 (1H, d, 10Hz), 7.47 (1H, s), 7.90 (1H, d, $J$=9.5 Hz), 8.30 (1H, d, $J$=9Hz) and 8.45 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 34.2, 42.4, 43.4, 53.1, 53.5, 66.7, 72.1, 74.6, 75.2, 109.5, 111.0, 114.5, 115.5, 120.3, 121.5, 122.2, 122.6, 123.1, 123.9, 124.0, 125.4, 126.1, 126.3, 126.5, 130.3, 130.5, 130.7, 132.6(2), 135.1(2), 144.3, 154.5, 172.2 and 180.2.

ESI Mass: Molecular Weight: 617.11; m/z: 618.08 [M+H]$^+$: Anal. calcd for C$_{35}$H$_{23}$ClN$_3$O$_3$S; C, 68.12; H, 4.08; Cl, 5.74; N, 9.08; O, 7.78 and S, 5.20.

(3S,6'S,7'S)-6'-(4-Chloro-2H-chromen-3-yl)-5-fluoro-7'-(1H-indole-3-carbonyl)-2-oxo-3',6',7',7a'-tetrahydro-1'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-7' carbonitrile (13e):

$^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 3.22 (1H, dd, $J_1$=3Hz, $J_2$=3Hz), 3.71 (2H, t, $J$=12Hz), 3.84 (1H, d, $J$=11Hz), 3.90 (1H, d, $J$=7Hz), 4.12 (1H, dd, $J_1$=5Hz, $J$=7Hz), 6.56 (1H, d, $J$=8.5Hz), 6.82-7.04 (2H, m), 7.13 (1H, t, $J$=9.5Hz), 7.22-7.25 (3H, m), 7.33 (1H, t, $J$=9.5 Hz), 7.38 (1H, d, 10Hz), 7.41 (1H, s), 7.83 (1H, d, $J$=9.5 Hz), 8.24 (1H, d, $J$=9Hz), 8.46 (1H, s) and 9.84 (1H, s).
$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 34.1, 42.3, 43.6, 53.6, 66.0, 75.3, 109.5, 111.2, 114.5, 115.7, 120.2, 121.6, 122.3, 122.7, 123.1, 123.4, 124.6, 125.6, 126.6, 126.9, 127.1, 130.4, 130.8, 130.9, 132.1(2), 135.0(2), 144.5, 154.1, 172.4 and 180.1.


5.3.3 Syntheses of spirooxindoles using proline

A mixture of various substituted isatins (1.0 mmol) (10a-f), dipolarophile (1.1 mmol) 9 and proline (1.1 mmol) (15) was refluxed in methanol. The reaction mixture was stirred for 170 min. After complete conversion of the product as indicated by

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1H NMR (500 MHz, DMSO-$d_6$): δ 3.20 (1H, dd, $J_1=3$Hz, $J_2=3$Hz), 3.84 (2H, t, $J=12$Hz), 3.89 (1H, d, $J=11$Hz), 3.87 (1H, d, $J=7$Hz), 4.14 (1H, dd, $J_1=5$Hz, $J=7$Hz), 6.54 (1H, d, $J=8.5$Hz), 6.90-7.09 (2H, m), 7.14 (1H, t, $J=9.5$Hz), 7.20-7.26 (3H, m), 7.33 (1H, t, $J=9.5$ Hz), 7.45(1H, d, $J=10$Hz), 7.48 (1H, s), 7.90 (1H, d, $J=9.5$ Hz), 8.37 (1H, d, $J=9$Hz), 8.52 (1H, s) and 9.82 (1H, s).
TLC, the solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the corresponding pure products 16a-f in good yields (73-89 %).

(1'S,2'S,3S)-2'-(4-Chloro-2H-chromen-3-yl)-1'-(1H-indole-3-carbonyl)-2-oxo 1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-carbonitrile (16a):

\[\text{\textsuperscript{1}H NMR (500 MHz, DMSO-\text{d}_6): } \delta 2.12 (1H, m), 2.5 (1H, m), 3.20 (2H, d, J=9.5Hz), 3.42 (1H, d, J=13.5Hz), 3.78 (1H, d, J=13.5Hz), 4.62 (1H, t, J=10.5Hz), 5.05 (1H, d, J=13.0Hz), 5.11 (1H, d, J=18Hz), 5.35 (1H, d, J=18Hz), 6.43 (1H, d, J=9Hz), 6.67 (1H, d, J=9.5 Hz), 6.91-7.10 (4H, m), 7.16-7.27 (2H, m), 7.31 (1H, d, J=10Hz), 7.67 (1H, d, J=9.5Hz), 7.72 (2H, dd, J\textsubscript{1}=9.5Hz, J\textsubscript{2}=9.5 Hz), 8.43 (1H, s), 9.4 (1H, s) and 9.82 (1H, s).

\[\text{\textsuperscript{13}C NMR (125 MHz, DMSO-\text{d}_6): } \delta 24.0, 26.6, 50.1, 54.3, 62.1, 65.6, 68.5, 75.0, 108.1, 114.2, 114.5, 115.2, 118.9, 119.0, 120.7, 121.5, 122.2, 122.7, 123.5, 124.7, 125.0, 127.5, 129.1, 130.4, 131.6, 132.0(2), 134.7(2), 142.5, 153.1, 173.4 and 181.7.

ESI Mass: Molecular Weight: 561.02; m/z: 561.78 [M+H]\textsuperscript{+}: Anal. calcd for C\textsubscript{33}H\textsubscript{25}ClN\textsubscript{4}O\textsubscript{5}; C, 70.65; H, 4.49; Cl, 6.32; N, 9.99 and O, 8.56.

(1'S,2'S,3S)-1-Allyl-2'-(4-chloro-2H-chromen-3-yl)-1'-(1H-indole-3-carbonyl)-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-carbonitrile (16b):

\[\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3): } \delta 2.2 (1H, m), 2.4 (1H, m), 3.16 (2H, d, J=9.5Hz), 3.37 (1H, d, J=13.5Hz), 3.82 (1H, d, J=13.5Hz), 4.54 (1H, t, J=10.5Hz), 4.90-5.03 (2H, m), 5.06 (1H, d, J=13.0Hz), 5.09 (1H, d, J=18Hz), 5.14-5.21 (1H,m), 5.37 (1H,d, J=17Hz), 5.45 (1H, d, J=18Hz), 5.66 (1H, dd, J=5Hz, J=4.5Hz), 6.30 (1H,d, J=9Hz),
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6.82 (1H, d, J=9.5 Hz), 6.94-7.11 (4H, m), 7.13-7.25 (2H, m),
7.30 (1H, d, J=10Hz), 7.58 (1H, d, J=9.5Hz), 7.75 (2H, dd,
J1=9.5Hz, J2=9.5 Hz), 8.43 (1H, s) and 9.30 (1H, s).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 23.7, 25.6, 50.1, 54.6, 62.3,
65.0, 65.6, 68.3, 75.1, 108.0, 114.2, 114.5, 115.1, 117.3, 118.9, 120.3, 121.7, 122.1,
122.4, 122.6, 123.2, 124.5, 125.7, 126.0, 128.7, 129.1, 130.5, 131.0, 132.2(2),
135.1(2), 143.0, 154.8, 174.3 and 180.5.

ESI Mass: Molecular Weight: 600.78; m/z: 601.45 [M+H]$^+$: Anal. calcd for
C$_{36}$H$_{25}$ClN$_4$O$_3$; C, 71.93; H, 4.86; Cl, 5.90; N, 9.32 and O, 7.99.

(1'S,2'S,3S)-1-Benzyl-2'-(4-chloro-2H-chromen-3-yl)-1'-(1H-indole-3-carbonyl)-
2-oxo-1',2',5',6',7',7'a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-carbonitrile
(16c):

$^1$H NMR (500 MHz, DMSO-d$_6$): δ 2.12 (1H, m), 2.3 (1H, m),
3.22 (2H, d, J=9.5Hz), 3.40 (1H, d, J=13.5Hz), 3.76 (1H, d,
J=13.5Hz), 4.61(1H, t, J=10.5Hz), 4.67-4.72 (1H, m), 4.79
(1H, d, J=12.5Hz), 5.12 (1H, d, J=13.0Hz), 5.15 (1H, d,
J=18Hz), 5.31(1H, d, J=18Hz), 6.41(1H, d, J=9Hz), 6.65(1H,
d, J=9.5 Hz), 6.90-7.11(4H, m), 7.15-7.25 (2H, m), 7.36 (1H, d, J=10Hz),
7.60-7.69 (3H, t, J=8.0 Hz), 7.71 (1H, d, J=9.5Hz), 7.75 (2H, dd,
J1=9.5Hz, J2=9.5 Hz), 7.83-7.88 (2H, m), 8.41(1H, s) and 9.32(1H, s).

$^{13}$C NMR(125 MHz, DMSO-d$_6$): δ 24.2, 26.5, 49.2, 50.5, 54.1, 62.7, 65.2, 68.1, 75.4,
108.8, 114.1, 114.3, 115.2, 118.7, 119.1, 120.5, 121.1, 122.4, 122.9, 123.2, 124.2,
125.4, 126.7, 127.1,(2) , 129.4, 129.9(2) ,130.3, 131.2, 131.9(2), 133.4(2), 137.6,
142.4, 153.0, 172.7 and 181.5.
ESI Mass: Molecular Weight: 651.15; m/z: 652.10 [M+H]^+: Anal. calcd for C_{40}H_{31}ClN_{4}O_{3}; C, 73.78; H, 4.80; Cl, 5.44; N, 8.60 and O, 7.37.

(1'S,2'S,3'S)-2'-(4-Chloro-2H-chromen-3-yl)-1'-(1H-indole-3-carbonyl)-2-oxo-1-(prop-2-ynyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-carbonitrile (16d):

\[ \text{NMR} \] (500 MHz, CDCl$_3$): \( \delta \) 2.31 (1H, m), 2.62 (1H, m), 2.83-2.92 (1H, m), 3.21 (2H, d, \( J=9.5 \text{Hz} \)), 3.44 (1H, d, \( J=13.5 \text{Hz} \)), 3.61 (1H, d, \( J=12 \text{Hz} \)), 3.93 (1H, d, \( J=13.5 \text{Hz} \)), 4.67 (1H, t, \( J=10.5 \text{Hz} \)), 4.83 (1H, d, \( J=17 \text{Hz} \)), 5.03 (1H, d, \( J=13.0 \text{Hz} \)), 5.06 (1H, d, \( J=18 \text{Hz} \)), 5.32 (1H, d, \( J=18 \text{Hz} \)), 6.34 (1H, d, \( J=9 \text{Hz} \)), 6.71 (1H, d, \( J=9.5 \text{Hz} \)), 6.82-7.05 (4H, m), 7.13-7.20 (2H, m), 7.31 (1H, d, \( J=10 \text{Hz} \)), 7.57 (1H, d, \( J=9.5 \text{Hz} \)), 7.67 (2H, dd, \( J_1=9.5 \text{Hz} \), \( J_2=9.5 \text{Hz} \)), 8.29 (1H, s) and 9.31 (1H, s).

\[ \text{C NMR} \] (125 MHz, CDCl$_3$): \( \delta \) 23.6, 26.4, 50.2, 53.2, 54.4, 62.3, 65.5, 68.8, 72.3, 74.1, 75.5, 108.1, 114.2, 113.6, 115.3, 118.4, 120.5, 121.9, 122.1, 122.4, 122.6, 123.5, 124.5, 125.4, 126.0, 129.2, 130.5, 131.8, 132.3 (2), 134.9 (2), 142.5 154.2, 173.4 and 181.0.

ESI Mass: Molecular Weight: 599.07; m/z: 599.89 [M+H]^+: Anal. calcd for C$_{36}$H$_{27}$ClN$_4$O$_3$; C, 72.18; H, 4.54; Cl, 5.92; N, 9.35 and O, 8.01.

(1'S,2'S,3'S)-2'-(4-Chloro-2H-chromen-3-yl)-5-fluoro-1'-(1H-indole-3-carbonyl)-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-carbonitrile (16e):

\[ \text{NMR} \] (500 MHz, CDCl$_3$): \( \delta \) 2.16 (1H, m), 2.47 (1H, m), 3.22 (2H, d, \( J=9.5 \text{Hz} \)), 3.47 (1H, d, \( J=13.5 \text{Hz} \)), 3.71 (1H, d, \( J=13.5 \text{Hz} \)), 4.66 (1H, t, \( J=10.5 \text{Hz} \)), 5.06 (1H, d,
$J=13.0\text{Hz}$, $5.10$ (1H, d, $J=18\text{Hz}$), $5.31$ (1H, d, $J=18\text{Hz}$), $6.41$ (1H, d, $J=9\text{Hz}$), $6.67$ (1H, d, $J=9.5\text{Hz}$), $6.90-7.10$ (4H, m), $7.14-7.25$ (2H, m), $7.29$ (1H, d, $J=10\text{Hz}$), $7.62$ (1H, d, $J=9.5\text{Hz}$), $7.70$ (2H, dd, $J_1=9.5\text{Hz}$, $J_2=9.5\text{Hz}$), $8.41$ (1H, s), $9.1$ (1H, s, NH) and $9.74$ (1H, s).

$^{13}$CNMR (125 MHz, CDCl$_3$): $\delta$ 23.7, 26.2, 50.6, 54.2, 62.7, 65.3, 68.7, 75.4, 108.3, 114.1, 114.5, 115.0, 118.6, 119.7, 120.4, 121.2, 122.5, 122.7, 123.3, 124.6, 125.2, 127.3, 129.4, 130.1, 131.3, 132.7 (2), 134.3 (2), 142.9, 152.7, 172.3 and 181.3.

ESI Mass: Molecular Weight: 578.45; m/z: 579.20 [M+H]$^+$: Anal. calcd for C$_{33}$H$_{24}$ClF$_4$N$_3$O$_3$; C, 68.45; H, 4.18; Cl, 6.12; F, 3.28; N, 9.68 and O, 8.29.

(1'S,2'S,3S)-2'-(4-Chloro-2H-chromen-3-yl)-1'-(1H-indole-3-carbonyl)-5-nitro-2-oxo-1',2',5',6',7',7'a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-1'-carbonitrile (16f):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.28 (1H, m), 2.32 (1H, m), 3.39 (2H, d, $J=9.5\text{Hz}$), 3.47 (1H, d, $J=13.5\text{Hz}$), 3.70 (1H, d, $J=13.5\text{Hz}$), 4.64 (1H, t, $J=10.5\text{Hz}$), 5.06 (1H, d, $J=13.0\text{Hz}$), 5.14 (1H, d, $J=18\text{Hz}$), 5.31 (1H, d, $J=18\text{Hz}$), 6.44 (1H, d, $J=9\text{Hz}$), 6.61 (1H, d, $J=9.5\text{Hz}$), 6.93-7.10 (4H, m), 7.19-7.26 (1H, m), 7.35 (1H, d, $J=10\text{Hz}$), 7.58 (1H, d, $J=9.5\text{Hz}$), 7.67 (2H, dd, $J_1=9.5\text{Hz}$, $J_2=9.5\text{Hz}$), 8.36 (1H, s), 9.31 (1H, s) and 9.83 (1H, s).

$^{13}$CNMR (125 MHz, CDCl$_3$): $\delta$ 24.1, 26.0, 50.8, 54.3, 62.7, 65.2, 68.0, 75.3, 108.2, 114.1, 114.5, 115.7, 118.1, 119.7, 120.3, 121.9, 122.3, 122.7, 123.5, 124.1, 125.5, 127.0, 129.3, 130.4, 131.6, 132.1 (2), 134.4 (2), 142.0, 153.2, 173.1 and 180.9.
ESI Mass: Molecular Weight: 606.02; m/z: 606.96 [M+H]+: Anal. calcd for C_{33}H_{24}ClN_{3}O_{3}; C, 65.40; H, 3.99; Cl, 5.85; N, 11.56 and O, 13.20.

5.3.4 Syntheses of spirooxindoles using sarcosine

A mixture of isatin 10a-f (1.0 mmol), sarcosine 17 (1.1 mmol) and (E)-2-(1H-indole-3-carbonyl)-3-(4-oxo-4H-chromen-3-yl) acrylonitrile 9 (1.1 mmol) in methanol was refluxed for 2 h. The solid precipitated in the reaction mixture was filtered and dried under vacuum to obtain spirooxindoles 18 a-f in crude form. Finally, the crudes were recrystallized from ethanol to obtain the pure products in good yields (76-91 %).

(2'S,3'S,4'S)-3'-(4-Chloro-2H-chromen-3-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-carbonitrile (18a):

\[\text{1}^1\text{H NMR (500 MHz, CDCl}_3\text{): } 2.12\ (3\text{H,s}),\ 2.4(1\text{H, }t, J=13\text{Hz}),\ 4.11(1\text{H, d, } J=11.5\text{Hz}),\ 4.51(1\text{H,dd, } J_1=12\text{Hz, J=12Hz}),\ 5.32(1\text{H, s}),\ 5.50\ (1\text{H, d, } J=17.5\text{Hz}),\ 6.83\ (1\text{H,d, } J=10.0\text{ Hz}),\ 6.91(1\text{H, }t, J=9.5\text{Hz}),\ 6.95\ (1\text{H,d, } J=9.5\text{Hz}),\ 7.10\ (2\text{H,t, } J=9.5\text{ Hz}),7.22\ (1\text{H, t, } J=9.5\text{Hz}),\ 7.26-7.34\ (2\text{H, m}),\ 7.36-7.41\ (2\text{H, m}),7.44-7.52\ (1\text{H,m}),\ 7.57\ (1\text{H,d, } J=9.5\text{Hz}),\ 8.34-8.40\ (1\text{H, m}),\ 8.92\ (1\text{H, s})\text{ and } 9.90\ (1\text{H, s}).\]

\[\text{1}^3\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 29.4,\ 33.6,\ 66.7,\ 67.3,\ 75.5,\ 76.1,\ 109.3,\ 112.1,\ 113.4,\ 115.2,\ 119.6,\ 120.0,\ 121.3,\ 122.1,\ 122.3,\ 122.5,\ 123.2,\ 123.6,\ 124.0,\ 124.4,\ 126.0,\ 130.3,\ 130.6,\ 132.1,\ 134.2,\ 136.5,\ 140.2,\ 142.0,\ 154.5,\ 172.3\text{ and } 180.1.\]

ESI Mass: Molecular Weight: 534.99; m/z: 535.87 [M+H]+: Anal. calcd for C_{31}H_{23}ClN_{4}O_{3}; C, 69.60; H, 4.33; Cl, 6.63; N, 10.47 and O, 8.97.
(2'S,3'S,4'S)-1-Allyl-3'-((4-chloro-2H-chromen-3-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-carbonitrile (18b):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.10 (3H, s), 2.32 (1H, $J=13$Hz), 4.02 (1H, d, $J=11.5$Hz), 4.45 (1H, dd, $J=12$Hz, $J=12$Hz), 4.92-5.01 (2H, m), 5.12-5.25 (1H, m), 5.30 (1H, s), 5.40 (1H, d, $J=17$Hz), 5.47 (1H, d, $J=17.5$Hz), 5.65 (1H, dd, $J=5$Hz, $J=4.5$Hz), 6.80 (1H, d, $J=10.0$ Hz), 6.89 (1H, t, $J=9.5$Hz), 6.92 (1H, d, $J=9.5$Hz), 7.10 (2H, t, $J=9.5$ Hz), 7.18 (1H, t, $J=9.5$Hz), 7.22-7.31 (2H, m), 7.34-7.39 (2H, m), 7.43-7.50 (1H, m), 7.55 (1H, d, $J=9.5$Hz), 8.31-8.39 (1H, m) and 8.90 (1H, s).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.0, 55.5, 57.0, 59.4, 60.5, 114.4, 117.9, 118.3125.7, 128.0, 128.5, 128.7, 129.9, 129.2, 131.1, 142.7, 156.4, 164.2, and 164.8.

ESI Mass: Molecular Weight: 575.05; m/z: 576.10 [M+H]$^+$: Anal. calcd for C$_{34}$H$_{27}$ClN$_4$O$_3$; C, 71.01; H, 4.73; Cl, 6.17; N, 9.74 and O, 8.35.

(2'S,3'S,4'S)-1-Allyl-3'-((4-chloro-2H-chromen-3-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-carbonitrile (18c):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.11 (3H, s), 2.2 (1H, $J=13$Hz), 4.10 (1H, d, $J=11.5$Hz), 4.52 (1H, dd, $J_1$=12Hz, $J=12$Hz), 4.61-4.69 (1H, m), 4.82 (1H, d, $J=12.5$Hz), 5.32 (1H, s), 5.50 (1H, d, $J=17.5$Hz), 6.82 (1H, d, $J=10.0$ Hz), 6.90 (1H, t, $J=9.5$Hz), 6.95 (1H, d, $J=9.5$Hz), 7.12 (2H, t, $J=9.5$ Hz), 7.24 (1H, t, $J=9.5$Hz), 7.28-7.33 (2H, m), 7.34-7.41 (2H, m), 7.44-7.53 (1H, m), 7.58 (1H, d, $J=9.5$Hz), 7.63-7.67 (3H, t, $J=8.0$ Hz), 7.80-7.83 (2H, m), 8.37-8.44 (1H, m) and 8.95 (1H, s).
$^{13}$C NMR (125 MHz, CDCl$_3$): δ 29.6, 33.9, 65.2, 66.4, 67.7, 75.2, 76.0, 109.7, 112.5, 113.7, 115.1, 117.5, 119.3, 120.5, 121.0, 122.1, 122.3, 122.7, 123.1, 123.7, 124.1, 124.5, 126.7, 129.1, 130.1, 130.5, 132.0, 134.7, 136.2, 140.0, 142.2, 154.1, 172.7 and 180.5.

ESI Mass: Molecular Weight: 575.05; m/z: 576.10 [M+H]$^+$: Anal. calcd for C$_{34}$H$_{25}$ClN$_4$O$_5$; C, 71.01; H, 4.73; Cl, 6.17; N, 9.74 and O, 8.35

(2'S,3'S,4'S)-3'-(4-Chloro-2H-chromen-3-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-1-(prop-2-ynyl)spiro[indoline-3,2'-pyrrolidine]-4'-carbonitrile (18d):

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.14(3H, s), 2.6 (1Ht, J=13Hz), 2.87-2.90 (1H, m), 3.65(1H, d, J=12Hz), 4.04 (1H, d, J=11.5Hz), 4.54(1H,dd, J$_1$=12Hz, J=12Hz), 4.87(1H,d, J=17Hz), 5.30 (1H, s), 5.56(1H, d, J=17.5Hz), 6.80 (1H,d, J=10.0 Hz), 6.90(1H, t, J=9.5Hz), 6.97(1H,d, J=9.5Hz), 7.14(2H, t, J=9.5 Hz), 7.20(1H, t, J=9.5Hz), 7.29-7.33 (2H, m), 7.36-7.42(2H, m), 7.46-7.50(1H, m), 7.59(1H, d, J=9.5Hz), 8.37-8.41(1H, m) and 8.91(1H, s).

$^{13}$CNMR (125MHz, CDCl$_3$): δ 29.6, 33.8, 53.0, 66.5, 67.6, 72.5, 74.3, 75.8, 76.3, 109.5, 112.0, 113.1,115.6, 119.8, 120.2, 121.5, 122.2, 122.3, 122.6, 123.4, 123.7, 124.2, 124.4, 126.1, 130.5, 130.7, 132.0, 134.3, 136.0, 140.7, 142.1, 154.9, 172.7 and 180.3.

ESI Mass: Molecular Weight: 573.04; m/z: 574.00 [M+H]$^+$: Anal. calcd for C$_{34}$H$_{25}$ClN$_4$O$_5$; C, 71.26; H, 4.40; Cl, 6.19; N, 9.78 and O, 8.38.
(2'S,3'S,4'S)-3'-(4-Chloro-2H-chromen-3-yl)-5-fluoro-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-carbonitrile (18e):

\[
1H \text{ NMR (500 MHz, CDCl}_3): \delta 2.13 \text{ (3H, s), 2.32 \text{ (1H, t, J=}13Hz), 4.21 \text{ (1H, d, J=}11.5Hz), 4.52 \text{ (1H, dd, J}_1=12Hz, J=12Hz), 5.34 \text{ (1H, s), 5.45 \text{ (1H, d, J=}17.5Hz), 6.73 \text{ (1H, d, J=}10.0Hz), 6.85 \text{ (1H, t, J=}9.5Hz), 6.89 \text{ (1H, d, J=}9.5Hz), 7.15 \text{ (2H, t, J=}9.5Hz), 7.25 \text{ (1H, t, J=}9.5Hz), 7.27 \text{ (1H, m), 7.30-7.37 (2H, m), 7.41-7.50 (1H, m), 7.55 \text{ (1H, d, J=}9.5Hz), 8.32-8.39 (1H, m), 8.86 \text{ (1H, s) and 9.91(1H, s).}}
\]

\[
^{13}C \text{ NMR (125 MHz, CDCl}_3): \delta 29.5, 33.0, 66.2, 66.9, 75.0, 76.2, 109.1, 112.4, 113.0, 115.3, 119.5, 120.7, 121.3, 122.1, 122.3, 122.7, 123.3, 123.5, 124.2, 124.7, 126.0, 130.1, 130.3, 131.9, 134.0, 135.7, 140.0, 142.1, 154.8, 171.9, 181.0.
\]

ESI Mass: Molecular Weight: 552.98; m/z: 553.75 [M+H]^+: Anal. calcd for C_{31}H_{23}ClF_{11}N_{5}O_{3}: C, 67.33; H, 4.01; Cl, 6.41; F, 3.44; N, 10.13 and O, 8.68

(2'S,3'S,4'S)-3'-(4-Chloro-2H-chromen-3-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-5-nitro-2-oxospiro[indoline-3,2'-pyrrolidine]-4'-carbonitrile (18f):

\[
^{1}H \text{ NMR (500 MHz, CDCl}_3): \delta 2.16 \text{ (3H, s), 2.42 \text{ (1H, t, J=}13Hz), 4.19 \text{ (1H, d, J=}11.5Hz), 4.41 \text{ (1H, dd, J}_1=12Hz, J=12Hz), 5.29 \text{ (1H, s), 5.41 (1H, d, J=}17.5Hz), 6.69 \text{ (1H, d, J=}10.0Hz), 6.73 \text{ (1H, t, J=}9.5Hz), 6.92 \text{ (1H, d, J=}9.5Hz), 7.13 \text{ (2H, t, J=}9.5Hz), 7.24 \text{ (1H, t, J=}9.5Hz), 7.27 \text{ (1H, m), 7.33-7.39 (2H, m), 7.44-7.54 (1H, m), 7.67 \text{ (1H, d, J=}9.5Hz), 8.25-8.36 (1H, m), 8.73 \text{ (1H, s) and 9.85(1H, s).}}
\]
$^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3$: $\delta$ 29.1, 33.3, 66.5, 67.2, 75.1, 76.6, 108.3, 112.4, 113.7, 115.0, 118.8, 120.5, 121.1, 121.7, 122.2, 122.6, 123.5, 123.9, 124.1, 124.5, 125.7, 130.0, 130.6, 131.9, 134.4, 135.5, 140.3, 142.8, 153.6, 171.7 \text{ and } 181.4.$

ESI Mass: Molecular Weight: 579.98; $m/z$: 580.74 [M+H]$^+$: Anal. calcd for C$_{31}$H$_{25}$ClN$_3$O$_5$: C, 64.20; H, 3.82; Cl, 6.11; N, 12.07 and O, 13.79.
5.4 CONCLUSIONS

In the course of our investigations, we have developed a novel method to access spiropyrrolidine-oxindoles by 1,3-dipolar cycloaddition reaction in a highly convergent manner. The products are generally obtained in good yields and with high diastereoselectivities. The construction of highly substituted pyrrolidines can be achieved with proper selection of starting materials.
5.5 REFERENCES


